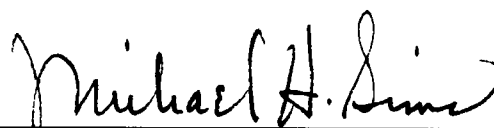


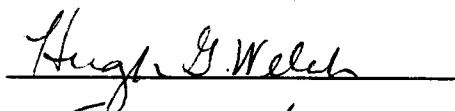
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EFFECTS OF NICOTINE, ATROPINE AND
5-METHOXY-N-N-DIMETHYLTRYPTAMINE
ON THE AUDITORY BRAINSTEM
RESPONSE AND ACOUSTIC
REFLEX IN CATS

A Thesis
Presented For The
Master of Science
Degree
The University of Tennessee, Knoxville

Janice Elisabeth Horohov

June 1985

Dedicated to

My husband, David,
for his constant support, encouragement and love.

My son, Nikolai,
for his smiling face and love when I needed it most.

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ABSTRACT

The pharmacological effects of nicotine on the nervous system have been extensively investigated. In particular its effect on various evoked potentials has been studied in regard to whether it acted directly on acetylcholine (ACh) receptors or caused the release of ACh or other neurotransmitters such as serotonin from nerve terminals. In this study the effect of nicotine on the auditory pathway was investigated using two electrodiagnostic procedures, the acoustic reflex (AR) and the auditory brainstem response (ABR).

The AR is the reflexive contortion of the middle ear muscles in response to loud sound stimuli. This contraction results in a change in compliance of the middle ear system. The ABR is the far field recording of neural (electrical) activity in the brainstem which occurs within the first 10 ms after sound stimulation. To determine if any changes occurred during different experimental manipulations, the AR latency, amplitude, and threshold and the ABR wave latencies and amplitudes were measured.

In particular several questions were asked. First were there any changes in the AR or ABR due to nicotine administration? Secondly, were the effects dose or time dependent? Thirdly, did nicotine cause the release of ACh from nerve terminal endings or act on ACh receptors? Fourthly, did nicotine cause the release of serotonin? Fifthly, were AR and ABR changes related?

Six cats were anesthetized by sequential i.m. injections of xylazine (1.0 mg/kg) and ketamine (10 mg/kg). Ipsilateral and

contralateral AR as well as monaural ABR were recorded from the left ear during each of the following the experiments: (a) saline, (b) nicotine, ($40 \text{ ug kg}^{-1}\text{min}^{-1}$), (c) nicotine, ($60 \text{ ug kg}^{-1}\text{min}^{-1}$), (d) atropine (0.4 mg/kg) followed by nicotine, ($60 \text{ ug kg}^{-1}\text{min}^{-1}$), and (e) 5_Methoxy-N-N-Dimethyltryptamine (a serotonin analogue) (10 ug kg^{-1}). Recordings were made after xylazine and ketamine and at time points of 5, 10, 20 and 30 minutes during the infusions.

There was a significant decrease in the AR threshold due to nicotine administration, and an increase in the AR amplitude after both atropine and nicotine were given. These results indicated a direct action on ACh receptors by nicotine. The ABR latency after giving nicotine increased more with pip-evoked responses than with the click-evoked responses. The amplitude of all ABR waves except wave VI decreased significantly for the click-evoked ABR. The pip-evoked responses showed biphasic changes in the amplitude of some waves. Recordings made using the -10 dB ART intensity pip stimulus were only affected by the higher nicotine dosage. There were no apparent time dependent differences.

Atropine had only a minor blocking effect on the ABR response and this was more apparent in the pip-evoked response. The increase in latency and decrease in amplitude seen with some waves of the ABR due to the injection of 5-MeODMT were independent of those seen with nicotine administration and were thus of different origin.

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CHAPTER I

INTRODUCTION

The integrity of the auditory pathway can be assessed using various electrodiagnostic techniques. Two such procedures are the auditory brainstem response (ABR) and the acoustic reflex (AR). Both involve the external ear canal, middle and inner ear cavities, and selected areas of the brainstem.

The ABR is a far field recording of the neural activity in the brainstem occurring during the first ten milliseconds after auditory stimulation. By employing a high energy sound stimulus with a short duration, the resulting response is a reflection of synchronous neural activity in the initial portion of the auditory pathway. A recording of this response consist of a series of peaks which correspond to physiologically (and perhaps anatomically) specific neural generators (Buchwald, 1983). The generators have been extensively investigated through the use of surgical manipulation and comparisons between the ABR and recordings of electrical potentials directly from nuclei and/or tracts (Achor and Starr, 1980a, 1980b; Moller,et al.,1981; Buchwald, 1983). A somewhat tenable explanation of the ABR is that peaks I-VI reflect activity in the acoustic nerve (VIIIth cranial nerve), the cochlear nucleus, the superior olivary complex, the lateral lemniscus, and the inferior colliculus, respectively (Achor and Starr, 1980a,b, Wada and Starr, 1983a,b, Buchwald, 1983). The possible overlapping of generators will be discussed later. Because of its relationship to

nuclei in the auditory pathway and the reliability of the waveform, the ABR has been used extensively as a diagnostic tool in the investigation of various neurological diseases (Sohmer, 1983).

The AR is but one of a battery of tests which can be performed in the area of impedance audiometry, all of which are based on compliance of the tympanic membrane and ossicular chain. In particular, the AR is the resultant transitory change in the compliance of the membrane and ossicles in the middle ear as a result of the reflexive contraction of middle ear muscles in response to loud sound (Klockhoff, 1961; Moller, 1961; Borg, 1972). The effectors for the reflexive pathway are the stapedius and tensor tympani muscles which are innervated by efferent fibers in the facial (VIIth) and trigeminal (Vth) cranial nerves, respectively. It is important to note that sound stimulation of one ear results in reflexive contraction of the muscles in that ear (ipsilateral reflex) as well as those in the nonstimulated ear (contralateral reflex). Sound initiates the reflex by stimulating cochlear hair cells and thus their afferent axons, the acoustic nerve, which proceeds to the ventral cochlear nucleus. Impulses from the ventral cochlear nucleus travel through the trapezoid body and then either directly to the motor nuclei of the cranial nerves or first to the medial superior olive and then to the respective motor nuclei which innervate ipsilateral muscles. Contralateral muscle contraction is evoked by impulses from the cochlear nucleus traveling to the medial superior olive where they are then conducted to both contralateral motor nuclei (Borg, 1973; Dujupesland, 1980). The AR is used extensively in the diagnosis of sensorineural hearing problems because

it can test both crossed and uncrossed pathways. Results of ipsilateral and contralateral recordings may be used together to help determine the locality of a disorder (Jerger and Hayes, 1980).

Although there has been much work done on the neural pathways involved in these procedures, there are still questions concerning the generators of the ABR and the muscles involved in the AR. Less attention, however has been given to neurotransmitters involved. There are diseases which, while they do not involve specific nuclei, are affected by varying concentrations of different neurotransmitters.

Evoked potentials such as the ABR have been used in the diagnosis of autism and other psychological disorders which might involve specific neurotransmitters (Piggott, 1979). With this in mind, the decision was made to investigate neurotransmitters which have a prominent role in the auditory pathway. The pertinent literature, which will be more extensively discussed in a later chapter, could be divided into three categories: (1) those dealing with nicotine and evoked potentials; (2) those pertaining to the investigation of potential neurotransmitters in the auditory pathway by the use of iontophoretic application of chemicals on cell bodies, and (3) those involved with serotonin and the acoustic startle reflex.

The first group of papers dealing with nicotine and evoked potentials, although suggesting the involvement of several different neurotransmitters, seem to more consistently implicate acetylcholine (ACh) and serotonin (5-HT) (Knapp and Domino, 1953; Guha and Pradham, 1976; Pradham, et al., 1967; Bharagava, et al., 1977, 1978, 1981). Even

though norepinephrine, dopamine, and vasopressin were suggested by some to be involved in the action of nicotine, there was more substantial evidence of a role in Ach release or agonism and on serotonin synthesis and release.

The second set of papers involved primarily the application of dopamine, GABA, serotonin, Ach, norepinephrine and nicotine directly on brainstem nuclei through the use of iontophoretic application. This procedure provided information about the percentage of cell bodies which were responsive to various substances. Specific localities investigated included cochlear hair cells, auditory nuclei, inferior colliculus, medial geniculate body, and auditory cortex. These studies produced strong evidence of an inhibitory effect of Ach on hair cells of the cochlea and stimulatory effect on other regions (Tebecis, 1970a,b,c; Tamaka and Katsuki, 1966; Bradley, et al., 1966).

The third set of papers involved the acoustic startle response (the response of rats to loud noises) and its modification by nicotine and various serotonin analogues (Davis, et al., 1980a,b; Fangold, 1981; Fechter, 1974). Studies showing changes in responsiveness to perceived sound could be related in some way to components of the acoustic reflex in particular and the auditory brainstem response.

As a result of the large number of articles related to nicotine and its role with many different neurotransmitters, it seemed worthwhile to investigate nicotine more closely. The effect of nicotine on various evoked potentials has been widely investigated yielding diverse conclusions. However it remains unclear whether nicotine acts directly or indirectly on acetylcholine (ACh) receptors

or possibly mobilizes one or more noncholinergic neurotransmitters. Nicotine administration has been demonstrated to result in either excitation or depression of evoked potentials (Murphree, 1979; Ashton and Millman, 1973).

These results were shown to be dose and time dependent. Through the use of nicotine agonists and antagonists as well as other drugs these changes have been analyzed, yet the results are contradictory. In particular, there were researchers who hypothesized that nicotine acted solely to directly excite nicotinic acetylcholine receptors (Stitzer, et al., 1970; Pradham, et al., 1967) Others reported that nicotine caused the release of acetylcholine from neuron terminals which then acted on either muscarinic or nicotinic receptors (Kaawamuura and Domino, 1969; Armitage, et al., 1969). Recent work however, has centered on the hypothesis that nicotine affects the release of more than one neurotransmitter. This theory, with many permutations, draws a common conclusion: the physiological effect of nicotine is the summation of many individual changes, these being dependent on dose, time course and route of administration, and which neurotransmitters are involved.

From the results of research done by others it appeared that investigation of the effects of nicotine relative to acetylcholine and serotonin could provide insight into some pending questions. Therefore, the research presented in this thesis was designated to answer several questions. First, is nicotine causing the release of Ach or acting directly on the nicotinic Ach receptor? Blockade of the

muscarinic receptors by atropine prior to nicotine treatment could shed light on this problem. Secondly, what is the dose response for nicotine? The use of two different nicotine doses (determined from preliminary trials using different concentrations ranging from $16 \text{ ug kg}^{-1}\text{min}^{-1}$ to $80 \text{ ug kg}^{-1} \text{ min}^{-1}$) given intravenously in a continuous thirty minute infusion could provide information about dose response effects on the ABR and AR. Thirdly, is there a role of nicotine in the release of serotonin on the auditory pathway? Through the use of 5-Methoxy-N,N-Dimethyltryptamine, the serotonin analogue, comparison of the effects of serotonin with those of nicotine might elucidate the relationship between them. Fourthly, do these drugs have an effect on middle ear muscle tone? If there is an alteration in the activity of the muscles after administration of a drug, it was hoped that corresponding changes in the ABR or AR might be detected. Fifthly, how much of an observed change in the ABR could be explained by an alteration in the AR? A comparison between the AR threshold levels and the ABR would determine if there were such a relationship.

CHAPTER II

LITERATURE REVIEW

1. ACOUSTIC REFLEX

The AR is a recording of the reflexive activity in middle ear muscles as a result of a loud sound (Dallos, 1964; Metz, 1951). Muscle activity is evidenced by a change in middle ear impedance or its inverse, compliance. In order to fully understand the procedure it is first necessary to understand the principles involved in the measurement. Impedance is the amount of energy, in this case sound, which is accepted or rejected per unit time. Compliance, which is used more than impedance in audiometric measurements, varies with sound pressure level (SPL) in the sealed external ear canal. Generally, as compliance increases, SPL decreases, which means that more energy is accepted by the tympanic membrane and middle ear bones. The SPL can be measured and converted to compliance expressed in cm^3 of air. The reason that compliance is normally expressed as equivalent volumes of air (Berlin and Cullen, 1983) is based on the fact that the air in an enclosed compartment has a measurable compliance. For example, if the compliance of the middle ear is 1.0 cm^3 , the compliance of the middle ear is equivalent to the compliance of 1.0 cm^3 of air. The SPL is calculated by using a continuous 226 Hz or 660 Hz tone delivered from a probe in the external ear canal (Berlin and Cullen, 1980). An additional tone such as the stimulus used for the AR can be presented with the probe tone. The components

of the external and middle ear act as impedance couplers which allows for the transfer of sound energy to the inner ear. There are three physical factors which influence the energy transfer, the mass of the system, its stiffness, and its resistance. Of these three stiffness has the greatest role in impedance changes in the ear.

In addition to the loudspeaker which emits the probe tone and stimulus tone, the probe contains a microphone and pressure transducer. When sound waves strike the tympanic membrane, part of the sound energy is transmitted through to the middle ear, part is absorbed by the structure and part is reflected back to the microphone. The reflected portion is identical in frequency but altered in phase and amplitude to the probe tone. The microphone determines the nature of the reflected sound. How much the tone has been altered is a reflection of the compliance characteristics of the system. Compliance can be determined while changing the pressure in the external ear canal. Graphic representation of the change in compliance with a change in air pressure is called a tympanogram. The tympanogram can also be thought of as a change in SPL in the sealed external ear cavity in response to increasing or decreasing air pressure.

Before recording the acoustic reflex, a tympanogram is performed to find the point of maximum compliance. The pressure in the canal is set at this point and stimulus tones of increasing or decreasing intensities are presented to the ear in order to determine the AR threshold (ART). The ART is the intensity in decibels (dB) at which

the first repeatable deflection of the needle on the compliance meter is seen. The compliance change is evidence that muscle contraction has occurred in the middle ear. Once the threshold has been determined, AR recordings can be made at different stimulus intensities above or below the ART. It has been shown that the ART is dependent upon the frequency of the stimulus as well as the type of stimulus (pure tone or noise) (Dallos, 1964; Jerger and Jerger, 1974). Dallos (1964) demonstrated that the AR amplitude increased as stimulus intensity increased up to a maximum at 30 dB above ART.

The AR was once thought to be primarily a protective mechanism (Borg, 1972; McPherson and Thompson, 1977). After presentation of the sound stimulus to the ear; sound waves travel through the external and middle ear and its energy is then transferred to the inner ear via vibration of the stapes footplate in the oval window. This transfer of energy to the inner ear results in pressure waves in the fluid in the cochlea thereby causing excitation of hair cells and their axons, the acoustic nerve. The acoustic nerve transmits impulses to the ventral cochlear nucleus. A major portion of the axons from this nucleus proceed through the trapezoid body to the facial or trigeminal motor nuclei. The efferent portion of the reflex then transmits impulses from these motor nuclei to the ipsilateral stapedial muscle via the facial nerve and tensor tympani muscle via the trigeminal nerve. Fibers from the ventral cochlear nucleus pass through the trapezoid body to the medial superior olive and then to the ipsilateral motor nuclei. Stimulation of one ear not only produces an ipsilateral reflex, but also a contralateral one. This involves a

common path with the ipsilateral reflex except where the impulses are transmitted via a second neuron to the medial superior olive. Another neuron then carries the impulses to the contralateral facial and trigeminal motor nuclei and then to their respective muscles (Djupestrand, 1983, Borg, 1972). It has been demonstrated that the ipsilateral AR is more excitable than the contralateral one and as a result has a lower threshold and shorter latency (Borg, 1972, 1968).

Determination of the components involved in the AR has been attempted using various methods including surgical manipulation and various means of disabling the individual muscles. Some of the earliest investigations were accomplished by observing movement of the muscle tendons to sound and direct electrical stimulation during surgery (this included electromyographic study of the individual muscles). With the advent of what is now an anequated impedance bridge it was possible to make indirect measurements of the reflex. This added little to the elucidation of neural components, but was more feasible as a clinical tool (Metz, 1951). Early impedance bridges operate basically the same as ones produced today, but were much more cumbersome. Many of the investigations were focused on the intra-aural muscles since they exert a major influence on the AR. There was however some work on central components. Borg (1982) created lesions in the inner ear, acoustic nerve, cochlear nucleus and trapezoid body in rabbits. All of the lesions resulted in an increased rise time, which is the time from 10-90% of maximum response. Cochlear lesions and stretching of the auditory nerve also produced a rise in reflex

threshold. Pathological cases, in which tumors were present in the central pathway, also produced distinct alterations in the AR amplitude and waveform morphology (Jerger and Jerger, 1977,1983). The time for the impulse to travel the entire reflex loop to the muscles is but a few milliseconds whereas it takes about 50 ms for the muscles to contract (Borg, 1972,1982). As a result central disorders might not be reflected in the AR response.

There has been an abundance of research done to determine which of the two intra-aural muscles has the most significant role in the reflex (borg, 1972; Love and Stream, 1978; Djueslasnd, 1980). Experimental measurement of the tension and contraction characteristics of the muscles has shown that the stapedius (St) contracts at a faster rate than the tensor tympani (TT). The TT contains both fast and slow twitch fibers while the St possesses only fast twitch ones (Teig, 1972). This certainly reflects a basic difference in the function of the two muscles. During surgery for middle ear disease, Djupesland (1967) recorded electromyograms from the muscles. Although both muscles increased their activity as a result of sound stimulation, the St responded about 10 ms earlier and exerted a greater force than the TT. Surgical severing of the connections between the TT muscle and the ossifcular chain had little effect on the AR (Borg, 1972; Sims, et al., unpublished 1985). Borg (1972) contended that in most animals both muscles are activated during the AR but that the St is the major contributor. In the same work he found the threshold for the TT to be 10 dB SPL higher than that for the St, which was also identical to that of the total reflex.

Further, the TT was found to be influenced by St activity. To the contrary, Love and Stream, (1978) reported that the AR is truly a biphasic response showing the specific response of both intraaural muscles. They hypothesized that the St initiates the response and causes the fixation of the ossicular chain, but that the TT is responsible for the major observed response. They based this hypothesis on the anatomy of the ear and the way in which the TT moves the tympanic membrane. It was stated that the St causes the sometimes observed increase in compliance while the TT causes the decrease in compliance. Although the evidence seems stronger that the St is the primary component of the reflex, for the purposes of this project it was not a crucial point.

When the AR is performed there are many different measurements which can be made, most of these are influenced by the frequency, intensity, type and duration of the stimulus (Borg, 1972; McPherson and Thompson, 1977; Dallos, 1964; Djupesland, 1983). Only one of these variables, intensity, was varied in this research. As mentioned previously, the response may vary depending upon whether it is ipsilateral or contralateral (Borg, 1972). Recordings were made both ipsilaterally and contralaterally in this work. Of the many possible measurements to be made of the AR recording, only threshold, latency and amplitude were measured.

Latency measurements have been made by many researchers. Latency for the ipsilateral AR generally decreases with increasing stimulus intensity and is longer for a contralateral response

(McPherson and Thompson, 1977, Dallos, 1964). Exactly how to measure latency has varied with different investigators (McPherson and Thompson, 1977). In this study latency was measured from stimulus onset to the initial deflection from baseline. The impedance bridge was connected to an oscilloscope (CRO) and the recordings photographed from the screen. This setup was necessary in order to record latency (McPherson and Thompson, 1977, Metz, 1951).

Amplitude, which is the magnitude of the response measured (in cm^3) from baseline to peak compliance change, has not been as widely used, although it has been used diagnostically by some (Jerger and Hayes, 1983). It must be kept in mind that amplitude is not related to ear canal size since the impedance bridge was standardized to avoid this. Amplitude generally increases with an increase in stimulus intensity, reflecting an increased contraction force of the muscles. This measurement is generally of a lesser magnitude contralaterally than ipsilaterally (Dallos, 1964; McPherson and Thompson, 1977; Jerger and Hayes, 1983). The use of ketamine as an anesthetizing agent has been shown to decrease the amplitude of the response (Thompson, et al., 1984). Since all recordings taken in this project were analyzed in reference to the ketamine values, any effect of anesthesia was negated.

Acoustic reflex recordings are used extensively in the diagnosis of middle and inner ear conductive hearing losses, as well as sensorineural (central) hearing disorders. Through the use of crossed and uncrossed AR it is possible to differentiate between eighth nerve and brainstem lesions (Jerger and Jerger, 1977). Jerger and Hayes

(1983) maintained that latency is too variable to use diagnostically, whereas amplitude and waveform morphological changes were characteristic of tumor patients. They did suggest that latency was variable due to morphological changes. The AR has also been used in the diagnosis of neuromuscular disorders such as myasthenia gravis (Johns, et al., 1979). While some researchers feel that the response is fairly repeatable (Borg and Moller, 1968), most feel that there is considerable variability between individuals as well as within an individual over time (McPherson and Thompson, 1977, Dallos, 1964).

2. AUDITORY BRAINSTEM RESPONSE

The ABR is the far field (electrodes at a distance from the neural generator) recording of electrical activity of the VIIIth cranial nerve and brainstem as a result of auditory stimulation. This electrical activity may be recorded using highly conductive subcutaneous platinum needle electrodes.

Sound waves which have vibratory motion, exhibit "alternating periods of condensation and rarefaction" (Durrant, 1983). This motion when traveling through a medium results in corresponding changes in pressure, a disturbance which is propagated. Sound travel requires time and this corresponds to the wave length. For example, high frequency sounds have shorter wave lengths than those with low frequencies. The ability of sound to be propagated is dependent upon the medium in which it travels. Any variables which affect the medium, affect the movement of the sound waves. As a result of this

phenomenon, the waves which enter the external ear canal and middle ear cavity are altered in a manner much like that performed by like filters (Durrant, 1983). The sound energy is then transferred to the inner ear by movement of the stapes in the oval window, the resulting pressure causing motion of endolymph in the inner ear. This results in displacement of hair cells or the basilar membrane causing them to hyperpolarize. The basilar membrane at the base of the cochlea vibrates preferentially to high frequency sound while the membrane in the apex responds to low frequency. It is therefore possible to describe frequency and amplitude characteristics of the sound energy by location, spread, and amplitude of the vibration of the basilar membrane (Tsuchitoni, 1983). Cochlear nerve fibers (first order neurons) innervate the sensory cells and function to translate this information into action potentials. In the cochlear nuclei second order auditory neurons cross the medulla in the trapezoid body and then enter the lateral lemniscus, many of which synapse in the inferior colliculus. Third order neurons from the inferior colliculus proceed to the medial geniculate body (an auditory center in the thalamus) and radiate to the auditory cortex (Morrest, 1983).

Electrical activity in the auditory pathway can be volume conducted through the head and picked up by subcutaneous electrodes. Evoked potentials, because they are time-locked to a stimulus occur within a given period of time following presentation of the stimulus. Most equipment used in these studies not only produce the sound stimulus but are also triggered by the sound to open a "time window" to record neural activity occurring during that interval. In the case of the

ABR, the time frame is 10 ms. Therefore at the onset of each stimulation all of the electrical activity for the next 10 ms is picked up by the electrodes. The electrical activity received by the electrodes is amplified since the signals are so small. The epoch following stimulation is electronically averaged: in this project 256 individual replications were so treated. Averaging is necessary to eliminate background noise which is arising continually from cortical and subcortical areas.

The ABR of human adults and canines typically consists of 5-7 consecutive waves which correspond to neural generators in the auditory pathway. Investigation into which areas of the brainstem generate the individual waves of the ABR has been extensive yet inconclusive. It is generally accepted that only some of the components of the auditory pathway contribute to the early ABR, Some areas may be excluded from the ABR due to time restraints and some due to insufficient synchronization of energy. Successful recording of the ABR requires that there be considerable neural synchrony (Tsuchitani, 1983). The following discussion of generators has been adjusted to correspond to wave labeling used in this study.

One of the early papers on the ABR was written by Jewett and Williston, (1971). Not only did they describe the general procedure but also attempted to define the generators for the first two waves by comparing ABR latencies with the latencies of potentials recorded directly from the round window. They concluded that wave I was caused by activity in the VIII cranial nerve, and wave II by activity in the

cochlear nuclei and their axons. All subsequent waves were said to originate from multiple sources located more rostrally in the brainstem. Work reported by Lev and Sohmer (1972) detailed the results of near-field (electrodes placed near to the neural generator) compared to far-field recordings. These comparisons led them to conclude that responses from the later auditory components such as the superior olive and inferior colliculus were more complex than earlier responses due to the more complicated structures. They agreed with the work of Jewett regarding the first two waves. Activity in the superior olive coincided with wave III and that of the inferior colliculus with wave V. In 1975 Buchwald and Huang reported their results from surgically produced lesions which destroyed various suspected generators in the cat brainstem. As a result of their classic work, a scheme was presented in which each wave of the ABR corresponded to a separate loci in the auditory pathway. Severing of neural connections resulted in loss or depression of the "corresponding" wave. Specifically they stated that wave I was generated by the acoustic nerve, II by the cochlear nucleus, III/IV by the medial superior olive, V by the lateral lemniscus and VI by the inferior colliculus. By a midline section they separated the ipsilaterally generated waves (I, II and part of V) from the contralateral ones (III/IV, VI and the rest of V). This work was considered by many to be definitive until others began doing more detailed work. Starr and Hamilton (1976), attempted to correlate abnormalities of the ABR with tumors found during surgery or at autopsy. Lesions of the inferior colliculus and tegmentum produced

changes in waves V and VI. Widespread brain lesions were usually accompanied by an ABR consisting only of wave I. Waves II and III were found to be dependent upon the integrity of the cochlear nucleus (CN) trapezoid body (TB) and superior olive (SO). In 1981, Moller published an article which cast some doubt on the one-to-one theory of one generator to one wave. He investigated the role of the acoustic nerve in the ABR and found that the action potential recorded directly from this nerve corresponded with the latency of wave II. This led to his hypothesis that both waves I and II are generated by the VIII cranial nerve. Achor and Starr (1980a) did similar work but on a more extensive scale. They compared the intracranial recordings of large amplitude voltage fields in and around the suspected generators to the latencies of ABR waves. Except for the first two components (I and II) they contended that the waves represent considerable neural overlap. Wave I was again shown to correspond to the auditory nerve and CN. The CN, ipsilateral SO, TB, contralateral SO and auditory nerve all appeared to contribute to wave II. Wave III was shown to consist of activity from the ipsilateral and contralateral SO as well as the lateral lemniscus (LL), and wave V from the both SO, both LL, and the TB. They found little activity from the inferior colliculus (IC) and contended that it had no role in the response. They concluded that there is considerable spatial and temporal distribution of the electrical fields. In a continuation of their previous study, Achor and Starr (1980b) made discrete lesions in brainstem areas and reported similar results to those above, adding that the effects of

the lesions were different for ipsilateral and contralateral stimulation. They discussed several reason for differences in various lesion studies as well as with tumor studies. The effects seen as a result of lesions could have been due to possible indirect effects of the lesions, severing of important connections between generators or actual destruction of the generator. Wada and Starr (1983a,b) investigated the role of the TB alone through the use of an anesthetic agent and lesions. They were attempting to determine whether the TB was itself a generator or an essential pathway between generators. Wave III was consistently abolished in both cases, wave II amplitude was decreased and wave V latency was fshifted to the left. The morphological characteristics of the waveform was considerably altered. From their results they concluded that the TB was not a generator but an essential pathway for contralaterally generated waves III, and V (50%). A third companion paper (1983c), reported the effects of lesions in the SO, LL, and IC. Lesions of the contralateral SO and LL altered wave III, and wave V was attenuated by lesions of the ipsilateral SO. Again, lesions in the inferior colliculus failed to cause any changes. They thought that the evoked response were a reflection of synaptic discharges and possibly some nerve fiber discharge. In summary, it seems apparent that there is not a "one generator to one wave" relationship but rather a more complex scheme. This must be remembered when analyzing any experimental results.

As with the AR, there are may factors which effect the ABR. Huang and Buchwald (1976) detailed the influence of stimulus intensity on

latency and amplitude of the ABR. They found that latency decreases and amplitude increases with increasing intensity of the stimulus. These changes were thought to be a reflection of peripheral influences since changes in the measurements of the first wave are paralleled by changes in subsequent waves. Many other authors agree with these trends and they have come to be commonly accepted (Moore, 1983; Jewett and Williston, 1971; Sims and Moore, 1984). Stockard, et al. (19078) investigated many variables from age to temperature. They found that age was important with respect to very young and very old individuals. Sex was also found to affect the response. Temperature decreases cause an increase in the latencies of the waves. Anesthesia has been shown to have some effect on the response although it may not be significant (Bobbin, et al., 1979).

Both clicks and pips were used as stimuli in this project. A click is a broad spectrum stimulus, and such rapid onset sounds as this are the best and most commonly used to record the ABR. This sort of stimulus allows for the best neural synchrony, but offers no frequency specific information. Tone pips, which are frequency specific, were used in this project in an attempt to correlate them with the AR recordings. Pips are less efficient in producing neural synchrony and the response is less robust but recognizable. Wave V has been stated to be the most reliable wave when using pips (Weber and Folsom, 1977).

The nonstimulated ear may be presented with a masking noise, usually at 30 dB below the intensity of the stimulus. Although it has

been shown that in normal hearing individuals masking has no effect, it has been shown to eliminate crossover sound in pathological ears (Hunes and Ochs, 1982). Since the effect of the drugs used in this project could not be predicted, it seemed worthwhile to mask the opposite ear.

As mentioned earlier, the locations of tumors has been used in the investigation of generators. It is a common procedure to use the ABR to aid in the diagnosis of certain audiological (Eggermint, 1983; Weber and Folsom, 1977) and neurological disorders (Sohmer, 1983). Both latency and amplitude are used in these cases as well as interpeak latency (especially I-V and III-V) and abnormal or missing peaks.

Hays and Jerger (1981) reported that changes in AR threshold were reflected by changes in the amplitude of ABR waves I, II and III. However, Borg (1981) contended that middle ear muscles had no role in the ABR response. Whether or not there is a relationship in this study will also be investigated.

3. SELECTION OF DRUGS

Nicotine is a weak base which can easily penetrate the blood brain barrier (Edwards and Warburton, 1983; Schmilerlow, et al., 1967; Abood, et al., 1981). In studies to determine the amount of nicotine which enters the brain, it was found that 20% of the cardiac output goes to the brain and 90% of the nicotine carried in this blood enters the brain. Much of the investigation into the concentration of this compound in the brain has been primarily concerned with the amount of

nicotine obtained from smoking. It has been determined that from a 25-30 mg (of nicotine) cigarette, about 20 ug enters the brain (Edwards and Warburton, 1983). Once the nicotine enters the brain, it appears to preferentially enter the gray matter. Radioactive labeling and iontophoretic application have shown that nicotine binds to cells in the medulla, mesencephalon, reticular formation, lateral and medial geniculate nuclei, thalamus, cerebellum, inferior colliculus, hippocampus and olfactory bulb as well as cortical Betz cells (Edwards and Warburton, 1983; Abood, et al., 1981). There is some disagreement as to the most favored area for nicotine binding, some feeling that it is the hippocampus (Schmilerlow, et al., 1967) while others believe it favors the thalamus and cortex, or hippocampus (Abood, et al., 1981).

Nicotine is not metabolized well if at all in the brain, and "washes out" quickly (Schmilerlow, et al., 1967; Edwards and Warburton, 1983). If nicotine is delivered to the brain, it decreases to 50% of the initial amount in 5 minutes and decreased to 1% by the end of one hour (Edwards and Warburton, 1983). The kidney and liver metabolize nicotine mainly via oxidation of the pyrrolidine ring. Nicotine may also serve as a methyl acceptor during biotransformation. Most of the chemical (90%) is metabolized and excreted in the urine as isomethylnicotinium, while the remainder is excreted intact (McKinnis, 1967; Edwards and Warburton, 1983). Colinine is the major metabolite of nicotine and has been shown to be less active chemically than nicotine (Schmilerlow, et al., 1967).

Nicotine stimulates both sympathetic and parasympatetic systems, and causes the adrenal medulla to release catacholamines (Conroe,1967; Hoff and Heckman, 1967; Pradham, et al., 1967). It is well known that nicotine stimulates nicotinic chloinerbic receptors at the neuromuscular junction (high doses depress) and also acts to enhance the action of Renshaw cells (interneurons) in the spinal cord (Conroe, 1967; Edwards and Warburton, 1983; Pradham, et al., 1967). Direct application of nicotine and ACh on individual brainstem neurons has shown that 58% respond to ACh, 36% excitatory and 22% inhibitory. Nicotine applied to cells was effective in stimulating the cells which had been excited by ACh, but had only a minor effect on the cells which ACh inhibited. Muscarine had an effect on both types and atropine (muscarinic cholinergic antagonist) blocked both types of receptors to some degree (Bradley, et al., 1967).

It appears that nicotine has complex effects upon the nervous system. In their review, Abood, et al., (1981) described the effects of nicotine as diverse and not purely cholinergic. Various adrenergic and cholinergic compounds, both agonists and antagonists, have been shown to alter responses to nicotine. Abood, et al., concluded that the net effect of nicotine was due in part to its site of action.

The debate over the action of nicotine permities the literature. Most of the work which addresses the debate is concerned with how nicotine affects ACh, either by releasing the neurotransmitter or mimicking ACh at the receptor sites. Some think that the effect is dose or time dependent, but make no conclusive statements (Hoff, 1967). Armitage et al. (1966,1967), published many papers concerning

the effects of nicotine on various systems. An early paper (1966) dealt with the increase in the rate of ear twitching as a result of injection of nicotine into the ventricles of the cat. The response was determined to be cholinergic since physostigmine (an anticholinesterase) enhanced it and ACh caused a weak but definite positive response. The ganglionic blocking drug hexamethonium inhibited the effects of nicotine. They concluded that nicotine either mimicks ACh or actually causes the release of ACh. In 1967, Armitage and Hall reported that nicotine acted by releasing ACh from nerve terminals. The decrease in blood pressure (BP) seen in cats after injection of nicotine into a lateral ventricle was mimicked by carbachol, a drug which releases ACh and the effect of nicotine was enhanced by physostigmine. Hemicholinium, blocks the transport of choline into nerve terminals, was used to stop the synthesis of ACh and effectively blocked the effect of nicotine and carbachol. Replacement of choline restored the initial effects. This paper was followed by another (1969) where the levels of ACh in the brain were monitored and found to increase after i.v. administration of nicotine. The increase in ACh corresponded with the desynchronization of the EEG. Armitage, et al (1969), concluded that there is a release of ACh from nerve terminals caused by nicotine. but whether this caused the change in the EEG could not be proved conclusively.

Morrison, et al. (1969), reported that nicotine administration to rats resulted in behavioral depression. They then pretreated rats with atropine and mecamylamine (ganglionic blocking drug), both of

which blocked the response, therefore the requirement for a muscarinic receptor was apparent. This supported the role of nicotine in releasing ACh. Guha and Pradham (1979) also adhered to this hypothesis of ACh release. They investigated nicotine's effect on the EEG and late component of the ABR. Both responses displayed biphasic responses: initial desynchronization followed by synchronization of the EEG, and initial decrease followed by an increase in the amplitude of the late ABR. They thought that the causes were different, the initial phase being due to muscarinic cholinergic stimulation (ACh release) and the second phase due to noncholinergic effects of nicotine.

Yamamoto and Domino (1965) investigated the influence of nicotine on the EEG and found the effect to be directly on nicotinic receptors. They reported that the arousal and corresponding activation of the EEG in sleeping cats after injection of nicotine was followed by sleepiness and depression of the EEG. They hypothesized that the two phases resulted from two different nicotine effects. The initial phase was due to the direct action of nicotine on nicotinic cholinergic receptors and the second phase was due to the release of vasopressin from the pituitary. The first phase was blocked by mecamylamine and did not occur after artificial increase in BP or respiratory rate (the BP and respiratory rate increased after nicotine injection). Both epinephrine and vasopressin (ADH) were given and neither produced the initial response. The nicotine metabolite colinine was also given and failed to cause desynchronization unless given at extremely high dosages. In 1970, Stitzer, et al. described

the effect of nicotine on lever pressing behavior in rats. This behavior was depressed by nicotine and was found to be dose dependent. Cholinergic antagonists blocked the effect. They concluded that nicotine was acting directly on nicotinic receptors. In a study where the investigators (Stolerman, et al., 1983) were attempting to determine the mechanism of action behind nicotine discrimination in the rat, it was concluded that the effect was mediated through direct action of nicotine on nicotinic cholinergic receptors, even though an increase in the release of 5-HT due to nicotine was expected.

Kawamura and Domino (1969) looked at the activation of the EEG in cats with bilateral midbrain sections which resulted in loss of the response. This response was also blocked by atropine and mecamylamine. As a result of their work they concluded that the action of nicotine on the EEG was based on nicotinic and muscarinic neurons of the midbrain reticular formation. Large doses of nicotine produced seizures and this activity was said to be localized in the hippocampus. A muscarinic agonist arecoline, produced activation of the EEG with the midbrain transsection and was blocked by atropine. These results seemed to implicate nicotine with both nicotinic and muscarinic activities.

Knapp and Domino (1962) attempted to assess nicotine's action as a neurotransmitter and the location of the effects in the CNS. They looked at the desynchronizing effect nicotine had on the EEG. By transecting the brain at different locations and cutting several cranial nerves they were able to determine that the effect was

central. As a result of using reserpine, a catecholamine and serotonin synthesis blocker, which did not alter the effect of nicotine they determined that the activating effect of nicotine was not due to catecholamine release. Administration of epinephrine, 5-HT and ADH all failed to cause activation in the surgical preparation. In a later article, Knapp and Domino (1963) found that the specific area of nicotine action differed in different species. These differences were thought to be due partially to permeability differences between species as well as anatomical variations. Prepontine surgical section in cats and rabbits did exhibit activation of the EEG due to nicotine while dogs treated in a similar manner did not. Another study dealing with the localization of the response is the one by Schaeppi (1967) where the desynchronization of the EEG was considered to be a result of stimulation of an "ascending desynchronization system." In a paper the following year, Schaeppi looked at nicotine activation of the electrocorticogram (ECOG). He showed that the response was separate from the effect of nicotine on blood pressure and that the response was dependent upon the dose and route of administration. The biphasic (activation followed by depression) response was concluded to be the result of "ascending desynchronization and synchronization systems." The site of activation was thought to be close to the fourth ventricle.

There has been research concerned with the role of nicotine with neurotransmitters other than ACh. Some mention was given previously of the secondary effect of nicotine being due to its action on ADH. In an article by Henningfield, et al. (1983), the change in pupil

dismeter after nicotine administration was said to be partially due to the release of catecholamines by nicotine. Bhargava, et al. (1977) demonstrated the release of serotonin by nicotine. His work with the ABR will be discussed in detail later. Some research has been done on the release of 5-HT by nicotine in rat brain tissue. Goodman and Weiss (1973) studied the mechanism of action for the increased efflux of 5-HT from rat brain slices, and they determined that the release was probably due to interaction of sodium ions and nicotine altering the permeability of tissue. However, Benwell and Balfour (1982) concluded that the effect of nicotine on 5-HT levels in the brain was not direct but mediated through a second neurotransmitter which nicotine activated. In their study nicotine administration had resulted in a decrease in 5-HT biosynthesis by the hippocampus. In another paper by Benwell and Balofur (1979) rats were given acute and chronic doses of nicotine and the brain levels of 5-HT monitored. This study showed a decrease in 5-HT levels in the hippocampus during administration and an increase in hypothalamic levels after withdrawal of nicotine. The results were most pronounced after long-term administration of nicotine.

The effect of nicotine on various electrical responses has been mentioned in preceding paragraphs. A list of electrophysiological recordings and behavioral studies is given in Tables 1 and 2. The effect of nicotine on the EEG is clearly an initial desynchronization (arousal) followed by synchronization, a response which is dose and time dependent. Many of the studies were in conjunction with smoking

Table 1. Effects of Nicotine on the Electroencephalogram

Author	Date	Response	Comments
Knapp, et al.,	(1962)	desynchronization convulsive	not related to peripheral actions of nicotine or to it's effect on blood pressue, catacholamines, 5-HT, or ADH a cholinergic effect; very large dosages of nicotine
Schaeppi,	(1962)	desynchronization synchronization	arousal, primary response secondary response
Knapp, et al.,	(1963)	activation	species differences to nicotine possibly due to permiability, response depends upon area of the brain, epinephrine and 5-HT also produced
Yamamoto, et al.,	(1965)	activation depression	ACH causes same response, response not affected by BP, epinephrine or ADH caused by arginine vasopressin
Schaepp+,	(1968)	desynchronization synchronization	(ECoG) not related to blood pressure changes, secondary affect
Armitage, et al.,	(1969)	activation	increase in ACH output occurred at the same time, but cannot be sure that responses are linked
Knapp, et al.,	(1969)	activation synchronization	occurred in midbrain transected cats, atropine blocked response, both nicotinic and muscarinic receptors in midbrain involved secondary
Kawamura, et al.,	(1969)	activation	blocked by atropine, localized in midbrain reticular formation both muscurinic and nicotinic receptors

Table 1 (continued)

Author	Date	Response	Comments
Stadnicki,	(1972)	desynchronization hyersynchronization	primary response, cause unclear secondary, occurs with higher dosages
Ashton and Millman,	(1973)	increased	magnitude Contingent negative variation (CNV), time-locked response from EEG, related to attentiveness, initial decrease then increase in amplitude
Guha and Pradham,	(1976)	stimulation depression	initial response, muscarinic cholinergic response secondary response, only depression with large dosages, noncholinergic response
Murphree,	(1979)	decreased alpha wave amplitude	arousal, nicotine is CNS depressant

Table 2. Effects of Nicotine on Other Physiological Variables

Author	Date	Response	Comments
Hall, et al.,	(1973)	VER increased amplitude	smoking caused arousal, enhances perception
Woodson, et al.,	(1982)	VER increased amplitude	smoking, due to nicotine (smoking a placebo had no effect), associated with attentiveness
Friedman and Meares,	(1980)	VER increased amplitude ABR decreased amplitude	smoking, increased sensitivity to visual stimuli (late component) decreased discrimination of meaningless noise
Guha and Pradham,	(1979)	ABR decreased amplitude increased amplitude	(late component), due to release ACh noncholinergic effect
Pradham, et al.,	(1967)	somatic reflexes altered	decreased or abolished monosynaptic reflexes, no effect on polysynaptic; high doses paralyze; nicotinic cholinergic response
Armitage, et al.,	(1966)	ear twitch reflex increased	nicotine mimics or releases ACH; increased response to air puffs in the ear
Henningfield, et al.,	(1983)	pupil diameter EMG (upper arm)	increased then decreased due to catacholamine release; increased muscle tension
Morrison, et al.,	(1969)	bar pressing	trained behavior; nicotine causes release ACH; atropine blocked response
Stitzer, et al.,	(1970)	lever pressing	trained behavior, decreased due to action on nicotinic receptors

research. It has been demonstrated that the agent in cigarettes which causes the observed effects is nicotine (Woodson, et al., 1982; Edwards and Warburton, 1983). One commonly used procedure in the investigation of the effects of smoking is the visual evoked response (VER). The amplitude of the VER has been shown to be consistently increased with the administration of nicotine while ABR responses (late components) decreased in amplitude demonstrating the variation in effect depending upon the site of action. Research into the role of nicotine on muscle reflexes has shown a substantial decrease in monosynaptic activity and no effect on polysynaptic ones (Pradham, et al., 1967). Electromyographic studies have shown increased muscle tone due to nicotine administration. This response is apparently related to the site of action (Henningfield, et al., 1983). Nicotine is known to have an excitatory effect on the neuromuscular junction. At high dosages of nicotine the effect is muscle paralysis (Gilmen, et al., 1980). As mentioned earlier, nicotine also excites inhibitory Renshaw cells in the spinal cord.

There has been a fair amount of investigation into the role of various neurotransmitters in the auditory pathway. In the cochlea acetylcholinesterases (AChase) have been isolated. Hilding and Wersall (1962) found AChase in all turns of the cochlea, and in nerve endings of all external and many of the internal rows of hair cells. They determined this through the use of stains specific for AChase. Presence of this enzyme which inactivated ACh indicated that the neurons were cholinergic in nature. In 1966, Bradley, et al. looked into the pharmacology of apparent cholinergic neurons in the medulla

and pons of the cat. Through iontophoretic application of ACh, they determined that this neurotransmitter excited 55.5% and inhibited 22%, respectively, of those cells tested. Nicotine was found to excite the cells excited by ACh but not those inhibited by it. Muscarine copied the effects of ACh totally. It was concluded that there are both nicotinic and muscarinic receptors in the medulla and pons, the excitatory ones being both muscarinic and nicotinic while the inhibitory ones were solely muscarinic. Brown, et al. (1968) reported that ACh is an inhibitory neurotransmitter in the cochlea. ACh was found to depress cochlear action potentials recorded from the round window. Atropine and mecamlamine had no effect on this response but the possibility of permeability problems was mentioned. The effect of ACh on the cochlea was also investigated by Tanaka and Katsuki (1966). They agreed with the above report that ACh is inhibitory. ACh and physostigmine were applied iontophoretically to the hair cells (along with GABA, atropine and epinephrine which were not effective) and found to have a depressant effect upon the amplitude of the cochlear microphonic and endocochlear potentials. The effect was found to be related to the frequency specificity of the basilar membrane. Curtis and Kuizum (1961) identified ACh activity in the inferior colliculus. They directly applied GABA, 5-HT, epinephrine and ACh to cells in the brainstem and found both GABA and ACh to have an effect. ACh stimulated a number of scattered cells throughout the inferior colliculus, all of which were also responsive to auditory stimulation. In 1977 Mendel published a short paper on the effect of atropine on

the ABR. He concluded that the large increases in amplitude and latency were due to blockade of the inhibitory effect of ACh. Tebecus (1970a,1970b,1970c) extensively studied the effects of many neurotransmitters in the medial geniculate nucleus (MGN). Two companion papers were written on the role of cholinergic neurons in the MGN. ACh had a slow, excitatory effect on 45% of the cells; 91% of which could also be electrically stimulated antidromically from the auditory cortex and 71% activated synaptically from the cortex. Connections from the inferior colliculus also were involved so that 74% of the ACh cells of the MGN could be stimulated from this area. ACh had a rapid depressive effect on 29% of the cells in the MGN. Some of these cells were included in the above discussion thereby having dual effects. Atropine had more of an effect on the responses than did nicotinic antagonists. Nicotine itself was not as effective as other substances in mimicking ACh. The second paper discussed the connections between the lower brainstem and MGN stressing the role of ACh. The relays between the MGN and the cortex were also described in terms of ACh receptors, here emphasizing that both nicotinic and muscurinic receptors are present.

The last paper in the series by Tebecus (1970c), was concerned with adrenergic and other monoamine neurotransmitters involved with the MGN. Serotonin, norepinephrine and dopamine were all found to be predominantly inhibitory on the MGN but to different degrees. Serotonin caused depression of 78% of the cells tested, excitation in 6% and a dual effect in 5%. There was no effect on 11% of the cells. The inhibition was typically rapid and short in duration. Treatment

with 5-HT inhibited the synaptic discharge as a result of auditory stimulation of the area. Similar treatment of inferior collicular cells also yielded the same inhibition. The investigation of the role of 5-HT and a 5-HT analogue on the acoustic startle, (the response of animals (rats) to loud sound stimulation), has given interesting results. Davis, et al. (1980) using 5-HT found that the reaction depended upon the site of action. When 5-HT acted on the spinal cord or brainstem it resulted in an increase in startle, while action in higher brain centers resulted in depression. With 5-Methoxy-N,N-Dimethyltryptamine (5-MeODMT), a 5-HT analogue, Davis (1980) demonstrated an increased startle response which indicated a lower CNS site of action. This analogue has also been used to alter raphe nuclei activity in cats (Trulson and Jacobs, 1979). They reported how this compound decreased activity in this area of the brain. The resulting decrease was shown to be dose-dependent. The amount of 5-MeODMT used has been shown to be important. Studies indicate that dosages as low as 20 ug/kg caused respiratory depression due to decreased phrenic nerve discharge (Dalley, 1982).

The major reason for embarking on this project was the discovery of a series of papers by Bhargava et al. (1977, 1978, 1981) dealing with nicotine and the ABR. The initial paper discussed the effect of 5-HT on the ABR, where they initially administered reserpine to rats to deplete their stores of 5-HT (and norepinephrine). This pretreatment caused an initial decrease followed by an increase in the amplitude of the response. The use of p-chlorophenylalanine (pcpa)

which also depleted levels of 5-HT likewise resulted in an increased amplitude. Injection of 5-HT itself caused a decrease in AR amplitude. Reserpine was believed to cause an initial increase in 5-HT levels causing the decrease seen. They concluded that 5-HT is an inhibitory neurotransmitter in the auditory pathway. A paper published in 1978 by Bhargava et al., described the effect of cholinergic drugs on the ABR. In this paper they concluded that the increase seen in the late ABR with muscarinic cholinergic compounds indicated a purely muscarinic cholinergic role. Nicotine was shown to have no effect. However when he investigated the effect of nicotine on the early ABR (1978), they found that muscarinic compounds resulted in an increase in amplitude and that nicotine caused a decrease in amplitude. In 1981 they again looked at the effect of nicotine on the ABR and reported that it was acting through 5-HT receptors. By again giving pcpa and reserpine and adding nicotine in combination with each one, they found that pcpa and reserpine antagonized the effect of nicotine. Their conclusions were that nicotine caused the release of 5-HT and that this caused the change in amplitude. These papers seem contradictory and the need for clarification seemed apparent. It was because of this that the project reported in this paper was undertaken.

CHAPTER III

METHODS

1. SELECTION OF ANIMALS AND EXPERIMENTAL DESIGN

A total of eight mixed-breed adult cats of both sexes, weighing between 2.26 and 4.1 kg were used in this study. The cats were vaccinated for rabies and feline rhinotrocheinos-calicivirus-panleukopenia and housed in an isolated area for two weeks prior to use. Cats selected for this study were examined and determined to be free of any disease which would interfere with the experiments. All of the cats were used in more than one experiment (Table 3) and each was fasted for twelve hours prior to use. At least seven days separated experimental use of any one cat.

This study consisted of five separate experiments (Table 4). In each experiment, a cat was given xylazine (Haver-Lockhart, Scawnee, KN) i.m., (1.0 mg/kg) and placed in a quiet area for 10-15 minutes. Next, ketamine (Bristol Laboratories, Syracuse, NY) was given i.m. (10 mg/kg) and the cat returned to a quiet area for five minutes. The cat was then placed in a sternally recumbant position on top of a heated water blanket with its head raised on a folded towel. Lacrilub (Allergan, Irvine, CA) was placed in each eye and a rectal probe was inserted to monitor temperature. The same protocol was followed for each experiment except Experiment one (saline infusion). In this experiment, ABR were recorded monaurally from both ears following injection of xylazine. Each experiment consisted of a preinfusion

Table 3. Assignment of Cats to Experiments

Cat I.D.	Weight (kg)	Sex	Experiments				
			1	2	3	4	5
C8407	3.6	F	X	X			
C8411	3.6-4.12	M	X	X	X	X	X
C8412	3.09	F	X	X	X	X	X
C8414	3.09-4.08	F	X	X	X	X	X
C8413	3.09	F	X	X	X	X	X
C8415	3.09	F	X		X	X	X
C8417	2.26	M	X	X	X		
C8422	3.64	M			X	X	X

Table 4. List of Experiments

Exp. No.	No. Cats	NDrug	Dosage	Route of Administration	Duration
1	7	saline	—	IV infusion	30 min
2	6	nicotine	40 ug kg ⁻¹ min ⁻¹	IV infusion	30 min
3	7	nicotine	60 ug kg ⁻¹ min ⁻¹	IV infusion	30 min
4	6	atropine	0.4 mg kg ⁻¹	IV injection	
		nicotine	60 ug kg ⁻¹ min ⁻¹	IV infusion	30 min
5	6	5-MeODMT	10 ug kg ⁻¹	IM injection	

period followed by a thirty minute infusion period during which recordings were made. Additional recordings were made after the infusion period. In Experiment five, the same time period followed a single injection of 5-MeODMT.

2. RECORDING THE ACOUSTIC REFLEX (AR)

A schematic for the equipment used to record the AR is shown in Figure 1. Before each experiment, an impedance meter (Amplaid model 702, Amplaid USA, Inc., Arlington Heights, IL) was calibrated by placing the probe tip into two different calibration chambers (0.2 and 4.0 cm³) and adjusting the meter to read the respective values. Once calibrated, the probe was hermetically sealed in the cat's external ear canal and the seal checked for leaks by creating and maintaining a pressure of +200 mm H₂O. Due to ear movement it was necessary to manually hold the probe in place during the course of the procedure.

A tympanogram was performed in order to determine compliance of the middle ear system, and to determine the point of maximum compliance needed to record the AR. This was done by first "clamping" the tympanic membrane in a position of poor compliance using a pressure of +200 mm H₂O and then decreasing the air pressure slowly to -200 mm H₂O while recording the corresponding changes in compliance. The point of maximum compliance was the pressure at which the highest compliance, or lowest sound pressure level (SPL) reading was obtained, usually -50 to 0 mm H₂O in the cats. Next, the pressure in the external ear canal was set at the point of maximum compliance prior to recording the AR. The AR threshold (ART) was determined by

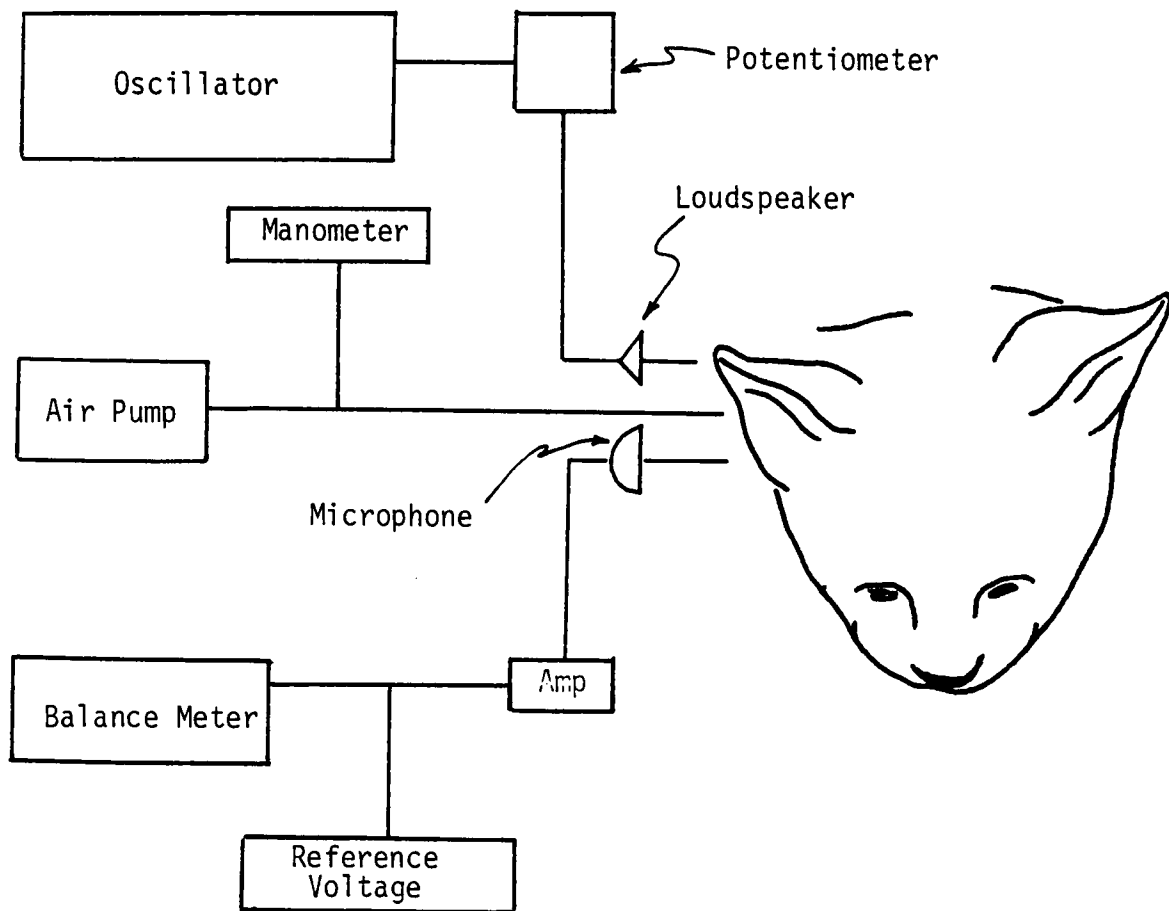


Figure 1. Schematic of equipment used in recording the acoustic reflex.

increasing the intensity of a two KHz stimulus tone from a subthreshold level until there was a consistent deflection of the needle from baseline. Output from the impedance meter was connected to a dual-beam storage oscilloscope (CRO) (Tektronix model 5113, Tektronix, Inc., Beaverton, OR). The compliance change resulting from a reflex was seen as a negative deflection of the beam from baseline. Sometimes this was preceded by a brief positive deflection. The traces were photographed with a polaroid camera for permanent record. Latency was measured to the nearest 0.01 ms and amplitude to the nearest 0.01 cm³ (Figure 2). Accurate latency and amplitude measurements of the response were made by using a very sensitive amplifier and a rapid sweep rate on the CRO (Figure 2).

Ipsilateral and contralateral recordings of the AR were made using stimulus intensities at ten and twenty dB (re 2X10⁻⁵ Newtons/m²) above ART (Table 5). Threshold for contralateral recordings were recorded in dB HL (re ANSI S3.6-1969, 1970 American National Standards Institute. Specification for audiometers. ANSI S3.6-1969. American National Standards Institute, Inc., New York, 1970). Threshold for ipsilateral recordings was recorded in dB SPL. Ipsilateral reflexes were obtained by delivering the stimulus to the ear containing the probe and reading from the same ear. Contralateral recordings were obtained by stimulating the ear not containing the probe and recording from the ear which did. For contralateral records, an earphone, supported by a ringstand, was placed against the contralateral ear. CRO recordings were usually made at a vertical calibration of 0.4cm³/div (one div=0.9 cm) and a horizontal calibration of 50 ms/div.

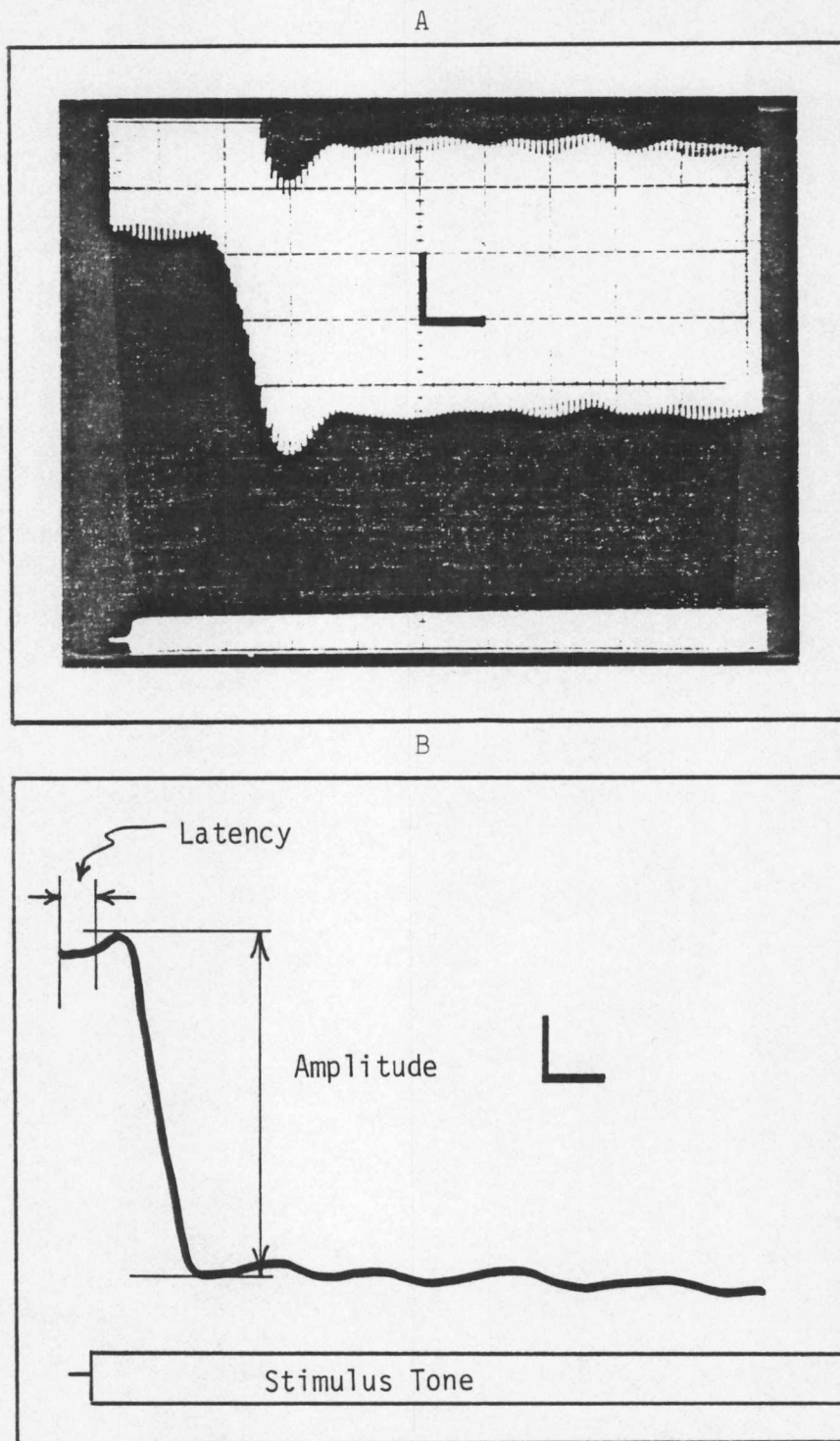


Figure 2. Acoustic reflex recordings. (A) Example of a contralateral reflex in a cat (#C8411) following an i.m. injection of xylazine (10 mg/kg) and ketamine (10 mg/kg). The stimulus was a pure tone (2 KHz) at 20 dB above ART. Vertical bar=0.4 cm³; Horizontal bar=50 ms. (B) Schematic of acoustic reflex showing how latency and amplitude were measured.

Table 5. Acoustic Reflex Recording Schedule

Experiment	Type		Stimulus Intensity		Time	
	Ipsi	Contra	dB SPL (I) +10 ART	dB HL (C) -10 ART	Before Infusion	After Infusion
1. Saline						
a. Xylazine	X	X	X	X	X	
b. Ketamine	X	X	X	X	X	
c. Infusion	X	X	X	X		X
2. Nicotine (40 ug/kg/min)						
a. Xylazine + Ketamine	X	X	X	X	X	
b. Infusion	X	X	X	X		X
3. Nicotine (60 ug/kg/min)						
a. Xylazine + Ketamine	X	X	X	X	X	
b. Infusion	X	X	X	X		X
4. Atropine (0.4 mg/kg) + Nicotine (60 ug/kg/min)						
a. Xylazine + Ketamine	X	X	X	X	X	
b. Atropine						
c. infusion	X	X	X	X		X
5. 5-MeODMT (10 ug/kg)						
a. Xylazine + Ketamine	X	X	X	X	X	
b. Inhection	X	X	X	X		X

3. RECORDING THE AUDITORY BRAINSTEM RESPONSE (ABR)

ABR were obtained using a computerized electrodiagnostic system (Nicolet Compact Four, Nicolet Instrument Corp., Madison, WI). A schematic of the equipment used to record an ABR is shown in Figure 3. Electrodes were the subcutaneous needle type (Grass E-2, Grass Medical Instruments, Quincy, Mass.) placed at the following positions: positive electrode at the vertex (CZ), negative electrode anterior to the pinna of the ear (A1), and the ground electrode (OZ) over the occipital cortex. Prior to recording the ABR impedance was checked to ensure that resistance was not greater than five ohms between any two electrodes. The signal was then amplified and averaged. The auditory stimulus simultaneously triggered the computer to record the response that occurred during the next 10 milliseconds. A total of 256 stimuli were delivered and the individual responses averaged by the computer. A sample recording is shown in Figure 4. Two repetitions of each stimulus regime insured repeatability. The recording was filtered through a band pass between 0.15 and 3KHz. The sound stimulus was a click generated by a 100 microsecond square-wave delivered to a electrically shielded Telex TDH 39P earphone mounted in a MX-AR/41 cushion. The clicks alternated between rarefaction and condensation in order to reduce the stimulus artifact. Stimulus intensities were 90, 80 and 70 dBHL delivered at a rate of 11.7/sec. In addition to clicks, tone pips were also used in order to have a more frequency-specific stimulus. That is a stimulus similar to that used to evoke the AR. The alternating (condensation and rarefaction) tones had a

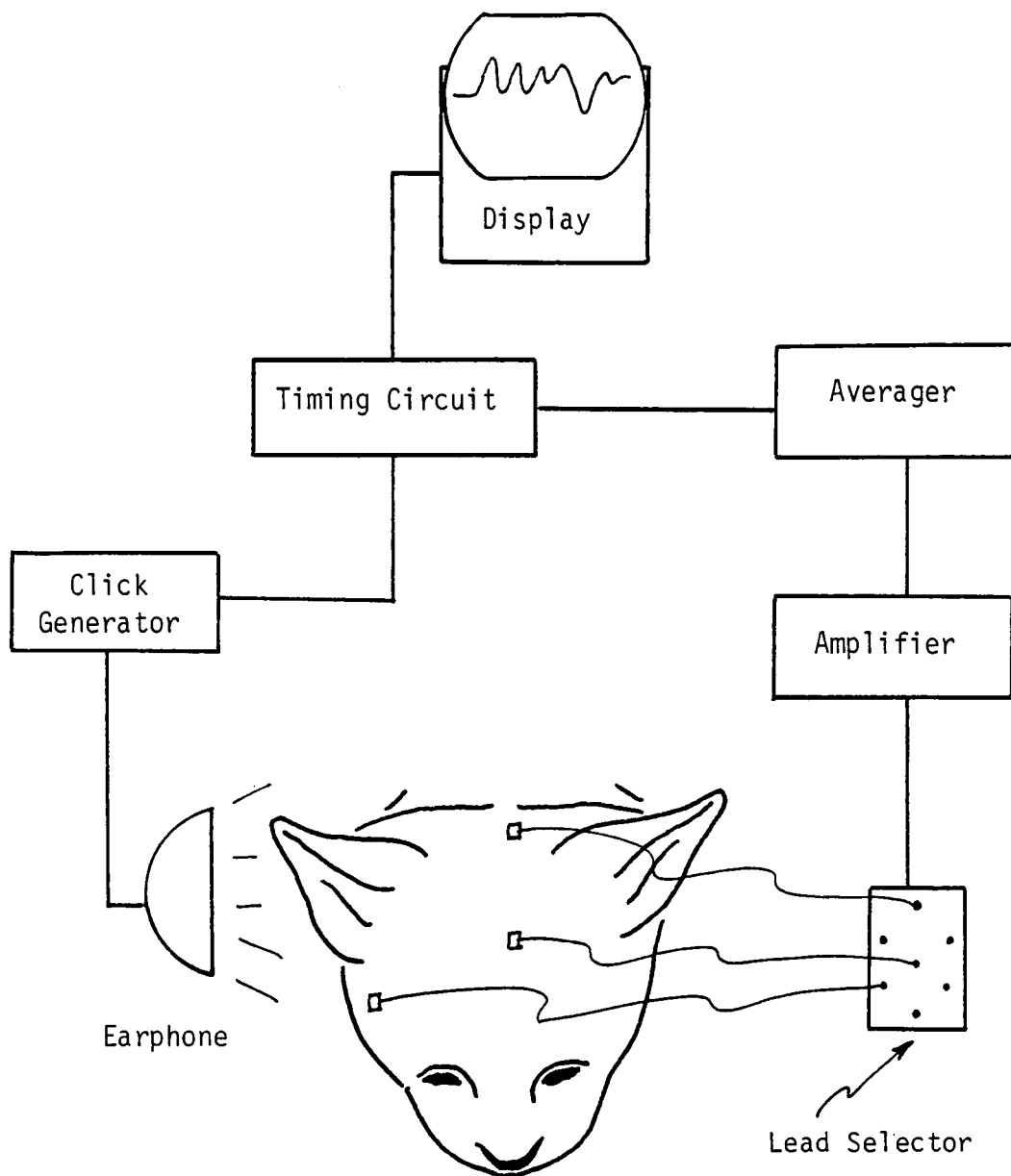


Figure 3. Schematic of equipment used to record the auditory brainstem response.

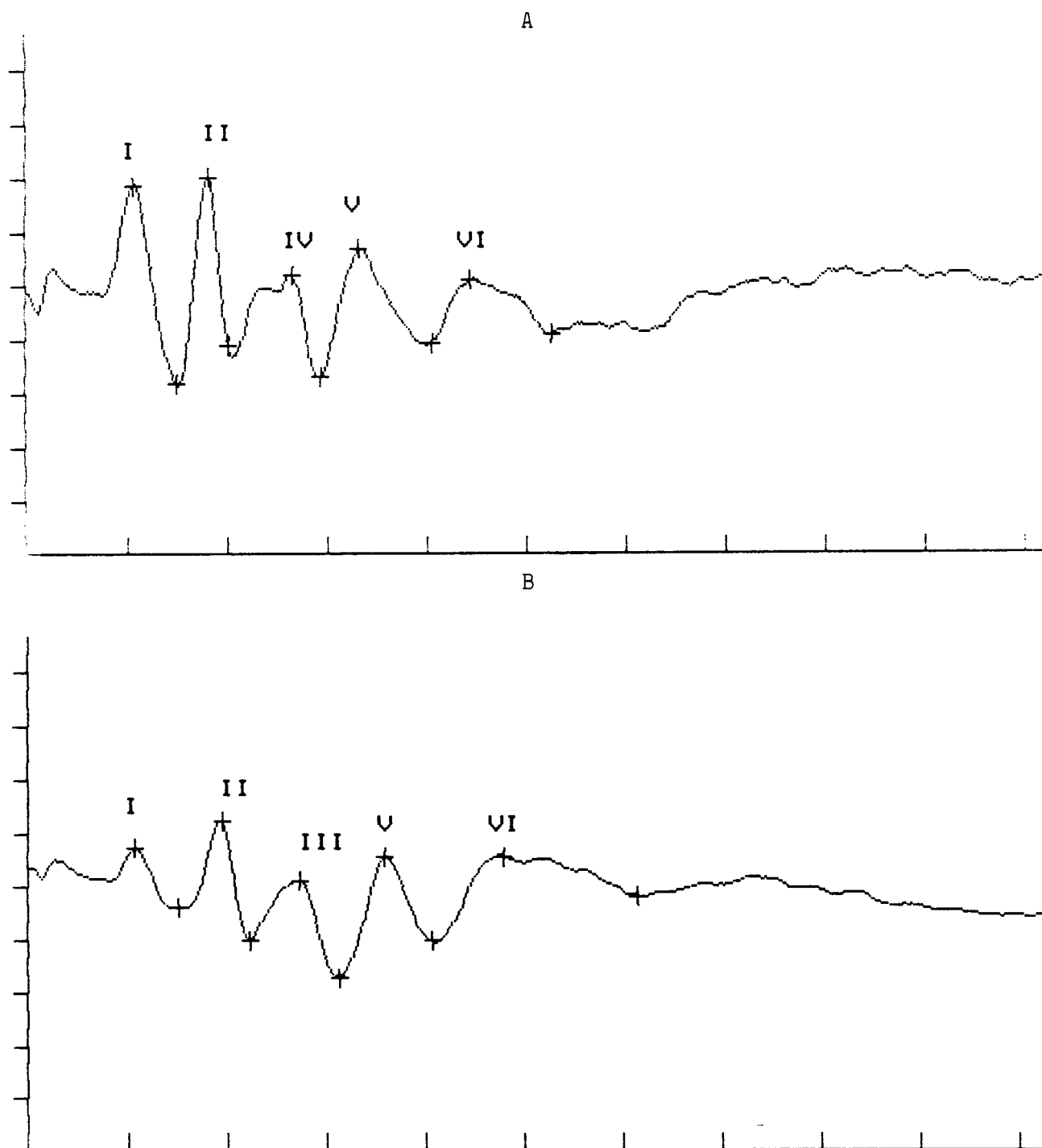


Figure 4. Examples of auditory brainstem responses as a result of click stimuli delivered to the left ear at an intensity of 90 dB HL during Experiment one. Each waveform is an average of 256 repetitions. The responses illustrate wave III and IV separate (A) and complexed to form one wave (B). Horizontal axis=1 ms/div; Vertical axis=1 μ v/div.

plateau of 150 msec, a two cycle ramp and a frequency of two KHz. The filter was set with band pass of 0.15 and 3KHz. The intensities used were 10 dB above and below the ART at a rate of 11.7/sec (Table 6). The earphone used for presentation of sound stimuli was placed snugly against the external ear but care was taken not to deform the external ear canal. A second earphone delivered a masking noise to the opposite ear (30 dBHL below stimulus intensity).

4. SAMPLE TIMES OF ABR AND AR DURING EXPERIMENTS

Acoustic reflexes were recorded both ipsilaterally and contralaterally from the left ear after xylazine, after ketamine and at the end of the infusion period during Experiment one. During Experiment two to five, AR were recorded only after ketamine and at the end of the infusion or injection period (Table 5). Electrodes were not moved from their original location anytime after ketamine injection. Ipsilateral ABR were measured from both ears after xylazine during Experiment one only (Table 6). During all subsequent experiments only the left ear was stimulated and recordings made after administration of ketamine and at 05, 10, 20, and 30 minutes after initiation of infusion (or injection of 5-MeODMT in Experiment five). After ketamine and at thirty minutes after initiation of infusion, a full battery of recordings were made including click stimuli at 90, 80 and 70 dBHL and logon stimuli at +10 and -10 dBSL (2KHz). At othertimes (05, 10, and 20 minutes) ABR were recorded using only 90 dbHL clicks and +10 and -10 db pips (Table 6). During Experiment four an additional recording was made after the administration of atropine.

Table 6. Auditory Brainstem Response Recording Schedule

Experiment	Ear		Stimulus Intensity						Time			
	R	L	CLICK (dB HL)			TONE PIP (dB HL)			(Minutes)			
			90	80	70	+10 ART	-10 ART	5	10	20	30	
1. Saline												
a. Xylazine	X	X	X	X	X	X		X				
b. Ketamine		X	X	X	X	X		X				
c. Infusion		X	X			X		X	X	X	X	X
		X		X	X							X
2. Nicotine (40 ug/kg/min)												
a. Xylazine + Ketamine		X	X	X	X	X		X				
b. Infusion		X	X			X		X	X	X	X	X
		X		X	X							X
3. Nicotine (60 ug/kg/min)												
a. Xylazine + Ketamine		X	X	X	X	X		X				
b. Infusion		X	X			X		X	X	X	X	X
		X		X	X							X
4. Atropine (0.4 mg/kg) + Nicotine (60 ug/kg/min)												
a. Xylazine + Ketamine		X	X	X	X	X		X				
b. Atropine		X	X			X		X				
c. Infusion		X	X			X		X	X	X	X	X
		X		X	X							X
5. 5-MeODMT (10 ug/kg)												
a. Xylazine + Ketamine		X	X	X	X	X		X				
b. Injection		X	X			X		X	X	X	X	X
		X		X	X							X

In this case only the 90 dBHL click evoked and the logon evoked recordings were made.

5. DRUG PREPARATION AND ADMINISTRATION

Saline. (Experiment one) After the completion of preinfusion recordings, one of the hind limbs was shaved on the inner surface and an indwelling catheter placed in the femoral vein and sutured in place. A saline drip was begun with a flow rate of two ml per minute. This rate was continued for thirty minutes and then stopped.

Nicotine. (Experiment two to four) Both the $40 \text{ ug kg}^{-1} \text{ min}^{-1}$ and $60 \text{ ug kg}^{-1} \text{ min}^{-1}$ solutions were prepared in much the same way. A stock solution of nicotine (Sigma Chemical Co. St. Louis, MO) was used and a new diluted solution was made up weekly. Each bottle of nicotine was prepared for a 3.6 kg. cat and the flow rate adjusted for each cat to ensure consistency in dosage. The nicotine was administered via an i.v. drip. Nearly all the cats began vomiting about five minutes after the initiation of the drip, but this behavior was short lived. The nicotine dosage was determined as a result of values given in the literature and several preliminary investigations in our lab. Infusion was used in this study because it was determined that a single injection of a large dose of nicotine can cause death while the same total dosage administered over a longer period did not (Kawamura and Domino, 1969; Gebber, 1969; unpublished data).

Atropine. (Experiment four) A pretreatment with 0.4 mg/kg of atropine i.v. was included in Experiment four (Table 5). Infusion of

nicotine at a concentration of $60 \text{ ug kg}^{-1} \text{ min}^{-1}$ for thirty minutes followed.

5-Methoxy-N-N-Dimethyltryptamine. (Experiment five) The 5-MeODMT (Sigma Chemical Co. St. Louis, MO) was made up fresh immediately prior to use each day. Due to its low solubility in saline, the drug was first solubilized with a few drops of 0.1 M HCl and then brought up to volume in saline with the pH adjusted to 7.0 using 0.1 M sodium chloride (NaCl). Each cat in this experiment was given one injection of 5-MeODMT (10 ug/kg) i.m..

6. RECOVERY

All cats were allowed to recover unassisted and were returned to their cages. Every cat recovered without incident. The catheters were not kept in place between experiments. No cat was used more than once a week and often longer periods of time elapsed between usage. There were no noticeable effects of any drug after the cat recovered.

7. MEASUREMENT OF RECORDINGS

Acoustic reflexes were measured directly from the polaroid pictures using a digitizer board (Figure 2). Each AR amplitude recorded after the initiation of the infusion or after the injection was divided by the amplitude after ketamine injection. This allowed an expression of AR amplitude as "percent change". The difference between the threshold after ketamine injection and that obtained

postinfusion was also calculated. All measurements of the ABR were made using an electronic cursor. Waves were identified and labeled using a procedure reported for dogs (Sims and Moore, 1984) (Figure 4). Latencies were measured from stimulus onset, to the peak of each consecutive wave to the nearest 0.01 msec. Amplitude measurements were made from the peak of each wave to the following trough to the nearest 0.01 uV. The tone pip measurements were converted to percent by dividing each number by its corresponding ketamine value. This was done to normalize the values since so many different intensities were used. Means were calculated on all values. Measurements from the traces were analyzed using the Statistical Analysis System (SAS) prepackaged programs. Threshold for contralateral AR which was recorded in dB HL was converted to dB SPL only when statistically comparing ipsilateral and contralateral thresholds. This was accomplished by the formula $SPL = HL + 9 \text{ dB}$. All ABR recordings were analyzed as corrected values (the numbers used were percentages of ketamine their respective ketamine values).

CHAPTER IV

RESULTS

1. ACOUSTIC REFLEX

Mean AR data compiled for Experiments one-five are given in Tables 7-11. The tables are arranged by experiment, and provide the means for threshold, latency, amplitude, percent amplitude change and threshold change.

In Experiment one, AR latency decreased with increasing stimulus intensity and was greater when recorded contralaterally than ipsilaterally. Amplitude of the response increased with increasing intensity of the stimulus and was smaller when recorded contralaterally than ipsilaterally. These results were also consistent among experimental groups. Whereas threshold for some cats was higher for contralateral than for ipsilateral, the most noticeable differences for ART were among cats. The same cats had consistently higher thresholds regardless of the experiment.

Statistical analysis of the AR (Table A-1, Appendix A) without separation for intensity and type (ipsilateral or contralateral), showed that for the variable latency; cat, side, intensity, and threshold were all significant ($p < .05$). For the variable amplitude: cat, intensity, threshold, experiment and the interactions (cat-drug and cat-time) were significant ($p < .05$). The Scheffe test, a multiple comparison procedure, compared the means of the factor levels to each other and thus determined where the differences were. This technique

Table 7. Acoustic Reflex Data, Means ($\pm$ SD) for Experiment One

Variable	Ten Decibels ART			Twenty Decibels ART		
	Preinfusion		Postinfusion	Preinfusion		Postinfusion
	Xylazine	Ketamine	30 min	Xylazine	Ketamine	30 min
<u>IPSILATERAL</u>						
Latency	45.50	53.44	53.91	30.83	38.43	40.24
(ms)	±5.17	±8.88	±9.81	±2.50	±6.37	±8.80
Amplitude	8.23	8.81	8.36	9.02	11.20	9.65
(cm ³)	±4.01	±4.25	±5.90	±3.57	±8.19	±5.17
Percent	120.13	100.00	91.70	125.62	100.00	97.43
Amplitude	±56.96	±0.00	±46.24	±101.16	±0.00	±52.47
Threshold	-1.00	0.00	-0.83	-1.00	0.00	-0.83
Change	±2.24	±0.00	±2.04	±2.24	±0.00	±2.04
(dBSPL)						
<u>CONTRALATERAL</u>						
Latency	69.45	66.07	61.02	48.93	48.74	53.85
(ms)	±15.29	±20.52	±22.68	±2.97	±14.52	±10.52
Amplitude	7.67	8.17	8.49	9.06	10.82	11.35
(cm ³)	±4.82	±4.39	±4.71	±2.97	±3.98	±5.19
Percent	131.00	100.00	114.09	101.19	100.00	117.00
Amplitude	±58.75	±0.00	±48.98	±42.33	±0.00	±55.82
Threshold	-3.00	0.00	-0.83	-3.00	0.00	-0.83
Change	±2.74	±0.00	±3.76	±2.74	±0.00	±3.76
(dBHL)						
	Ipsilateral (dBSPL)			Contralateral (dBHL)		
	Xylazine	Ketamine	30 min	Xylazine	Ketamine	30 min
Threshold	72.00	73.30	72.50	70.00	73.33	72.50
	±6.12	±6.06	±6.89	±4.50	±2.60	±4.20

Table 8. Acoustic Reflex Data, Means ($\pm$ SD) for Experiment Two

Variable	Ten Decibels ART		Twenty Decibels ART											
	Preinfusion Ketamine	Postinfusion 30 min	Preinfusion Ketamine	Postinfusion 30 min										
<u>IPSilATERAL</u>														
Latency (ms)	43.13 $\pm$ 13.70	49.90 $\pm$ 15.98	35.07 $\pm$ 7.54	38.86 $\pm$ 6.02										
Amplitude (cm ³)	10.07 $\pm$ 4.45	8.59 $\pm$ 4.74	10.16 $\pm$ 2.71	9.26 $\pm$ 4.51										
Percent Amplitude	100.00 $\pm$ 0.00	87.56 $\pm$ 26.33	100.00 $\pm$ 0.00	88.89 $\pm$ 24.05										
Threshold Change (dBSPL)	0.00 $\pm$ 0.00	-8.33 $\pm$ 7.53	0.00 $\pm$ 0.00	-8.33 $\pm$ 7.53										
<u>CONTRALATERAL</u>														
Latency (ms)	62.73 $\pm$ 12.60	66.34 $\pm$ 18.48	50.49 $\pm$ 7.68	46.92 $\pm$ 6.89										
Amplitude (cm ³)	7.91 $\pm$ 2.57	8.22 $\pm$ 3.10	9.62 $\pm$ 2.30	11.35 $\pm$ 4.09										
Percent Amplitude	100.00 $\pm$ 0.00	106.54 $\pm$ 28.91	100.00 $\pm$ 0.00	128.07 $\pm$ 41.89										
Threshold Change (dBHL)	0.00 $\pm$ 0.00	-7.50 $\pm$ 6.12	0.00 $\pm$ 0.00	-7.50 $\pm$ 6.12										
<table> <tr> <th></th><th colspan="2">Ipsilateral (dBSPL)</th><th colspan="2">Contralateral (dBHL)</th></tr> <tr> <th></th><th>Ketamine</th><th>30 min</th><th>Ketamine</th><th>30 min</th></tr> </table>						Ipsilateral (dBSPL)		Contralateral (dBHL)			Ketamine	30 min	Ketamine	30 min
	Ipsilateral (dBSPL)		Contralateral (dBHL)											
	Ketamine	30 min	Ketamine	30 min										
Threshold	78.33 $\pm$ 5.85	70.00 $\pm$ 6.06	79.17 $\pm$ 5.84	71.66 $\pm$ 6.32										

Table 9. Acoustic Reflex Data, Means ($\pm$ SD) for Experiment Three

Variable	Ten Decibels ART		Twenty Decibels ART										
	Preinfusion Ketamine	Postinfusion 30 min	Preinfusion Ketamine	Postinfusion 30 min									
<u>IPSILATERAL</u>													
Latency (ms)	62.70 ± 2.12	54.61 ± 24.84	35.49 ± 3.70	37.21 ± 7.82									
Amplitude (cm ³)	10.33 ± 5.27	8.50 ± 4.48	11.23 ± 4.84	9.64 ± 3.69									
Percent Amplitude	100.00 ± 0.00	79.74 ± 17.74	100.00 ± 0.00	88.83 ± 28.01									
Threshold Change (dBSPL)	0.00 ± 0.00	-10.71 ± 3.45	0.00 ± 0.00	-10.71 ± 3.45									
<u>CONTRALATERAL</u>													
Latency (ms)	57.85 ± 10.06	62.24 ± 29.03	49.49 ± 10.15	48.81 ± 11.21									
Amplitude (cm ³)	8.62 ± 3.98	8.09 ± 3.69	11.35 ± 2.69	10.28 ± 3.30									
Percent Amplitude	100.00 ± 0.00	104.49 ± 52.62	100.00 ± 0.00	92.24 ± 28.73									
Threshold Change (dBHL)	0.00 ± 0.00	-5.00 ± 5.00	0.00 ± 0.00	-5.00 ± 5.00									
<table> <tr> <th rowspan="2"></th><th colspan="2">Ipsilateral (dBSPL)</th><th colspan="2">Contralateral (dBHL)</th></tr> <tr> <th>Ketamine</th><th>30 min</th><th>Ketamine</th><th>30 min</th></tr> </table>						Ipsilateral (dBSPL)		Contralateral (dBHL)		Ketamine	30 min	Ketamine	30 min
	Ipsilateral (dBSPL)		Contralateral (dBHL)										
	Ketamine	30 min	Ketamine	30 min									
Threshold	80.71 ± 6.73	71.43 ± 4.50	79.29 ± 3.50	74.29 ± 5.56									

Table 10. Acoustic Reflex Data, Means ($\pm$ SD) for Experiment Four

Variable	Ten Decibels ART		Twenty Decibel ART															
	Preinfusion Ketamine	Postinfusion 30 min	Preinfusion Ketamine	Postinfusion 30 min														
<u>IPSILATERAL</u>																		
Latency (ms)	44.55 ± 4.16	44.98 ± 7.31	38.06 ± 4.59	36.53 ± 6.58														
Amplitude (cm ³)	11.19 ± 4.84	15.95 ± 3.34	13.30 ± 4.54	15.91 ± 3.37														
Percent Amplitude	100.00 ± 0.00	164.71 ± 33.24	100.00 ± 0.00	134.78 ± 70.48														
Threshold Change (dB SPL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00														
<u>CONTRALATERAL</u>																		
Latency (ms)	57.22 ± 9.83	55.23 ± 14.42	46.03 ± 1.76	45.37 ± 3.87														
Amplitude (cm ³)	11.68 ± 4.54	13.27 ± 3.04	12.74 ± 3.61	15.47 ± 2.98														
Percent Amplitude	100.00 ± 0.00	125.52 ± 51.13	100.00 ± 0.00	130.55 ± 53.72														
Threshold Change	0.00 ± 0.00	-2.50 ± 2.74	0.00 ± 0.00	-2.50 ± 2.74														
<table> <tr> <th rowspan="2"></th><th colspan="2">Ipsilateral (dB SPL)</th><th colspan="2">Contralateral (dB HL)</th></tr> <tr> <th>Ketamine</th><th>30 min</th><th>Ketamine</th><th>30 min</th></tr> <tr> <td>Threshold</td><td>79.17 ± 5.85</td><td>79.17 ± 8.10</td><td>80.83 ± 4.92</td><td>78.33 ± 4.92</td></tr> </table>						Ipsilateral (dB SPL)		Contralateral (dB HL)		Ketamine	30 min	Ketamine	30 min	Threshold	79.17 ± 5.85	79.17 ± 8.10	80.83 ± 4.92	78.33 ± 4.92
	Ipsilateral (dB SPL)		Contralateral (dB HL)															
	Ketamine	30 min	Ketamine	30 min														
Threshold	79.17 ± 5.85	79.17 ± 8.10	80.83 ± 4.92	78.33 ± 4.92														

Table 11. Acoustic Reflex Data, Means ($\pm$ SD) for Experiment Five

Variable	Ten Decibels ART		Twenty Decibels ART										
	Preinfusion Ketamine	Postinfusion 30 min	Preinfusion Ketamine	Postinfusion 30 min									
<u>IPSILATERAL</u>													
Latency (ms)	43.59 ± 6.81	51.16 ± 14.81	43.04 ± 2.57	41.80 ± 4.09									
Amplitude (cm ³)	5.89 ± 3.83	7.78 ± 2.19	7.62 ± 3.62	8.43 ± 3.33									
Percent Amplitude	100.00 ± 0.00	176.73 ± 84.53	100.00 ± 0.00	128.01 ± 62.49									
Threshold Change (dB SPL)	0.00 ± 0.00	-2.50 ± 6.89	0.00 ± 0.00	-2.50 ± 6.89									
<u>Contralateral</u>													
Latency (ms)	58.75 ± 27.44	61.27 ± 14.39	46.53 ± 13.04	52.28 ± 9.43									
Amplitude (cm ³)	6.39 ± 2.48	6.19 ± 2.76	7.85 ± 3.17	6.22 ± 2.88									
Percent Amplitude	100.00 ± 0.00	113.79 ± 84.27	100.00 ± 0.00	80.38 ± 46.87									
Threshold Change (dB HL)	0.00 ± 0.00	1.67 ± 5.16	0.00 ± 0.00	1.67 ± 5.16									
<table> <tr> <th rowspan="2"></th><th colspan="2">Ipsilateral (dB SPL)</th><th colspan="2">Contralateral (dB HL)</th></tr> <tr> <th>Ketamine</th><th>30 min</th><th>Ketamine</th><th>30 min</th></tr> </table>						Ipsilateral (dB SPL)		Contralateral (dB HL)		Ketamine	30 min	Ketamine	30 min
	Ipsilateral (dB SPL)		Contralateral (dB HL)										
	Ketamine	30 min	Ketamine	30 min									
Threshold	79.17 ± 5.85	76.67 ± 5.80	79.17 ± 5.85	80.83 ± 2.58									

delineated that for amplitude Experiment five was different from Experiment four and both were different from the other three. Percent amplitude gave acceptable significance levels for cat, threshold, sample time and the two interactions. For threshold, cat type, experiment sample time and both interactions were significant ($p < .05$). Cat, threshold, drug, sample time and the cat-drug interaction all significantly ($p < .05$) predicted changes in the threshold. Experiments involving the use of nicotine alone (Experiments two and three) were different from the other three.

For further statistical analysis, the AR was separated by type and intensity levels. For ipsilateral reflexes at +10 dBHL ART (Table A-2), it was found that the threshold level was a significant predictor of latency. Experiment was significant for amplitude, with Experiment four different from the rest. Experiment was not significant for percent amplitude, but cat, threshold and the cat-time interaction were. For the change in threshold, cat, experiment and the cat-drug interaction were all significant predictors. The Scheffe test determined that Experiments two and three were significantly different from the other experiments. For ipsilateral AR at +20 ART (Table A-3) cat was important for predicting latency. Experiment,, notably Experiment four, and cat were significant in predicting the amplitude. None of the variables were significant for percent amplitude.

Contralaterally at +10 dBHL ART (Table A-4), cat and threshold effectively predicted the latency changes. Amplitude, cat and experiment (Experiment four) were significant. This did not hold for

percent amplitude. At +20 dBHL ART (Table A-5) only cat was a significant predictor of latency. For amplitude, experiment (Experiment four) was significant but once again this did not hold for percent of amplitude. Change in threshold was significantly predicted by cat, experiment, threshold and the cat-drug interaction. The Scheffe test showed that the effect of nicotine at $40 \text{ ug kg}^{-1}\text{min}^{-1}$ was different from saline. It seems that the most significant effects were on the change in threshold due to nicotine administration (Experiments two and three). Experiment four was often significant ($p < .05$) in predicting the amplitude value.

Latency was not significantly affected by experiment (Table 12). Amplitude was significantly ($p < .05$) affected by the administration of atropine (Experiment four) ipsilaterally at both stimulus intensities and contralaterally at +10 dBHL ART. The contralateral amplitude recorded at +20 dBHL ART was significantly decreased during Experiment five (Table 12). None of the experiments were significant for predicting percent amplitude. Nicotine (Experiments two and three) significantly decreased the ipsilateral reflex threshold and experiment two significantly decreased the contralateral AR threshold.

2. AUDITORY BRAINSTEM RESPONSE

Means of the ABR data elicited by clicks are presented in Tables 13-23. In Experiment one, there was an increase in latency and decrease in amplitude with a decrease in stimulus intensity. Latency

Table. 12. Acoustic Reflex; Summary of Scheffe Test

Exp. No.	Amplitude				Threshold Change	
	Ipsilateral +10	Contralateral +20	Ipsilateral +10	Contralateral +20	Ipsilateral	Contralateral
1	B*	B	B	A	A	A C
2	AB	B	B	A	BC	BC
3	AB	B	B	A	B	BC
4	A	A	A	A	A	BC
5	B	B	B	B	A C	A

*Experiments with the same letter are not statistically significant ($p > .05$)

Table 13. Auditory Brainstem Response Data, Means ($\pm$ SD) for Experiment One; 90 dBHL click-evoked

Wave	Preinfusion		Sample Times During Infusion (min)			
	Xylazine	Ketamine	05	10	20	30
Latency $\pm$ SD (ms)						
I	1.00 ± 0.02	1.02 ± 0.04	1.03 ± 0.03	1.04 ± 0.03	1.05 ± 0.03	1.04 ± 0.02
II	1.76 ± 0.04	1.80 ± 0.04	1.81 ± 0.05	1.79 ± 0.05	1.81 ± 0.07	1.81 ± 0.05
III/IV	2.46 ± 0.07	2.52 ± 0.08	2.56 ± 0.11	2.49 ± 0.17	2.54 ± 0.13	2.58 ± 0.13
V	3.26 ± 0.06	3.35 ± 0.04	3.37 ± 0.11	3.39 ± 0.16	3.38 ± 0.14	3.38 ± 0.12
VI	4.32 ± 0.09	4.31 ± 0.12	4.42 ± 0.14	4.41 ± 0.14	4.44 ± 0.21	4.41 ± 0.18
Amplitude $\pm$ SD (μ V)						
I	3.30 ± 0.73	2.94 ± 0.67	3.03 ± 0.68	3.16 ± 0.71	3.11 ± 0.87	3.31 ± 0.77
II	2.62 ± 1.35	2.47 ± 1.46	2.58 ± 1.20	2.59 ± 1.13	2.62 ± 1.06	2.66 ± 1.10
III/IV	2.73 ± 1.21	2.32 ± 1.10	2.25 ± 1.13	2.30 ± 1.01	2.21 ± 0.94	2.35 ± 1.04
V	2.79 ± 1.59	2.37 ± 1.40	2.38 ± 1.17	2.34 ± 1.26	2.32 ± 1.01	2.71 ± 1.48
VI	1.05 ± 0.54	1.02 ± 0.64	0.89 ± 0.57	0.92 ± 0.56	0.90 ± 0.55	0.89 ± 0.50

Table 14. Auditory Brainstem Response Data, Means ($\pm$ SD) for Experiment Two; 90 dBHL click-evoked

Wave	Preinfusion Ketamine	Sample Times During Infusion (ms)			
		05	10	20	30
Latency $\pm$ SD (ms)					
I	1.01 ± 0.04	1.04 ± 0.05	1.04 ± 0.06	1.03 ± 0.04	1.04 ± 0.04
II	1.78 ± 0.04	1.82 ± 0.06	1.82 ± 0.07	1.82 ± 0.04	1.82 ± 0.05
III/IV	2.50 ± 0.08	2.57 ± 0.12	2.51 ± 0.18	2.43 ± 0.16	2.57 ± 0.08
V	3.38 ± 0.12	3.42 ± 0.11	3.43 ± 0.13	3.42 ± 0.13	3.43 ± 0.08
VI	4.27 ± 0.11	4.45 ± 0.12	4.35 ± 0.21	4.50 ± 0.13	4.45 ± 0.08
Amplitude $\pm$ SD (μ V)					
I	3.25 ± 0.52	2.66 ± 0.74	2.87 ± 0.62	2.95 ± 0.65	3.01 ± 0.59
II	3.32 ± 1.16	2.92 ± 1.28	3.01 ± 1.38	2.88 ± 1.25	2.86 ± 1.03
III/IV	2.91 ± 1.26	2.56 ± 1.33	2.31 ± 1.03	2.33 ± 1.09	2.30 ± 1.05
V	2.77 ± 1.52	2.39 ± 1.24	2.57 ± 1.51	2.65 ± 1.45	2.57 ± 1.44
IV	0.91 ± 0.38	1.04 ± 0.29	1.10 ± 0.44	1.16 ± 0.67	0.93 ± 0.50

Table 15. Auditory Brainstem Response Data, Means ($\pm$ SD) for Experiment Three; 90 dBHL click-evoked

Wave	Preinfusion Ketamine	Sample Times During Infusion (min)			
		05	10	20	30
Latency $\pm$ SD (ms)					
I	1.06 ± 0.11	1.09 ± 0.09	1.08 ± 0.09	1.09 ± 0.09	1.09 ± 0.10
II	1.82 ± 0.08	1.85 ± 0.06	1.84 ± 0.07	1.84 ± 0.07	1.85 ± 0.06
III/IV	2.56 ± 0.05	2.60 ± 0.06	2.56 ± 0.05	2.58 ± 0.06	2.66 ± 0.20
V	3.36 ± 0.09	3.40 ± 0.09	3.38 ± 0.08	3.31 ± 0.09	3.40 ± 0.05
VI	4.41 ± 0.11	4.46 ± 0.09	4.49 ± 0.12	4.45 ± 0.11	4.49 ± 0.11
Amplitude $\pm$ SD (μ V)					
I	2.75 ± 0.55	2.31 ± 0.58	2.39 ± 0.55	2.40 ± 0.44	2.44 ± 0.38
II	2.33 ± 0.93	2.21 ± 0.95	2.25 ± 1.16	2.18 ± 1.02	2.46 ± 1.17
III/IV	2.29 ± 0.73	2.16 ± 0.62	2.14 ± 0.53	2.13 ± 0.59	1.99 ± 0.72
V	2.46 ± 1.24	2.21 ± 0.99	2.26 ± 0.85	2.18 ± 0.94	2.30 ± 0.85
VI	0.88 ± 0.51	0.73 ± 0.16	0.64 ± 0.09	0.76 ± 0.26	0.65 ± 0.15

Table 16. Auditory Brainstem Response Data, Means ($\pm$ SD) for
Experiment Four; 90 dBHL click-evoked

Wave	Preinfusion		Sample Times During INFUSION (min)			
	Ketamine	Atropine	05	10	20	30
Latency $\pm$ SD (ms)						
I	1.01 ± 0.02	1.01 ± 0.03	1.02 ± 0.03	1.02 ± 0.03	1.01 ± 0.03	1.02 ± 0.02
II	1.76 ± 0.06	1.79 ± 0.04	1.80 ± 0.03	1.80 ± 0.03	1.80 ± 0.04	1.80 ± 0.05
III/IV	2.50 ± 0.04	2.57 ± 0.09	2.55 ± 0.07	2.55 ± 0.07	2.53 ± 0.08	2.52 ± 0.09
V	3.29 ± 0.10	3.33 ± 0.07	3.35 ± 0.09	3.35 ± 0.09	3.34 ± 0.10	3.35 ± 0.11
VI	4.33 ± 0.12	4.41 ± 0.16	4.48 ± 0.16	4.44 ± 0.18	4.47 ± 0.20	4.44 ± 0.21
Amplitude $\pm$ SD (μ V)						
I	2.96 ± 0.94	3.01 ± 1.10	2.76 ± 0.73	2.78 ± 0.78	2.70 ± 0.81	2.90 ± 0.71
II	2.55 ± 0.44	2.58 ± 0.71	2.62 ± 0.43	2.56 ± 0.50	2.32 ± 0.57	2.49 ± 0.45
III/IV	2.15 ± 0.46	1.90 ± 0.53	2.16 ± 0.37	2.19 ± 0.31	2.14 ± 0.36	2.14 ± 0.48
V	2.01 ± 0.33	1.94 ± 0.46	2.13 ± 0.49	2.08 ± 0.41	2.12 ± 0.50	2.25 ± 0.50
VI	0.58 ± 0.41	0.93 ± 0.44	0.86 ± 0.50	0.72 ± 0.49	0.74 ± 0.39	0.78 ± 0.44

Table 17. Auditory Brainstem Response Data, Means ($\pm$ SD) for Experiment Five; 90 dBHL click-evoked

Wave	Preinfusion Ketamine	Sample Times During Infusion (min)			
		05	10	20	30
Latency $\pm$ SD (min)					
I	1.00 ± 0.02	1.02 ± 0.05	1.03 ± 0.04	1.02 ± 0.04	1.02 ± 0.02
II	1.76 ± 0.04	1.78 ± 0.06	1.77 ± 0.05	1.78 ± 0.05	1.77 ± 0.03
III/IV	2.48 ± 0.03	2.50 ± 0.08	2.53 ± 0.09	2.54 ± 0.09	2.53 ± 0.07
V	3.28 ± 0.04	3.35 ± 0.13	3.33 ± 0.12	3.36 ± 0.12	3.33 ± 0.07
VI	4.32 ± 0.13	4.36 ± 0.15	4.34 ± 0.17	4.37 ± 0.11	4.38 ± 0.18
Amplitude $\pm$ SD (μ V)					
I	3.67 ± 0.74	3.22 ± 0.61	3.44 ± 0.59	3.46 ± 0.80	3.72 ± 0.87
II	2.87 ± 1.27	2.57 ± 0.93	2.53 ± 0.86	2.47 ± 0.89	2.69 ± 0.96
III/IV	2.34 ± 0.78	2.09 ± 0.83	2.14 ± 0.79	2.13 ± 0.89	2.32 ± 0.66
V	2.24 ± 1.14	1.80 ± 0.85	1.95 ± 1.02	2.02 ± 1.00	2.14 ± 0.90
VI	1.34 ± 0.53	0.74 ± 0.55	0.88 ± 0.52	0.86 ± 0.61	1.01 ± 0.03

Table 18. Auditory Brainstem Response Data, Means ($\pm$ SD) for Experiment One; 80 dBHL click-evoked

Wave	Preinfusion Xylazine Ketamine		Postinfusion (min) 30
Latency $\pm$ SD (ms)			
I	1.66 ± 0.66	1.09 ± 0.04	1.08 ± 0.04
II	1.82 ± 0.05	1.83 ± 0.04	1.86 ± 0.06
III/IV	2.49 ± 0.09	2.51 ± 0.17	2.60 ± 0.15
V	3.36 ± 0.10	3.45 ± 0.62	3.46 ± 0.15
VI	4.45 ± 0.14	4.53 ± 0.34	4.56 ± 0.13
Amplitude $\pm$ SD (μ V)			
I	2.81 ± 0.99	2.53 ± 0.72	2.76 ± 0.95
II	2.20 ± 1.19	2.28 ± 2.28	1.96 ± 1.93
III/IV	2.53 ± 1.29	2.06 ± 1.01	1.94 ± 1.07
V	2.08 ± 1.47	2.09 ± 1.25	2.32 ± 1.85
VI	0.82 ± 0.47	0.68 ± 0.56	0.48 ± 0.31

Table 19. Auditory Brainstem Response Data, Means ($\pm$ SD) for Experiments Two and Three; 80 dBHL click-evoked

Wave	Preinfusion Ketamine	Postinfusion 30 min	Preinfusion Ketamine	Postinfusion 30 min
<u>Experiment Two</u>				
	Latency $\pm$ SD (min)		Amplitude $\pm$ SD (μ V)	
I	1.07 $\pm$ 0.60	1.09 $\pm$ 0.06	2.67 $\pm$ 0.37	2.57 $\pm$ 0.73
II	1.84 $\pm$ 0.05	1.88 $\pm$ 0.06	2.93 $\pm$ 1.22	2.52 $\pm$ 1.01
III/IV	2.61 $\pm$ 0.23	2.54 $\pm$ 0.15	2.48 $\pm$ 1.06	2.16 $\pm$ 1.00
V	3.40 $\pm$ 0.09	3.49 $\pm$ 0.10	2.45 $\pm$ 1.23	2.31 $\pm$ 1.22
VI	4.50 $\pm$ 0.13	4.51 $\pm$ 0.10	0.43 $\pm$ 0.23	0.63 $\pm$ 0.50
<u>Experiment Three</u>				
	Latency $\pm$ SD (ms)		Amplitude $\pm$ SD (μ V)	
I	1.12 $\pm$ 0.11	1.14 $\pm$ 0.09	2.06 $\pm$ 0.61	2.13 $\pm$ 0.50
II	1.88 $\pm$ 0.08	1.91 $\pm$ 0.07	1.85 $\pm$ 1.05	1.81 $\pm$ 0.87
III/IV	2.59 $\pm$ 0.06	2.63 $\pm$ 0.03	2.11 $\pm$ 0.77	1.79 $\pm$ 0.61
V	3.44 $\pm$ 0.13	3.44 $\pm$ 0.08	1.86 $\pm$ 0.89	1.72 $\pm$ 0.75
VI	4.51 $\pm$ 0.26	4.60 $\pm$ 0.19	0.59 $\pm$ 0.41	0.54 $\pm$ 0.16

Table 20. Auditory Brainstem Response Data, Means ($\pm$ SD) for Experiments Four and Five; 80 dBHL click-evoked

Wave	Preinfusion Ketamine	Postinfusion 30 min	Preinfusion Ketamine	Postinfusion 30 min
<u>Experiment Four</u>				
	Latency $\pm$ SD (ms)		Amplitude $\pm$ SD (μ V)	
I	1.07 ± 0.04	1.07 ± 0.03	2.24 ± 0.52	2.11 ± 0.79
II	1.84 ± 0.08	1.87 ± 0.04	2.01 ± 0.76	1.86 ± 0.78
III/IV	2.61 ± 0.09	2.55 ± 0.14	1.81 ± 0.33	1.84 ± 0.35
V	3.42 ± 0.14	3.46 ± 0.07	1.58 ± 0.52	1.63 ± 0.66
VI	4.55 ± 0.26	4.55 ± 0.13	0.61 ± 0.31	0.55 ± 0.33
<u>Experiment Five</u>				
	Latency $\pm$ SD (ms)		Amplitude $\pm$ SD (μ V)	
I	1.05 ± 0.04	1.06 ± 0.02	2.84 ± 0.56	3.05 ± 0.75
II	1.80 ± 0.05	1.82 ± 0.02	2.19 ± 1.02	2.10 ± 0.88
III/IV	2.58 ± 0.08	2.53 ± 0.08	1.71 ± 0.79	1.79 ± 0.62
V	3.38 ± 0.11	3.40 ± 0.08	1.65 ± 0.93	1.75 ± 0.78
VI	4.30 ± 0.12	4.52 ± 0.44	0.36 ± 0.32	0.72 ± 0.45

Table 21. Auditory Brainstem Response Data, Means ($\pm$ SD) for Experiment One; 70 dBHL click-evoked

Wave	Preinfusion Xylazine Ketamine		Postinfusion 30 (min)
Latency $\pm$ SD (ms)			
I	1.12 ± 0.08	1.15 ± 0.05	1.16 ± 0.05
II	1.87 ± 0.04	1.93 ± 0.07	1.92 ± 0.06
III/IV	2.51 ± 0.14	2.68 ± 0.29	2.71 ± 0.20
V	3.42 ± 0.08	3.51 ± 0.12	3.51 ± 0.08
VI	4.48 ± 0.21	4.71 ± 0.18	4.82 ± 0.30
Amplitude $\pm$ SD (ms)			
I	2.00 ± 0.79	1.23 ± 0.61	1.62 ± 0.84
II	1.77 ± 1.04	1.25 ± 0.55	1.37 ± 0.57
III/IV	1.60 ± 0.96	1.13 ± 0.72	1.27 ± 0.99
V	2.28 ± 1.14	1.84 ± 1.24	1.96 ± 1.24
VI	0.74 ± 0.32	0.60 ± 0.49	0.51 ± 0.13

Table 22. Auditory Brainstem Response Data, Means ($\pm$ SD) for Experiments Two and Three; 70 dBHL click-evoked

Wave	Preinfusion Ketamine	Postinfusion 30 min	Preinfusion Ketamine	Postinfusion 30 min
<u>Experiment Two</u>				
	Latency $\pm$ SD (ms)		Amplitude $\pm$ SD (μ V)	
I	1.14 ± 0.05	1.14 ± 0.04	1.48 ± 0.42	1.45 ± 0.64
II	1.83 ± 0.06	1.93 ± 0.08	2.13 ± 0.80	1.88 ± 0.69
III/IV	2.57 ± 0.19	2.65 ± 0.24	1.72 ± 1.01	1.71 ± 0.96
V	3.51 ± 0.10	3.54 ± 0.14	2.41 ± 1.02	2.15 ± 0.52
VI	4.73 ± 0.23	4.82 ± 0.32	0.53 ± 0.27	0.61 ± 0.18
<u>Experiment Three</u>				
	Latency $\pm$ SD (ms)		Amplitude $\pm$ SD (μ V)	
I	1.18 ± 0.12	1.20 ± 0.09	1.27 ± 0.36	1.32 ± 0.62
II	1.98 ± 0.09	1.97 ± 0.08	1.11 ± 0.60	1.10 ± 0.71
III/IV	2.67 ± 0.18	2.57 ± 0.18	1.20 ± 0.68	1.24 ± 0.43
V	3.56 ± 0.12	3.58 ± 0.07	1.38 ± 0.72	1.58 ± 0.71
VI	4.74 ± 0.18	4.89 ± 0.16	0.50 ± 0.25	0.49 ± 0.28

Table 23. Auditory Brainstem Response Data, Means ($\pm$ SD) for Experiments Four and Five; 70 dBHL click-evoked

Wave	Preinfusion Ketamine	Postinfusion 30 min	Preinfusion Ketamine	Postinfusion 30 min
<u>Experiment Four</u>				
Latency $\pm$ SD (ms)		Amplitude $\pm$ SD (μ V)		
I	1.14 ± 0.06	1.13 ± 0.04	1.05 ± 0.35	0.86 ± 0.06
II	1.94 ± 0.09	1.94 ± 0.06	1.04 ± 0.37	1.04 ± 0.44
III/IV	2.77 ± 0.36	2.58 ± 0.19	1.07 ± 0.48	1.09 ± 0.35
V	3.54 ± 0.13	3.56 ± 0.13	1.17 ± 0.55	1.21 ± 0.60
VI	4.51 ± 0.31	4.56 ± 0.13	0.39 ± 0.13	0.45 ± 0.08
<u>Experiment Five</u>				
Latency $\pm$ SD (ms)		Amplitude $\pm$ SD (μ V)		
I	1.12 ± 0.04	1.12 ± 0.03	1.49 ± 0.41	1.59 ± 0.30
II	1.81 ± 0.07	1.89 ± 0.04	1.36 ± 0.41	1.31 ± 0.41
III/IV	2.58 ± 0.23	2.57 ± 0.13	1.31 ± 0.64	1.30 ± 0.55
V	3.49 ± 0.11	3.40 ± 0.18	1.38 ± 0.77	1.47 ± 0.63
VI	4.58 ± 0.17	4.55 ± 0.25	0.22 ± 0.10	0.33 ± 0.34

values were less variable than the amplitude values. This was true at all intensities.

Means of ABR elicited by tone pips are presented in Tables 24-33. These means are expressed as percent of ketamine values for latency and amplitude.

Statistical analysis of the ABR data whether elicited by clicks or tone pips indicated that cat, frequency, intensity and wave were all significant ($p < .05$), Side was not significant (Table 6). Next each stimulus type (click or tone pip) was analyzed separately (Tables A-7 and A-8). For both stimulus types, cat, intensity, experiment, and wave were all significant predictors of latency and amplitude. The individual cat being tested was almost always significant no matter how the data was separated, as was the interaction of cat with experiment. Frequency was further analyzed by wave (Tables A-9 through A-29).

Analyses of the ABR elicited by 90 dBHL clicks are given in Tables A-9 through A-13. Experiment one consistently had the shortest mean latency and the largest mean amplitude for all waves according to the Scheffe ranking. For wave I, experiment was only significant for predicting amplitude changes. The Scheffe test determined that all of the experiments were different from Experiment one. The variable time (which elapsed during infusion) was also significant. Wave II latency, drug and sample time were significant. Here only Experiment four was significantly different from Experiment one. Amplitude was also effected by experiment. Experiment one was significantly different from all of the other experiments. Wave III/IV was altered

Table 24. Auditory Brainstem Response Data, Means ($\pm$ SD) for
Experiment One; +10 dB ART tone pip-evoked

Wave	Preinfusion		Sample Times During Infusion (min)			
	Xylazine	Ketamine	05	10	20	30
Percent Latency $\pm$ SD						
I	96.66 $\pm$ 4.83	100.00 $\pm$ 0.00	98.50 $\pm$ 6.78	97.55 $\pm$ 6.70	97.53 $\pm$ 8.65	98.71 $\pm$ 8.30
III	101.18 $\pm$ 7.64	100.00 $\pm$ 0.00	97.09 $\pm$ 18.38	102.12 $\pm$ 9.35	102.10 $\pm$ 7.27	101.64 $\pm$ 5.42
V	100.47 $\pm$ 7.21	100.00 $\pm$ 0.00	100.94 $\pm$ 1.94	100.16 $\pm$ 2.75	99.27 $\pm$ 6.38	99.43 $\pm$ 2.35
Percent Amplitude $\pm$ SD						
I	225.23 $\pm$ 169.08	100.00 $\pm$ 0.00	156.68 $\pm$ 100.64	148.89 $\pm$ 125.66	124.38 $\pm$ 80.51	119.89 $\pm$ 62.67
III	341.28 $\pm$ 426.00	100.00 $\pm$ 0.00	145.53 $\pm$ 70.00	178.92 $\pm$ 113.01	192.88 $\pm$ 119.35	185.32 $\pm$ 152.09
V	245.38 $\pm$ 217.29	100.00 $\pm$ 0.00	206.72 $\pm$ 208.57	171.27 $\pm$ 132.77	186.04 $\pm$ 133.52	183.74 $\pm$ 135.00

Table 25. Auditory Brainstem Response Data, Means ($\pm$ SD) for
Experiment Two; +10 dB ART tone pip-evoked

Wave	Preinfusion	Sample Times During Infusion (min)			
	Ketamine	05	10	20	30
Percent Latency $\pm$ SD					
I	100.00 $\pm$ 0.00	102.77 $\pm$ 5.07	99.04 $\pm$ 1.57	97.73 $\pm$ 2.55	100.89 $\pm$ 2.55
III	100.00 $\pm$ 0.00	100.74 $\pm$ 4.06	101.57 $\pm$ 4.14	98.38 $\pm$ 5.21	101.15 $\pm$ 4.20
V	100.00 $\pm$ 0.00	102.82 $\pm$ 3.88	100.81 $\pm$ 3.70	101.05 $\pm$ 2.93	102.02 $\pm$ 2.93
Percent Amplitude $\pm$ SD					
I	100.00 $\pm$ 0.00	739.26 $\pm$ 1622.20	1244.27 $\pm$ 2819.76	570.70 $\pm$ 1190.23	234.12 $\pm$ 542.88
III	100.00 $\pm$ 0.00	104.14 $\pm$ 46.06	101.57 $\pm$ 41.38	105.83 $\pm$ 54.06	101.53 $\pm$ 66.92
V	100.00 $\pm$ 0.00	97.87 $\pm$ 32.18	91.18 $\pm$ 21.46	100.78 $\pm$ 44.96	101.99 $\pm$ 30.56

Table 26. Auditory Brainstem Response Data, Means ($\pm$ SD) for Experiment Three; +10 dB ART tone pip-evoked

Wave	Preinfusion	Sample Times During Infusion (min)			
	Ketamine	05	10	20	30
Percent Latency $\pm$ SD					
I	100.00 $\pm$ 0.00	100.66 $\pm$ 4.50	100.28 $\pm$ 6.44	101.59 $\pm$ 3.82	102.53 $\pm$ 4.47
III	100.00 $\pm$ 0.00	100.89 $\pm$ 2.64	100.05 $\pm$ 2.34	100.73 $\pm$ 1.70	101.62 $\pm$ 2.94
V	100.00 $\pm$ 0.00	100.08 $\pm$ 2.32	99.50 $\pm$ 1.59	100.95 $\pm$ 1.75	101.98 $\pm$ 1.76
Percent Amplitude $\pm$ SD					
I	100.00 $\pm$ 0.00	91.72 $\pm$ 39.51	96.56 $\pm$ 47.11	93.69 $\pm$ 19.82	106.56 $\pm$ 52.83
III	100.00 $\pm$ 0.00	81.97 $\pm$ 19.12	90.45 $\pm$ 32.38	101.08 $\pm$ 22.30	97.56 $\pm$ 37.22
V	100.00 $\pm$ 0.00	177.43 $\pm$ 244.81	152.50 $\pm$ 102.54	121.68 $\pm$ 58.78	128.17 $\pm$ 97.22

Table 27. Auditory Brainstem Response Data, Means ($\pm$ SD) for
Experiment Four; +10 dB ART tone pip-evoked

Wave	Preinfusion		Sample Times During Infusion (min)			
	Ketamine	Atropine	05	10	20	30
Percent Latency $\pm$ SD						
I	100.00 $\pm$ 0.00	101.01 $\pm$ 2.14	98.85 $\pm$ 4.43	99.33 $\pm$ 4.30	98.67 $\pm$ 4.00	98.37 $\pm$ 4.22
III	100.00 $\pm$ 0.00	99.28 $\pm$ 6.48	97.41 $\pm$ 7.04	97.51 $\pm$ 7.00	97.27 $\pm$ 7.52	96.67 $\pm$ 5.90
V	100.00 $\pm$ 0.00	99.90 $\pm$ 6.93	99.94 $\pm$ 1.92	101.68 $\pm$ 1.52	101.47 $\pm$ 3.65	101.05 $\pm$ 2.01
Percent Amplitude $\pm$ SD						
I	100.00 $\pm$ 0.00	112.98 $\pm$ 32.58	114.27 $\pm$ 17.81	131.12 $\pm$ 14.88	107.30 $\pm$ 8.25	122.56 $\pm$ 41.21
III	100.00 $\pm$ 0.00	106.29 $\pm$ 33.68	101.87 $\pm$ 34.82	102.26 $\pm$ 26.85	96.80 $\pm$ 19.68	102.78 $\pm$ 26.03
V	100.00 $\pm$ 0.00	106.46 $\pm$ 35.40	112.89 $\pm$ 51.52	103.80 $\pm$ 37.64	87.15 $\pm$ 38.23	101.88 $\pm$ 37.52

Table 28. Auditory Brainstem Response Data, Means ($\pm$ SD) for
Experiment Five; +10 dB ART tone pip-evoked

Wave	Preinfusion	Sample Times During Infusion (min)			
	Ketamine	05	10	20	30
Percent Latency $\pm$ SD					
I	100.00 $\pm$ 0.00	98.95 $\pm$ 5.64	100.31 $\pm$ 2.98	100.86 $\pm$ 3.89	101.15 $\pm$ 5.66
III	100.00 0.00	101.41 $\pm$ 8.00	98.87 $\pm$ 3.11	100.66 $\pm$ 5.00	100.58 $\pm$ 10.31
V	100.00 $\pm$ 0.00	101.32 $\pm$ 3.29	100.18 $\pm$ 1.69	100.75 $\pm$ 3.07	99.53 $\pm$ 2.67
Percent Amplitude $\pm$ SD					
I	100.00 $\pm$ 0.00	98.02 $\pm$ 13.77	98.48 $\pm$ 26.82	99.94 $\pm$ 37.64	91.06 $\pm$ 23.15
III	100.00 $\pm$ 0.00	106.13 $\pm$ 32.76	116.57 $\pm$ 21.01	98.51 $\pm$ 27.13	101.91 $\pm$ 49.22
V	100.00 $\pm$ 0.00	115.60 $\pm$ 57.55	112.19 $\pm$ 46.65	102.40 $\pm$ 51.50	110.36 $\pm$ 42.02

Table 29. Auditory Brainstem Response Data, Means ($\pm$ SD) for
Experiment One; -10 dB ART tone pip-evoked

Wave	Preinfusion		Sample Times During Infusion (min)			
	Xylazine	Ketamine	05	10	20	30
Percent Latency $\pm$ SD						
I	92.36 $\pm$ 13.72	100.00 $\pm$ 0.00	93.87 $\pm$ 12.11	94.33 $\pm$ 10.70	96.82 $\pm$ 13.39	96.88 $\pm$ 12.99
III	96.54 $\pm$ 9.74	100.00 $\pm$ 0.00	99.01 $\pm$ 5.39	98.82 $\pm$ 8.10	97.71 $\pm$ 5.20	99.98 $\pm$ 6.57
V	98.72 $\pm$ 4.33	100.00 $\pm$ 0.00	102.34 $\pm$ 4.05	98.85 $\pm$ 3.42	99.95 $\pm$ 2.07	102.07 $\pm$ 4.04
Percent Amplitude $\pm$ SD						
I	222.19 $\pm$ 243.13	100.00 $\pm$ 0.00	231.80 $\pm$ 387.03	116.44 $\pm$ 86.05	244.69 $\pm$ 300.15	243.99 $\pm$ 259.00
III	198.67 $\pm$ 104.16	100.00 $\pm$ 0.00	153.67 $\pm$ 104.51	148.40 $\pm$ 48.55	156.43 $\pm$ 84.35	207.19 $\pm$ 164.05
V	112.53 $\pm$ 60.17	100.00 $\pm$ 0.00	84.26 $\pm$ 30.73	80.34 $\pm$ 27.87	85.46 $\pm$ 35.29	88.28 $\pm$ 22.95

Table 30. Auditory Brainstem Response Data, Means ($\pm$ SD) for Experiment Two; -10 dB ART tone pip-evoked

Wave	Preinfusion Ketamine	Sample Times During Infusion (min)	05	10	20	30
Percent Latency $\pm$ SD						
I	100.00 $\pm$ 0.00	107.34 $\pm$ 15.24	104.42 $\pm$ 8.14	100.73 $\pm$ 7.89	107.07 $\pm$ 14.07	
III	100.00 $\pm$ 0.00	101.41 $\pm$ 7.17	99.95 $\pm$ 4.29	96.79 $\pm$ 4.50	102.12 $\pm$ 9.43	
V	100.00 $\pm$ 0.00	102.81 $\pm$ 3.15	101.73 $\pm$ 4.73	100.07 $\pm$ 3.98	103.63 $\pm$ 6.71	
Percent Amplitude $\pm$ SD						
I	100.00 $\pm$ 0.00	309.48 $\pm$ 387.72	225.66 $\pm$ 270.38	89.31 $\pm$ 82.45	360.46 $\pm$ 512.86	
III	100.00 $\pm$ 0.00	109.57 $\pm$ 57.61	124.91 $\pm$ 78.07	139.10 $\pm$ 157.21	66.20 $\pm$ 40.85	
V	100.00 $\pm$ 0.00	99.39 $\pm$ 45.28	150.65 $\pm$ 81.79	107.89 $\pm$ 55.09	93.35 49.26	

Table 31. Auditory Brainstem Response Data, Means ($\pm$ SD) for Experiment Three; -10 dB tone pip-evoked

Wave	Preinfusion Ketamine	Sample Times During Infusion (min)	05	10	20	30
Percent Latency $\pm$ SD						
I	100.00 $\pm$ 0.00	99.22 $\pm$ 10.64	96.18 $\pm$ 10.34	98.79 $\pm$ 11.27	96.26 $\pm$ 5.80	
III	100.00 $\pm$ 0.00	100.80 $\pm$ 4.51	101.01 $\pm$ 2.26	101.10 $\pm$ 5.87	100.54 $\pm$ 7.86	
V	100.00 $\pm$ 0.00	99.85 $\pm$ 3.27	100.67 $\pm$ 2.59	100.50 $\pm$ 3.05	101.57 $\pm$ 3.34	
Percent Amplitude $\pm$ SD						
I	100.00 $\pm$ 0.00	141.89 $\pm$ 119.60	167.21 $\pm$ 121.47	186.36 $\pm$ 154.91	145.61 $\pm$ 105.39	
III	100.00 $\pm$ 0.00	131.05 $\pm$ 66.19	149.45 $\pm$ 86.53	168.31 $\pm$ 148.66	125.03 $\pm$ 132.09	
V	100.00 $\pm$ 0.00	141.64 $\pm$ 143.55	127.74 $\pm$ 144.00	136.99 $\pm$ 66.74	125.03 $\pm$ 140.72	

Table 32. Auditory Brainstem Response Data, Means ($\pm$ SD) for
Experiment Four; -10 dB tone pip-evoked

Wave	Preinfusion		Sample Times During Infusion (min)			
	Ketamine	ATropine	05	10	20	30
Percent Latency $\pm$ SD						
I	100.00 $\pm$ 0.00	104.06 $\pm$ 12.89	95.46 $\pm$ 7.43	94.13 $\pm$ 4.14	96.37 $\pm$ 4.37	99.88 $\pm$ 10.14
III	100.00 $\pm$ 0.00	103.99 $\pm$ 2.87	101.67 $\pm$ 3.28	100.64 $\pm$ 2.72	99.55 $\pm$ 2.38	99.42 $\pm$ 8.58
V	100.00 $\pm$ 0.00	102.40 $\pm$ 2.28	100.82 $\pm$ 1.81	100.84 $\pm$ 2.00	99.36 $\pm$ 2.26	91.94 $\pm$ 18.10
Percent Amplitude $\pm$ SD						
I	100.00 $\pm$ 0.00	2211.57 $\pm$ 7734.82	1750.68 $\pm$ 4042.47	1745.03 $\pm$ 4044.84	3565.58 $\pm$ 8541.23	3235.34 $\pm$ 7723.39
III	100.00 $\pm$ 0.00	84.96 $\pm$ 34.42	79.89 $\pm$ 30.22	87.99 $\pm$ 18.75	98.04 $\pm$ 47.86	88.26 $\pm$ 31.23
V	100.00 $\pm$ 0.00	119.64 $\pm$ 76.98	139.54 $\pm$ 37.25	148.42 $\pm$ 47.89	147.01 $\pm$ 62.29	152.21 $\pm$ 43.16

Table 33. Auditory Brainstem Response Data, Means ($\pm$ SD) for Experiment Five; -10 dB ART tone pip-evoked

Wave	Preinfusion Ketamine	Sample Time	During Infusion (min)			
		05	10	20	30	
Percent Latency $\pm$ SD						
I	100.00 $\pm$ 0.00	98.69 $\pm$ 12.39	96.23 $\pm$ 6.81	97.04 $\pm$ 7.49	99.20 $\pm$ 3.21	
III	100.00 $\pm$ 0.00	98.71 $\pm$ 3.54	97.67 $\pm$ 3.67	96.04 $\pm$ 3.52	98.73 $\pm$ 6.49	
V	100.00 $\pm$ 0.00	100.96 $\pm$ 2.74	101.08 $\pm$ 3.29	101.19 $\pm$ 3.45	100.18 $\pm$ 3.34	
Percent Amplitde $\pm$ SD						
I	100.00 $\pm$ 0.00	139.26 $\pm$ 126.93	119.04 $\pm$ 62.84	116.69 $\pm$ 103.24	125.83 $\pm$ 63.94	
III	100.00 $\pm$ 0.00	160.67 $\pm$ 128.44	216.76 $\pm$ 210.91	167.33 $\pm$ 107.24	161.72 $\pm$ 148.46	
V	100.00 $\pm$ 0.00	125.17 $\pm$ 48.15	131.95 $\pm$ 37.04	111.05 $\pm$ 30.40	132.70 $\pm$ 40.82	

by experiment and length of time elapsed during infusion. Again the effect of saline in Experiment one was different from all other drug combinations. The amplitude was affected by experiment. The mean amplitude for Experiment one was significantly different from all experiments except Experiment four. Experiment two was significantly different from the rest and had the shortest amplitude. The mean latency of wave V for Experiment one was only significantly different from Experiment five. This latency was also affected by the interaction of cat and time. Amplitude was altered by experiment and sample time. As with latency, the mean amplitude of Experiment one was significantly different from that of Experiment five. Drug was not significant for wave VI latency but was for the amplitude although the Scheffe test failed to isolate any differences.

Summarizing the effects of these experiments on the click evoked response (Table 24), (Figures 5-8), the latency of wave I was not significantly affected by any experiment. The amplitude of this wave was significantly ($p < .05$) decreased from that of Experiment one with all other experiments. The latency of wave II was only significantly increased by atropine and nicotine (Experiment four), while its amplitude was significantly decreased by all experiments compared to Experiment one. Wave III/IV latency was increased significantly ($p < .05$) above the latency during Experiment one by the rest of the experiments. The amplitude of this wave was significantly altered by Experiments two, three and five. Wave V latency was only significantly increased by Experiment four and its amplitude by Experiments two and five. Wave VI latency was not significantly

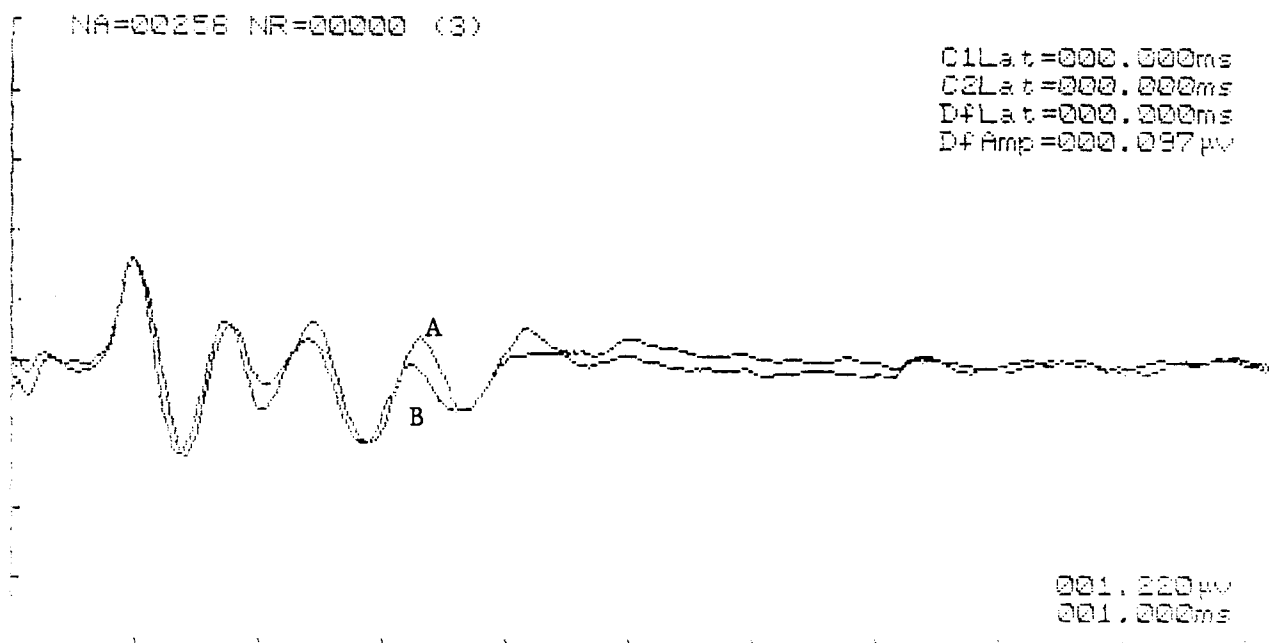


Figure 5. Examples of auditory brainstem responses as a result of click stimuli delivered to the left ear at an intensity of 90 dB HL during Experiment two. Each waveform is an average of 256 repetitions. The responses illustrate changes as a result of nicotine administration at $30 \text{ ug kg}^{-1}\text{min}^{-1}$ (A) overlaid on the same cat's preinfusion recording (B). Horizontal axis=1 ms/div; vertical axis=1 $\mu\text{V}/\text{div}$.

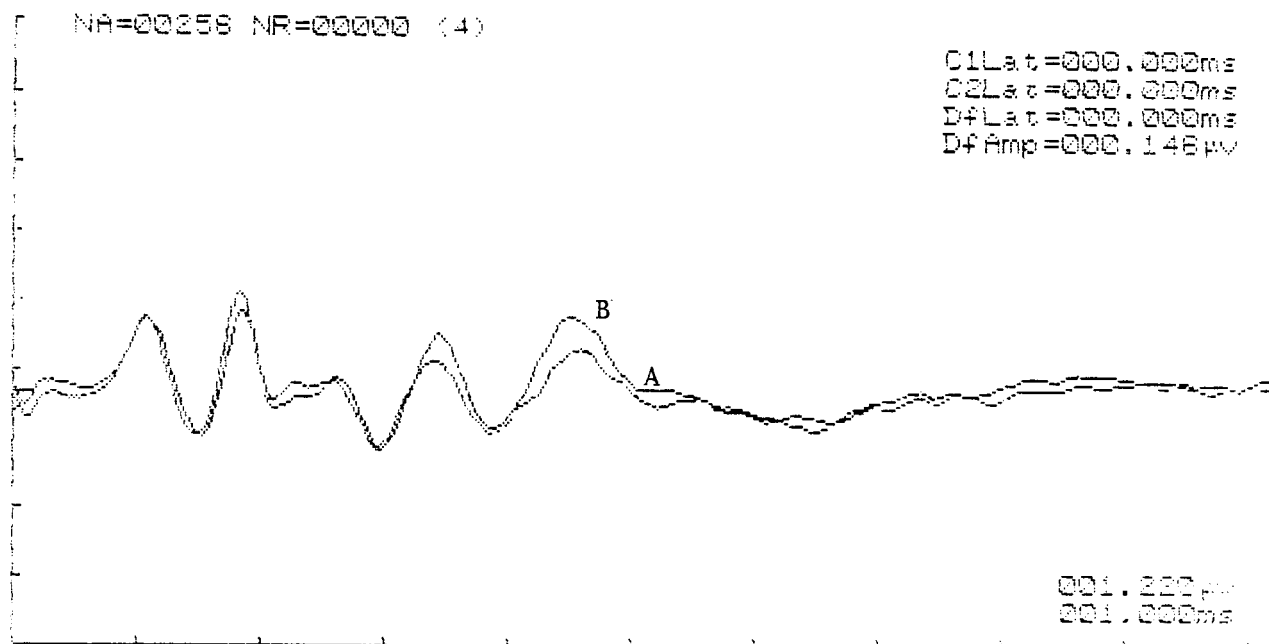


Figure 6. Examples of auditory brainstem responses as a result of click stimuli delivered to the left ear at an intensity of 90 dB HL during Experiment three. Each waveform is an average of 256 repetitions. The responses illustrate the effects of nicotine administration at $60 \text{ ug kg}^{-1}\text{min}^{-1}$ (A) overlaid on the same cat's preinfusion recording (B). Horizontal axis=1 ms/div; vertical axis=1 uV/div.

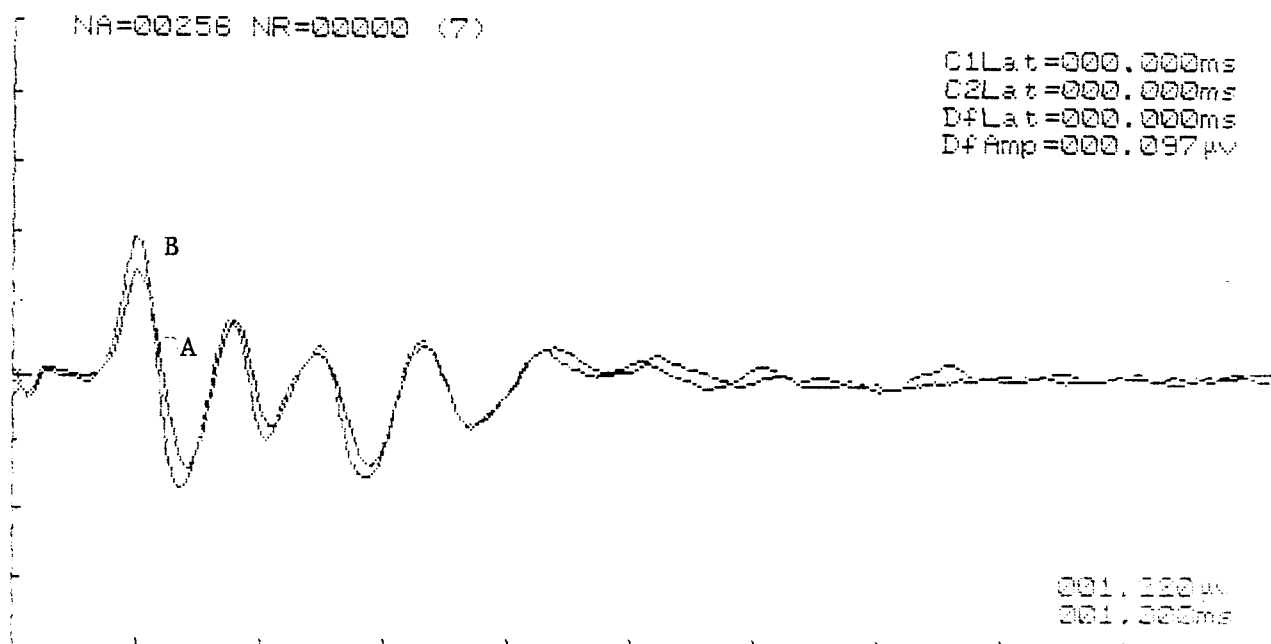


Figure 7. Examples of auditory brainstem responses as a result of click stimuli delivered to the left ear at an intensity of 90 dB HL during Experiment four. Each waveform is an average of 256 repetitions. The responses illustrate the effects of atropine and nicotine administration (A) overlaid on the same cat's preinfusion recording (B). Horizontal axis=1 ms/div; vertical axis=1 µV/div.

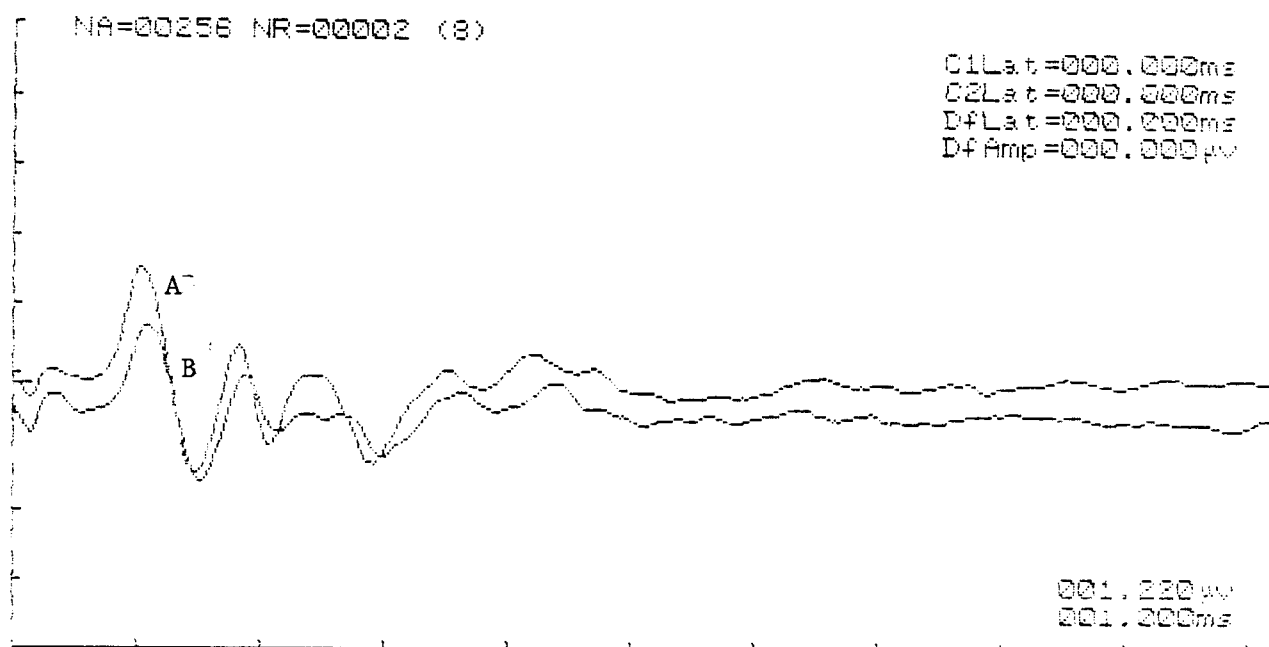


Figure 8. Examples of auditory brainstem responses as a result of click stimuli delivered to the left ear at an intensity of 90 dB HL during Experiment five. Each waveform is an average of 256 repetitions. The responses illustrate the effects of 5-MeODMT at 10 µg kg⁻¹ (A) overlaid on the same cat's preinjection recording (B). Horizontal axis=1 ms/div; vertical axis=1 uV/div.

altered by any experiment while the amplitude was but the Scheffe test did not isolate the experiment.

Atropine alone in Experiment four was only significant for the amplitude of wave VI when Experiment four was compared to Experiment three. Sample time was not significant for nicotine at $40 \text{ ug kg}^{-1} \text{ min}^{-1}$ compared to nicotine at $60 \text{ ug kg}^{-1} \text{ min}^{-1}$.

There were no significant differences in ABR elicited with either 80 or 70 dBHL clicks (Tables A-14 through A-23) for any wave (the only exception was cat for the amplitude of wave III/IV at 80 dBHL).

The ABR elicited with tone pips (Tables A-24 through A-30) were similar to the ABR elicited by clicks in that cat was always significant, and the cat-experiment interaction was often significant. The latency of wave I was affected by experiment at both intensities. The mean latencies for Experiments one, two and three were not different from each other. At +10 dB ART Experiments four and five were different from each other and all other experiments. The amplitude of the -10 dB ART evoked response was not significantly affected by the experiment but the amplitude elicited by +10 dBHL was. In this case Experiment five had the highest amplitude and Experiment one had the lowest, and both were different from the rest. Wave III latency was affected at both intensities by experiment and the effect was basically the same with Experiment three having the longest and Experiments one and five having the shortest latencies. Experiment three was, in both cases, significantly different from all the others. For amplitude there was greater variation. Experiment five had the largest amplitude in both cases, but was not significantly different

from Experiments one or two for -10 dB ART elicited ABR while it was different from both of these with the +10 dBHL elicited ABR. Experiments three and four were not different at either intensity. The amplitude and latency of wave V were significantly affected by experiment at both intensities. The comparison of reflex threshold to the tone pip elicited ABR revealed that threshold for the AR was not significant in predicting the ABR amplitude or latency of any wave.

The latency of wave I evoked by the higher intensity tone pip stimulus was significantly affected by Experiments four and five, and the amplitude was increased by all Experiments when compared to Experiment one (Tables 35 and 36). Wave III latency was significantly altered by Experiments two, three, and four and its amplitude by all experiments when compared to Experiment one. Latency of wave V was significantly affected by Experiments three and five and amplitude by Experiments two, three and five. Wave I latency of the ABR evoked by the lower intensity tone pip stimulus was significantly affected by Experiments four and five. None of the experiments significantly altered the amplitude of this wave. Wave III latency and amplitude values during Experiments three and four were both different from those during Experiment one. The latency of wave V was significantly affected by Experiments four and five and its amplitude by Experiments three, four and five.

Table 34. Auditory Brainstem Response; Summary of Scheffe Test:
(90 dB HL click-evoked)

Exp. No.	Latency Wave				Amplitude Wave			
	I	II	III/IV	V	I	II	III/IV	V
1	A*	B	B	B	A	A	A	A
2	A	AB	A	AB	BC	B	C	B
3	A	AB	A	AB	C	B	B	AB
4	A	A	A	AB	B	B	B	AB
5	A	AB	A	A	BC	B	B	B

*Experiments with the same letter are not significantly different ($p > .05$)

Table 35. Auditory Brainstem Response; Summary of Scheffe Test:
(+10 dB ART tone pip-evoked)

Exp. No.	Latency			Amplitude		
	I	Wave III	V	I	Wave III	V
1	A*	D	B	C	C	C
2	A	BC	B	B	B	A
3	A	A	A	B	AB	C
4	B	B	B	B	B	B
5	C	CD	C	A	A	A

*Experiments with the same letter are not statistically significant ($p > .05$)

Table 36. Auditory Brainstem Response; Summary of Scheffe Test:
(-10 dB ART tone pip-evoked)

Exp. No.	Latency Wave			Amplitude Wave		
	I	III	V	I	III	V
1	A*	C	A	A	A	A
2	A	BC	A	A	A	AB
3	AB	A	A	A	B	C
4	BC	B	B	A	B	C
5	C	C	B	A	A	B

*Experiments with the same letter are not statistically
Significant ($p > .05$)

CHAPTER V

DISCUSSION

1. ACOUSTIC REFLEX

Threshold intensity for the AR was as previously reported, the contralateral reflex was higher than that for the ipsilateral reflex. (Borg and Moller, 1968). Threshold was significantly different ($p < .05$) for both nicotine dosages. Subject variability with time was considered important by Djuipesland (1980); however in this study the individual cats did not change with time. The same cats had consistently high thresholds. Atropine blocked the ipsilateral response to nicotine. The time elapsed during infusion was considered significant but since only two (or three for xylazine) recordings were made these results are perhaps the same as showing drug to be significant. Nicotine has been shown to excite the neuromuscular junction and to increase the EMG response of various muscles (Gilman, et al., 1980; Henningfield, et al., 1983; Domino, 1979). The response to nicotine reported here may be due solely to the action of nicotine on the middle ear muscles by directly exciting them, thus making them more sensitive to reflex stimulation.

The AR latency was significantly affected by threshold level, side and stimulus intensity. A relationship among threshold, intensity and latency has been documented by McPherson and Thompson (1977) and Dallos (1964). They reported that latency is affected by factors which alter the threshold, and that latency is inversely

proportional to stimulus intensity. Dallos (1964) found that the latency decreases with increasing stimulus intensity up to 30 dB above ART. Latency is also shorter ipsilaterally than contralaterally, and this is related to the greater sensitivity of the ipsilateral reflex. Latency was not altered by any of the experiments even though they did affect the threshold. According to McPherson and Thompson (1977), this should have altered the latency. Obviously the effect on threshold was not great enough to result in latency changes.

The amplitude of the AR response increased with increasing stimulus intensity (Jerger and Hayes, 1983) and was greater ipsilaterally than contralaterally. The drug effects on amplitude were consistent between sides and stimulus intensities. Recordings of the AR made after infusion during Experiment four consistently had the greatest amplitudes while those recorded after injection during Experiment five had the shortest. Mean amplitude for Experiment four was significantly different from Experiment one ($p < .05$) ipsilaterally at both intensities and contralaterally at +10 dB ART. This amplitude measurement ranked immediately above the value for the nicotine dosage of $60 \text{ ug kg}^{-1} \text{ min}^{-1}$. In this case it appears that atropine enhanced the effect of nicotine, possibly by blocking competitive muscarinic activity. The effect of 5-MeODMT was depressive on the amplitude although this was only significantly different from saline infusion contralaterally at an intensity of +20 dBHL ART. Even though reflex activity in the cats treated with 5-MeODMT was often close to the value for nicotine at $40 \text{ ug kg}^{-1} \text{ min}^{-1}$, in every case amplitude values

for Experiment two were not significantly different from those of Experiment one. Therefore a common mode of action is questionable. Amplitude expressed as a percent of the amplitude with ketamine in most instances did not show any differences between experiments.

It appears that the effects of the various treatments on the AR in this study were mainly due to the action of nicotine on middle ear muscles at the neuromuscular junction. The contractile speed of the muscles was apparently not changed by the drugs. Nicotine may have raised or lowered the excitability threshold of the muscles and slightly increased the amplitude of the response. The significant difference in amplitude seen with atropine administration may have been a reflection of blocking inhibitory effects on amplitude, somewhere in the reflex pathway. The effects of 5-MeODMT in decreasing amplitude, could have been due to a central effect, possibly inhibiting. The only times that this effect was not significantly different from either nicotine dose, it was also not different from the result of saline infusion. Therefore, it is doubtful that nicotine and serotonin had similar actions on the AR. The frequent differences seen between cats and the cat-drug interaction show that the individuals reacted differently to the drugs. This is not an uncommon reaction (Gilman, et al., 1980).

2. AUDITORY BRAINSTEM RESPONSE

With the ABR, as with the AR, many previously reported responses were observed. The latency and amplitude measurements were significantly different ($p < .05$) with respect to the two stimulus

types used (clicks or tone pips). In addition latency and amplitude measurements at the different intensity levels within each stimulus type were significant ($p < .05$). Specifically the Scheffe test revealed significant amplitude and latency differences between the responses evoked by 90, 80 and 70 dBHL clicks and found the mean latencies increased with decreasing stimulus intensity and the amplitude decreased with decreasing stimulus intensity (Moore, 1983). With pips (2KHz) as a stimulus, there were also differences. The +10 dBHL stimulus consistently gave a shorter latency and greater amplitude than those evoked by the -10 dB pips.

Waveform morphological characteristic did not change during the experiments. Waves III and IV together formed one wave in most cases and were therefore analyzed as one wave. On occasion when there was a separation of waves III and IV, the one with the greatest amplitude (wave IV) was measured. When separate, wave III was usually only a notch on the upward slope of IV and had no measurable amplitude. It has been stated that there is no III/IV complex in cats (Buchwald, 1983) but this was clearly not the case in my study (Figure 3). The effect of side was not significant ($p > .05$) during the initial xylazine recordings (Table A-6) and thus it was decided to record only from one ear during the course of the experiment. Analysis of all ABR (amplitude and latency) showed that cat, intensity, sex, stimulus frequency and wave were all significant ($p < .05$). The responses evoked by pips were quite variable. Wave V, however, was the most consistent and easily identified (Weber and Folsom, 1977). Problems

in identifying all six waves led to measuring only waves I, III and V. Even then, wave I was difficult to delineate in the -10 dB responses. Understandably, the greater the pip intensity used the better the response, and cats with higher thresholds had the best pip responses. Statistical analysis of clicks elicited at 70 and 80 dBHL yielded no significant differences as a result of drug administration. This may have occurred because of greater variability among cats and the fact that only two recordings were made (three during Experiment one).

Recordings made with the 90 dBHL click stimulus were the most consistent and provided the best results. With all waves except VI, latencies were shorter and amplitude was greater than in other experiments. Drug treatments affected the latency of all waves except I and VI. The drugs caused a significant change in the amplitude of all waves. The latency and amplitude of all waves showed significant differences between cats and for the cat-drug interaction. Not only was this evident during the experiments, but was also not surprising since, as mentioned earlier, differences in the individual reactions to drugs is normal (Gilman, et al., 1980). The latency of wave I was not significantly altered by any of the drugs. The amplitude during all subsequent experiments was decreased ($p < .05$) from saline values. The two nicotine dosages produced the greatest changes. Experiment three was different from Experiment four, but Experiment two was not. Atropine caused an apparent blockade of the action of nicotine. The decrease in amplitude was consistent with all work done with the ABR and nicotine (Bhargava, et al., 1978, 1981; Friedman and Meares, 1980). It is also in agreement with the work using ACh where this

neurotransmitter was found to decrease the amplitude of cochlear microphonics and was considered to be an inhibitory agent in the cochlea (Brown, 1969; Tamara, 1966).

Wave II latency during experiment four was statistically different from all other experiments including the saline controls. However, the effect of nicotine was not significantly different from atropine ($p < .05$). The amplitude measurements were very similar to those seen with wave I. This is not surprising since they probably have the same or share the same generators, specifically the auditory nerve and cochlear nuclei (Moller, 1980; Borg, 1981; Achor and Starr, 1980a,b). The two nicotine levels produced the lowest ABR amplitude but were not different from any of the other treatments except the saline control.

Waves III/IV and V were very similar to each other in their response to the experimental treatments, again probably inferring common or overlapping generators. Both of these waves when recorded during Experiment five had the longest latency and were statistically different from Experiment one. With wave III/IV latency, the saline control was significantly different from all of the other treatments. Analysis of wave V latency separated Experiment five effects from those of Experiment one. As for amplitude there was no significant difference for either wave between the effects of nicotine at $60 \mu\text{g kg}^{-1} \text{ min}^{-1}$ and those of the same dose of nicotine plus atropine. Wave III/IV amplitude in Experiments three, five, and two was different ($p < .05$) from Experiment one. Wave V amplitude from the saline

control experiment was significantly different ($p < .05$) from that of either Experiment two or five. The role of 5-MeODMT was similar to that of nicotine especially with respect to the effects of a lower dose on amplitude. The effects of the drugs on wave VI were not separated by the Scheffe comparison of the means, even though for other waves experiment was significant for amplitude.

Statistical analysis of the response evoked by pips demonstrated some degree of similarity between the stimulus intensities. The results from the +10 dB ART pip was the most consistent. In contrast to the response evoked by clicks, saline did not always have the shortest latency and greatest amplitude. These trends appear to indicate that Experiment five had ABR with the shortest latency and the highest amplitude than that in other experiments. Nicotine at $60 \text{ ug kg}^{-1} \text{ min}^{-1}$ caused a longer latency but had mixed amplitude effects. There were significantly lower amplitudes for wave V at both intensity levels. Considering that wave V was the most reliable and the easiest to identify, the results for this wave are probably more meaningful than the others. Atropine reversed the effects of nicotine at $60 \text{ ug kg}^{-1} \text{ min}^{-1}$.

Wave V Latency and amplitude, produced by tone pips were considerably different from that produced by click stimulus. One cannot conclude that they reflect the same physiological events and it may even be that the effects of the drugs were specifically related to the nature of the stimulus. The relationship between the threshold of the reflex and the amplitude of the ABR, considered to be significant by Hayes and Jerger (1981) was not different ($p > .05$) in

this study. The change in threshold as a result of nicotine administration thus appears to have had no effect on the ABR recording. This is in agreement with the reports by Borg (1981) that middle ear muscles probably have little role if any in the ABR response. There were no changes in the response during the period of nicotine infusion. Possibly nicotine was being rapidly metabolized and/or washed out of brainstem areas at about the same rate that it was being infused. Studies cited earlier (Edwards and Warburton, 1983; McKinnis, 1967) described the rapid metabolism of nicotine and its clearance from the brain. The 5-MeODMT treatment was given in one injection and apparently was not metabolized to any appreciable degree during the experiment. The effect of cat and the interaction between cat and drug, as mentioned previously was not surprising.

A comparison of the responses at matched times during infusion of the two nicotine dosages failed to establish any differences in latency or amplitude. Analysis of Experiments two and three only revealed a difference for the amplitude of wave III/IV for the click-evoked response. It therefore appears that there were not a significant dose-response in this case. A dosage of $80 \text{ ug kg}^{-1} \text{ min}^{-1}$ proved fatal to one cat during preliminary trials.

Atropine only significantly blocked the nicotine response in a few cases. It appears that atropine only partially blocks the action of nicotine, causing the response to be more like that for the lower nicotine dose. Atropine alone failed to increase the amplitude of the ABR in this study. This is in contrast to the results obtained

by Mendal (1977). The combination of atropine and nicotine was never greater in amplitude than that of saline control recordings. Atropine did appear to lessen the depressive effects of nicotine on the amplitude of the ABR response.

The speculated effect of nicotine on the release of serotonin was reported by Bhargava et al. (1977). The decrease in amplitude he saw as a result of serotonin administration was similar to the decrease in my study with 5-MeODMT which was significantly different from the amplitude of responses during Experiment one. There was also an increase in latency associated with this drug. The effects of 5-MeODMT appear to have occurred in a manner unlike that of nicotine. It thus seems that the effects of nicotine in this project may have been due to an action on cholinergic receptors and therefore had little or no action on serotonin.

As to which neurotransmitters may an influence on the individual waves (Figure 9), ACh and serotonin may have been influential on the amplitude of wave I. Wave II latency was only altered significantly (decreased) by atropine so the influence of ACh, especially muscarinic receptors is indicated. It was suggested by Bradley, (1967) that stimulation of muscarinic receptors results in a different action than stimulation of nicotinic receptors. This may have been the case in this project. The amplitude of the ABR response was decreased by all of the drug treatments. This could indicate a decreased number of neurons or an inhibitory effect. The latency of wave III/IV was increased by all of the drugs and the amplitude decreased by both dosages of nicotine and also 5-MeODMT. Wave V was affected

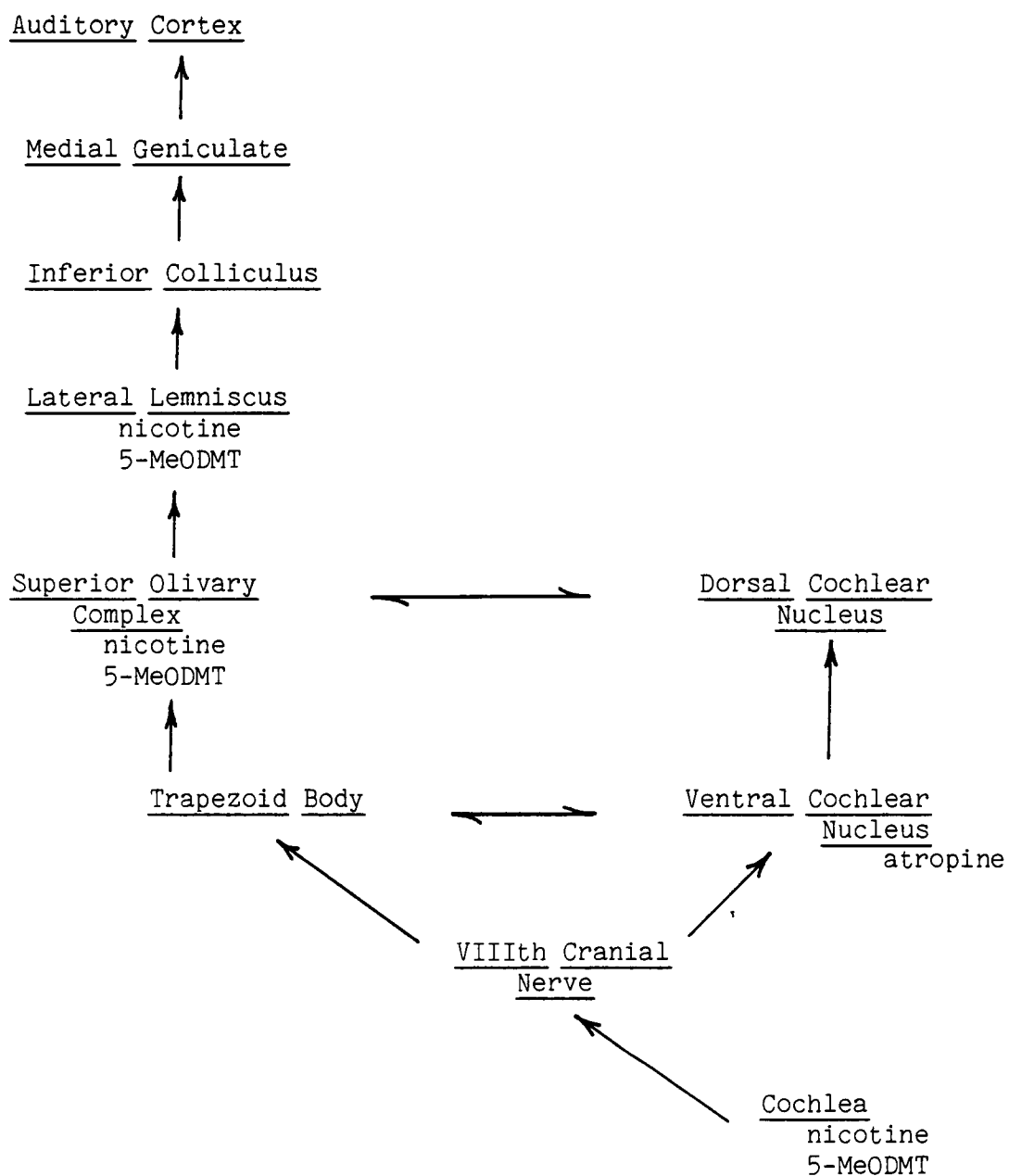


Figure 9. Auditory pathway and hypothesized drug action sites

predominantly by 5-MeODMT, latency being longer and amplitude smaller. Nicotine at the lower dosage also significantly decreased the amplitude.

CHAPTER VI

CONCLUSIONS

1. Nicotine significantly decreased ($p < .05$) the AR threshold both ipsilaterally and contralaterally. This was probably due to the direct action of nicotine on the neuromuscular ACh receptors.

2. Atropine significantly increased ($p < .05$) the AR amplitude ipsilaterally at both intensities and contralaterally at +10 dB ART. This was probably due to blockade of inhibitory effects by atropine.

3. The amplitude of the AR at +20 dB ART was significantly ($p < .05$) decreased by 5-MeODMT. This was thought to be due to some central inhibitory effect of the drug.

4. Nicotine caused a significant ($p < .05$) in the latency of wave III/IV for the click-evoked response and waves III and V for the pip-evoked response. These changes were probably due to an inhibitory effect of nicotine.

5. Nicotine significantly decreased ($p < .05$) the amplitude of waves I, II, III/IV and V of the click-evoked response and wave III (at +10 dB ART only) and V for the pip-evoked ABR. This may have been due to an inhibitory effect of nicotine.

6. Nicotine increased the amplitude of the pip-evoked waves I, III and V at +10 dB ART.

7. Only the higher dose of nicotine (Experiment three) had a significant ($p < .05$) effect on the -10 dB ART pip-evoked response.

8. The only significant difference in dose response was seen with the pip-evoked responses where the amplitude of wave V increased

during Experiment two and decreased during Experiment three. Therefore, the nicotine was probably being metabolized at about the same rate as it was being infused.

9. The measurements made during Experiment four were only significantly different ($p < .05$) from those during Experiment three for wave I amplitude of the click-evoked response. The two experiments were significantly different for many of the waves when tone pips were used to evoke the response, and where usually not significantly different from those of Experiment two. It was concluded that at most the atropine partially blocked the response to nicotine, but this effect was minor.

10. The effects of Experiment five on the ABR were often significantly different ($p < .05$) from those of either nicotine dosage. It was felt that the change due to this drug were independent of those seen with nicotine.

11. Nicotine was probably acting on the ACh receptor sites in the auditory pathway and had an independent effect from 5-MeODMT.

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APPENDIX
STATISTICAL ANALYSIS

Table A-1. Acoustic Reflex Regression Analysis, All Variables

Model	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	51	33783.84	6.17	.0001
Error	217	23279.29		
Total	268	57063.13		
Cat	7	3078.31	4.10	.0003
Type	1	8506.21	79.29	.0001
Int	1	8159.83	76.06	.0001
Thresh	6	2088.24	3.24	.005
Exper	4	695.60	1.62	.2
Time	1	158.76	0.74	.5
Cat*Exper	19	2032.68	1.00	.5
Cat*Time	1	1360.44	1.15	.4
<u>Amplitude</u>				
Model	51	3737.76	11.95	.0001
Error	217	1330.67		
Total	268	5068.73		
Cat	7	637.19	14.84	.0001
Type	1	3.57	0.58	.45
Int	1	152.38	24.85	.0001
Thresh	6	252.45	6.86	.0001
Exper	4	864.11	35.22	.0001
Time	2	21.67	1.77	.17
Cat*Exper	19	643.79	5.53	.0001
Cat*Time	11	266.86	3.96	.0001
Scheffe of Exper				
	4	>	3	>
	A		B	
			B	
			B	
				5
				C

Table A-1 (continued)

Source	df	Sum of Squares	F	Prob. > F
<u>Percent Amplitude</u>				
Model	51	204762.51	3.45	.0001
Error	217	252840.70		
Total	268	457603.21		
Cat	7	51841.20	6.35	.0001
Type	1	170.07	0.15	.70
Int	1	997.94	0.86	.36
Thresh	1	19818.19	2.83	.01
Exper	4	7146.64	1.53	.19
Time	2	16091.33	6.91	.001
Cat*Exper	19	60084.87	2.71	.0003
Cat*Time	11	53200.78	4.15	.0001
<u>Threshold Change</u>				
Model	51	4089.50	16.87	.0001
Error	217	1031.14		
Total	268	5120.63		
Cat	7	865.83	26.03	.0001
Type	1	2.73	0.57	.5
Int	1	1.30	0.27	.6
Thresh	6	1196.48	41.97	.0001
Exper	4	543.66	28.60	.0001
Time	2	50.78	5.43	.005
Cat*Exper	19	642.02	7.11	.0001
Cat*Time	11	75.79	1.45	.2
Scheffe of Exper				
	5	>	4	>
	A		A	
	1	>	2	>
	A		B	
	3			
	B			

Table A-1 (continued)

Source	df	Sum of Squares	F	Prob. > F
<u>Threshold</u>				
Model	15	13214.56	50.79	.0001
Error	253	4621.21		
Total	268	17935.71		
Cat	7	4367.35	43.64	.0001
Int	1	0.61	0.07	.85
Type	1	56.40	6.26	.01
Exper	4	1094.21	30.37	.0001
Time	2	655.63	36.39	.0001
Cat*Exper	19	1239.77	7.24	.0001
Cat*Time	11	383.04	3.87	.0001
Scheffe of Exper	4 > 5 > 3 > 2 > 1 A A B B C			

Table A-2. Acoustic Reflex Regression Analysis,
Ipsilateral; +10 dB ART

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	49	8864.22	2.67	.02
Error	17	1151.05		
Total	55	10015.27		
Cat	7	942.61	1.99	.12
Thresh	6	1274.05	3.14	.03
Exper	4	439.85	1.62	.21
Time	2	2276.64	1.68	.22
Cat*Exper	19	1441.13	1.12	.4
Cat*Time	11	1774.95	2.38	.052
<u>Amplitude</u>				
Model	49	1319.93	2.45	.023
Error	17	187.16		
Total	66	1507.09		
Cat	7	155.81	2.02	.11
Thresh	6	95.66	1.45	.25
Exper	4	128.72	3.83	.02
Time	2	6.41	0.29	.75
Cat*Exper	19	180.61	0.86	.62
Cat*Time	11	157.34	1.30	.30
Scheffe of Exper	4 > 3 > 2 > 1 > 5			
	A	A	A	
		B	B	B

Table A-2 (continued)

Source	df	Sum of Squares	F	Prob. > F
<u>Percent Amplitude</u>				
Model	49	136734.95	2.11	.05
Error	17	22435.50		
Total	66	15917.45		
Cat	7	33824.54	3.66	.01
Thresh	6	28518.25	3.60	.02
Exper	4	4262.87	0.81	.54
Time	2	5675.33	2.15	.15
Cat*Exper	10	43603.03	1.74	.13
Cat*Time	11	42935.27	2.96	.02
<u>Threshold Change</u>				
Model	49	1479.04	6.03	.0001
Error	17	85.14		
Total	66	1564.18		
Cat	7	218.66	6.24	.001
Thresh	6	378.32	12.52	.0001
Exper	4	216.77	10.02	.0002
Time	2	7.84	0.78	.5
Cat*Exper	19	325.99	3.43	.007
Cat*Time	11	43.01	0.78	.66
Scheffe of Exper 4 > 1 > 5 > 2 > 3				
	A	A	A	B B
			C	C

Table A-3. Acoustic Reflex Regression Analysis,
Ipsilateral; +20 dB ART

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	49	1848.84	1.26	.3082
Error	17	508.87		
Total	66	2357.71		
Cat	7	160.17	0.76	.02
Thresh	6	109.14	0.61	.72
Exper	1	87.05	1.56	.23
Time	2	10.02	0.17	.95
Cat*Exper	14	11.22	1.08	.44
Cat*Time	11	186.48	0.57	.83
<u>Amplitude</u>				
Model	49	1202.07	2.78	.12
Error	17	149.33		
Total	66	1351.91		
Cat	7	191.92	3.11	.03
Thresh	6	27.62	0.52	.78
Exper	4	184.68	5.24	.006
Time	2	1.37	0.08	.93
Cat*Exper	19	196.37	1.17	.37
Cat*Time	11	94.95	0.95	.5
Scheffe of Exper 4 > 3 > 1 > 2 > 5				
A B B B B				

Table A-3 (continued)

Source	df	Sum of Squares	F	Prob. > F
<u>Percent Amplitude</u>				
Model	49	96562.01	1.34	.3
Error	17	24992.29		
Total	66	121554.29		
Cat	7	21666.98	2.11	.1
Thresh	6	2533.65	0.29	.94
Exper	4	631.90	0.11	.1
Time	2	3299.18	1.12	.35
Cat*Exper	19	21034.87	0.75	.73
Cat*Time	11	23969.93	1.48	.23

Table A-4. Acoustic Reflex Regression Analysis,
Contralateral; +10 dB ART

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	49	18451.89	2.35	.02
Error	17	2728.02		
Total	66	21179.91		
Cat	7	3867.60	3.44	.02
Thresh	6	3529.23	3.67	.02
Exper	4	393.36	0.61	.66
Time	2	14.19	0.04	.96
Cat*Exper	19	4818.07	1.58	.17
Cat*Time	11	3327.34	1.88	.12
<u>Amplitude</u>				
Model	49	853.12	2.36	.03
Error	17	125.48		
Total	46	977.60		
Cat	7	191.77	3.71	.013
Thresh	6	13.77	0.31	.92
Exper	4	240.96	8.16	.0007
Time	2	3.44	0.23	.79
Cat*Exper	19	162.67	1.16	.38
Cat*Time	11	75.07	0.92	.54
Scheffe of Exper	4 > 3 > 1 > 2 > 5			
	A	B	B	B B

Table A-4 (continued)

Source	df	Sum of Squares	F	Prob. > F
<u>Percent Amplitude</u>				
Model	49	73466.78	0.89	.6446
Error	11	28787.48		
Total	66	102254.26		
Cat	7	12114.57	1.02	.45
Thresh	6	5395.37	0.53	.78
Exper	4	2430.40	0.36	.83
Time	2	4348.62	1.28	.30
Cat*Exper	19	34510.39	1.07	.45
Cat*Time	11	17254.24	0.93	.54
<u>Threshold Change</u>				
Model	49	1004.73	6.35	.0001
Error	18	58.14		
Total	67	1062.87		
Cat	7	223.42	9.88	.0001
Thresh	6	272.72	14.07	.0001
Exper	4	123.93	9.59	.0002
Time	2	1.87	0.29	.75
Cat*Exper	19	212.80	3.47	.006
Cat*Time	11	28.47	0.80	.64
Scheffe of Exper 5 > 1 > 4 > 3 > 2				
	A	A	A	
		B	B	B
		C	C	C

Table A-5. Acoustic Reflex Regression Analysis,
Contralateral; +20 dB ART

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	49	4366.88	1.26	.3049
Error	18	1276.54		
Total	67	5643.42		
Cat	7	1490.22	3.00	.03
Thresh	6	320.78	0.75	.61
Exper	4	124.09	0.44	.48
Time	2	115.28	0.81	.46
Cat*Exper	19	953.45	0.71	.77
Cat*Time	11	272.98	0.35	.96
<u>Amplitude</u>				
Model	49	888.99	1.94	.06
Error	18	168.11		
Total	67	1057.09		
Cat	7	125.62	1.92	.13
Thresh	6	24.63	0.44	.84
Exper	4	237.87	6.37	.002
Time	2	29.24	1.57	.24
Cat*Exper	19	210.68	1.19	.36
Cat*Time	11	114.88	1.31	.29
Scheffe of Exper	4 > 3 > 1 > 2 > 5			
	A	A	A	A B

Table A-5 (continued)

Source	df	Sum of Squares	F	Prob. > F
<u>Percent Amplitude</u>				
Model	49	56082.39	1.27	.29
Error	18	16448.14		
Total	67	73430.53		
Cat	7	8490.99	1.33	.29
Thresh	6	3855.06	0.70	.65
Exper	4	3855.22	1.05	.41
Time	2	3846.46	2.10	.15
Cat*Exper	19	18422.09	1.06	.45
Cat*Time	11	14438.07	1.44	.24

Table A-6. Auditory Brainstem Response Regression Analysis,
All Variables

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	20	299.95	599.21	.0001
Error	212	5.31		
Total	232	305.26		
Cat	5	0.39	3.88	.0046
Side	1	0.01	0.26	.61
Int	8	1.94	9.71	.0001
Frequency	1	13.85	553.23	.0001
Wave	5	275.19	2198.94	.0001
<u>Amplitude</u>				
Model	20	300.28	31.63	.0001
Error	212	100.65		
Total	232	400.93		
Cat	5	86.78	45.70	.0001
Side	1	0.19	0.34	.53
Int	8	23.54	6.20	.0001
Frequency	1	61.11	128.73	.0001
Wave	5	65.86	28.17	.0001

Table A-7. Auditory Brainstem Response Regression Analysis,
All click-evoked Variables

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	23	1953.65	7081.79	.0001
Error	1342	16.10		
Total	1365	1969.79		
Cat	7	4.11	48.96	.0001
Exper	4	1.03	21.39	.0001
Int	2	3.71	154.81	.0001
Time	5	0.18	3.04	.10
Wave	5	1.94	3.77	.0001
Scheffe of Int 70 > 80 > 90 A B C				
<u>amplitude</u>				
Model	23	1023.65	112.51	.0001
Error	1342	530.88		
Total	1365	1534.53		
Cat	7	273.43	98.74	.0001
Exper	4	24.35	15.76	.0001
Int	2	156.69	180.05	.0001
Time	5	2.63	1.33	.25
Wave	5	502.54	254.07	.0001
Scheffe of Int 90 > 80 > 70 A B C				

Table A-8. Auditory Brainstem Response Regression Analysis,
tone pip-evoked Variables

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	21	932.05	1203.73	.0001
Error	990	38.33		
Total	1010	970.38		
Cat	7	22.08	81.46	.0001
Exper	4	5.40	84.87	.0001
Int	1	7.74	199.86	.0001
Time	5	0.39	2.01	.07
Wave	3	887.11	7724.04	.0001
Scheffe of Int -10 > 10				
A B				
<u>Amplitude</u>				
Model	20	104.67	60.20	.0001
Error	990	190.74		
Total	1010	190.74		
Cat	7	53.89	88.34	.0001
Exper	4	7.39	21.24	.0001
Int	1	35.12	403.91	.0001
Time	5	0.11	0.26	.93
Wave	3	9.94	38.11	.009
Scheffe of Int 10 > -10				
A B				

Table A-9. Auditory Brainstem Response Regression Analysis,
Wave I; 90 dBHL click-evoked

Source	df	Sun of Squares	F	Prob. > F
<u>Latency</u>				
Model	77	0.07	2.37	.001
Error	72	0.03		
Total	149	0.09		
Cat	7	0.006	2.42	.03
Exper	4	0.001	0.85	.50
Time	4	0.006	4.27	.004
Exper*Time	16	0.003	0.53	.92
Cat*Exper	18	0.04	5.89	.0001
Cat*Time	28	0.01	1.00	.18
<u>Amplitude</u>				
Model	77	2.21	3.24	.0001
Error	72	0.64		
Total	149	2.85		
Cat	7	0.14	2.30	.04
Exper	4	0.50	14.05	.0001
Time	4	0.16	4.57	.002
Exper*Time	16	0.17	1.18	.30
Cat*Exper	18	1.09	6.86	.0001
Cat*Time	28	0.12	0.48	.98
Scheffe of Exper	1 > 4 > 5 > 2 > 3			
	A	B	B	B
		C	C	C

Table A-10. Auditory Brainstem Response Regression Analysis,
Wave II; 90 dBHL click-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	77	0.06	2.74	.0001
Error	72	0.02		
Total	149	0.08		
Cat	7	.009	4.88	.0002
Exper	4	.005	4.71	.002
Time	4	.006	5.21	.001
Exper*Time	16	.002	0.54	.92
Cat*Exper	18	.029	6.02	.0001
Cat*Time	28	.007	0.90	.61
Scheffe of Exper	4 > 2 > 5 > 3 > 1 A A A A B B B B			
<u>Amplitude</u>				
Model	77	7.40	3.54	.0001
Error	72	1.96		
Total	149	9.36		
Cat	7	0.47	2.46	.03
Exper	4	1.24	11.45	.0001
Time	4	0.05	0.45	.77
Exper*Time	16	0.44	1.01	.46
Cat*Exper	18	4.79	9.78	.0001
Cat**Time	28	0.38	0.50	.98
Scheffe of Exper	1 > 4 > 5 > 3 > 2 A B B B B			

Table 11. Auditory Brainstem Response Regression Analysis,
Wave III/IV; 90 dBHL click-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	77	0.55	9.88	.0001
Error	72	0.05		
Total	72	0.60		
Cat	7	0.22	41.18	.0001
Exper	4	0.05	16.41	.0001
Time	4	0.01	3.38	.01
Exper*Time	16	0.01	0.96	.51
Cat*Exper	18	0.21	15.88	.0001
Cat*Time	28	0.03	1.39	.13
Scheffe of Exper	5 > 3 > 4 > 2 > 1 A A A A B			
<u>Amplitude</u>				
Model	77	3.75	4.15	.0001
Error	72	0.89		
Total	149	4.59		
Cat	7	0.66	8.06	.0001
Exper	4	0.93	19.80	.0001
Time	4	0.05	0.99	.42
Exper*Time	16	0.38	2.04	.02
Cat*Exper	18	1.23	5.85	.0001
Cat*Time	28	0.51	1.56	.07
Scheffe of Exper	1 > 4 > 3 > 5 > 2 A A C B B B			

Table A-12. Auditory Brainstem Response Regression Analysis,
Wave V; 90 dBHL click-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	77	0.07	3.41	.0001
Error	72	0.02		
Total	149	0.09		
Cat	7	.02	9.13	.0001
Exper	4	0.01	5.68	.0005
Time	4	0.01	6.21	.0002
Exper*Time	16	0.004	1.04	.43
Cat*Exper	18	0.025	5.21	.0001
Cat*Time	28	0.014	1.88	.02
Scheffe of Exper	5 > 4 > 2 > 3 > 1 A A A A B B B B			
<u>Amplitude</u>				
Model	77	5.19	3.27	.001
Error	72	1.69		
Total	149	6.68		
Cat	7	0.58	4.03	.0009
Exper	4	0.69	8.30	.0001
Time	4	0.22	2.69	.04
Exper*Time	16	0.46	1.41	.16
Cat*Exper	18	0.23	5.99	.0001
Cat*Time	28	0.88	1.53	.58
Scheffe of Exper	1 > 4 > 3 > 2 > 5 A A A B B B B			

Table A-13. Auditory Brainstem Response Regression Analysis,
Wave VI; 90 dBHL click-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	77	0.07	2.75	.0001
Error	72	0.02		
Total	149	0.09		
Cat	7	0.01	2.29	.04
Exper	4	0.003	2.45	.054
Time	4	0.01	2.64	.0001
Exper*Time	16	0.003	0.61	.87
Cat*Exper	18	0.04	6.03	.0001
Cat*Time	28	0.01	1.26	.22
Scheffe of Exper 4 > 3 > 2 > 5 > 1				
<u>Amplitude</u>				
Model	77	16.58	2.01	.002
Error	72	7.73		
Total	149	24.31		
Cat	7	2.43	3.23	.005
Exper	4	1.48	3.44	.01
Time	4	0.28	0.65	.63
Exper*Time	16	1.10	0.64	.84
Cat*Exper	18	7.31	3.79	.0001
Cat*Time	28	3.93	1.31	.18
Scheffe of Exper 2 > 4 > 3 > 1 > 5				

Table A-14. Auditory Brainstem Response Regression Analysis,
Wave I; 80 dBHL click-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency Wave</u>				
Model	41	0.02	0.90	.5184
Error	16	0.01		
Total	57	0.03		
<u>Amplitude</u>				
Model	41	0.44	1.11	.4066
Error	16	0.22		
Total	57	0.87		

Table A-15. Auditory Brainstem Response Regression Analysis,
Wave II; 80 dBHL click-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	41	0.02	1.57	.1774
Error	16	0.00		
Total	57	0.02		
<u>Amplitude</u>				
Model	41	1.80	1.36	.2597
Error	16	0.52		
Total	57	2.32		

Table A-16. Auditory Brainstem Response Regression Analysis,
Wave III/IV; 80 dBHL click-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	41	0.03	1.21	.3524
Error	16	0.01		
Total	57	0.04		
<u>Amplitude</u>				
Model	41	1.46	1.91	.8110
Error	16	0.24		
Total	51	1.76		

Table A-17. Auditory Brainstem Response Regression Analysis,
Wave V; 80 dBHL click-evoked

Source	df	Sum of Squares	df	Prob. > F
<u>Latency</u>				
Model	41	0.02	1.30	.2912
Error	16	0.00		
Total	57	0.02		
<u>Amplitude</u>				
Model	41	5.64	1.35	.2599
Error	16	1.63		
Total	57	7.27		

Table A-18. Auditory Brainstem Response Regression Analysis,
Wave VI; 80 dbHL click-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	41	0.07	0.85	.6790
Error	16	0.03		
Total	57	0.10		
<u>Amplitude</u>				
Model	41	80.25	0.84	.6804
Error	16	37.10		
Total	57	117.35		

Table A-19. Auditory Brainstem Response Regression Analysis,
Wave I; 70 dBHL click-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	42	0.02	0.89	.6317
Error	15	0.01		
Total	57	0.03		
<u>Amplitude</u>				
Model	42	2.16	14.20	.2325
Error	15	0.54		
Total	57	2.70		

Table A-20. Auditory Brainstem Response Regression Analysis,
Wave II; 70 dBHL click-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	42	0.012	1.23	.3438
Error	15	0.004		
Total	57	0.016		
<u>Amplitude</u>				
Model	42	2.42	1.24	.3385
Error	15	0.59		
Total	57	3.11		

Table A-21. Auditory Brainstem Response Regression Analysis,
Wave III/IV; 70 dBHL click-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	42	0.12	0.64	.8750
Error	15	0.07		
Total	57	0.19		
<u>Amplitude</u>				
Model	42	3.47	1.34	.2734
Error	15	0.82		
Total	57	4.29		

Table A-22. Auditory Brainstem Response Regression Analysis,
Wave V; 70 dBHL click-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	42	0.02	1.13	.4142
Error	15	0.01		
Total	57	0.03		
<u>Amplitude</u>				
Model	42	9.42	1.45	.2225
Error	15	2.33		

Table A-23. Auditory Brainstem Response Regression Analysis.
Wave VI; 70 dBHL click-evoked

Source	df	Sum of Squares	f	Prob. > F
<u>Latency</u>				
Model	42	0.04	0.62	.8878
Error	14	0.01		
Total	56	0.05		
<u>Amplitude</u>				
Model	42	24.66	1.21	.3652
Error	14	6.82		
Total	56	31.48		

Table A-24. Auditory Brainstem Evoked Response Regression Analysis,
Wave 1; +10 dB ART tone pip-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	77	2.88	10.28	.0001
Error	72	0.26		
Total	149	3.14		
Cat	7	2.00	78.55	.0001
Exper	4	0.49	33.94	.0001
Time	4	0.01	0.45	.77
Exper*Time	16	0.04	0.72	.76
Cat*Exper	18	0.23	3.49	.0001
Cat*Time	28	0.09	0.95	.54
Scheffe of Exper	3 > 1 > 2 > 4 > 5 A A A B C			
<u>Amplitude</u>				
Model	77	12.38	8.09	.0001
Error	72	1.43		
Total	149	13.81		
Cat	7	5.34	38.30	.0001
Exper	4	2.29	28.79	.0001
Time	4	0.10	1.22	.30
Exper*Time	16	0.27	0.84	.63
Cat*Exper	18	3.83	10.70	.0001
Cat*Time	28	0.67	1.20	.26
Scheffe of Exper	5 > 3 > 4 > 2 > 1 A B B B C			

Table A-25. Auditory Brainstem Response Regression Analysis,
Wave III; +10 dB ART tone pip-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	77	13.11	7.21	.0001
Error	72	1.70		
Total	149	14.81		
Cat	7	6.00	39.94	.0001
Exper	4	2.37	25.13	.0001
Time	4	0.00	0.02	.99
Exper*Time	16	0.33	0.88	.58
Cat*Exper	18	2.76	6.49	.0001
Cat*Time	28	0.88	1.32	.17
Scheffe of Exper	3 > 4 > 2 > 5 > 1 A B B D D C C			
<u>Amplitude</u>				
Model	77	25.95	6.58	.0001
Error	72	3.69		
Total	149	29.64		
Cat	7	15.48	43.16	.0001
Exper	4	4.29	20.92	.0001
Time	4	0.16	0.76	.55
Exper*Time	16	0.85	1.03	.45
Cat*Exper	18	4.72	5.12	.0001
Cat*Time	28	2.13	1.49	.09
Scheffe of Exper	5 > 3 > 2 > 4 > 1 A A C B B B			

Table A-26. Auditory Brainstem Response Regression Analysis,
Wave V; +10 dB ART tone pip-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	77	13.85	24.19	.0001
Error	72	0.54		
Total	149	14.39		
Cat	7	7.92	152.12	.0001
Exper	4	2.16	72.85	.0001
Time	4	0.05	1.75	.14
Exper*Time	16	0.13	1.11	.36
Cat*Exper	18	3.45	25.77	.0001
Cat*Time	28	0.25	1.20	.26
Scheffe of Exper	3 > 2 > 1 > 4 > 5 A B B B C			
<u>Amplitude</u>				
Model	77	48.06	14.11	.0001
Error	72	3.19		
Total	149	51.25		
Cat	7	38.07	122.93	.0001
Exper	4	3.23	18.24	.0001
Time	4	0.14	0.80	.53
Exper*Time	16	0.56	0.80	.68
Cat*Exper	18	6.37	8.00	.0001
Cat*Time	28	1.33	1.07	.39
Scheffe of Exper	2 > 5 > 4 > 1 > 3 A A B B C			

Table A-27. Auditory Brainstem Response Regression Analysis,
Wave I; -10 dB ART tone pip-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	77	5.27	2.78	.0001
Error	72	1.77		
Total	149	7.04		
Cat	7	2.43	14.12	.0001
Exper	4	0.48	4.83	.002
Time	4	0.09	0.88	.47
Exper*Time	16	0.27	0.68	.79
Cat*Exper	18	1.51	3.40	.0001
Cat*Time	28	0.49	0.71	.84
Scheffe of Exper	1 > 2 > 3 > 4 > 5 A A A C C B B			
<u>Amplitude</u>				
Model	77	4.77	1.95	.0024
Error	72	2.49		
Total	149	7.05		
Cat	7	1.64	7.36	.0001
Exper	4	0.13	1.06	.38
Time	4	0.03	0.27	.89
Exper*Time	16	1.44	0.96	.61
Cat*Exper	18	1.58	2.76	.0012
Cat*Time	28	0.98	1.11	.35
Scheffe of Exper	5 > 4 > 2 > 3 > 1 A A A A A			

Table A-28. Auditory Brainstem Response Regression Analysis,
Wave III; -10 dB ART tone pip-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	77	7.04	5.91	.0001
Error	72	1.11		
Total	149	8.15		
Cat	7	3.13	28.91	.0001
Exper	4	0.94	15.15	.0001
Time	4	0.06	0.94	.44
Exper*Time	16	0.26	1.06	.41
Cat*Exper	18	1.61	5.80	.0001
Cat*Time	28	0.90	2.08	.007
Scheffe of Exper	3 > 4 > 2 > 1 > 5 A B B C C C			
<u>Amplitude</u>				
Model	77	15.89	9.51	.0001
Error	72	1.56		
Total	149	17.45		
Cat	7	12.09	79.55	.0001
Exper	4	0.50	5.81	.0004
Time	4	0.12	1.39	.24
Exper*Time	16	0.54	1.54	.10
Cat*Exper	18	1.68	4.29	.0001
Cat*Time	28	1.08	1.78	.03
Scheffe of Exper	5 > 1 > 2 > 3 > 4 A A A B B			

Table A-29. Auditory Brainstem Response Regression Analysis,
Wave V; -10 dB ART tone pip-evoked

Source	df	Sum of Squares	F	Prob. > F
<u>Latency</u>				
Model	77	9.15	3.27	.0001
Error	72	2.61		
Total	149	11.76		
Cat	7	3.56	14.02	.0001
Exper	4	1.19	8.22	.0001
Time	4	0.14	0.98	.42
Exper*Time	16	0.63	1.09	.37
Cat*Exper	18	2.48	3.79	.0001
Cat*Time	28	0.92	0.91	.60
Scheffe of Exper 3 > 1 > 2 > 4 > 5 A A A B B				
<u>Amplitude</u>				
Model	77	15.02	8.43	.0001
Error	72	1.67		
Total	149	16.69		
Cat	7	7.41	45.69	.0001
Exper	4	0.33	4.11	.005
Time	4	0.26	2.85	.03
Exper*Time	16	0.53	1.44	.14
Cat*Exper	18	4.07	9.81	.0001
Cat*Time	28	1.60	2.48	.001
Scheffe of Exper 1 > 2 > 5 > 4 > 3 A A C C B B				

VITA

Janice Elisabeth Horohov was born in Philadelphia, Pennsylvania, on November 7, 1957. She attended public school in the Centennial school district and graduated from William Tennent Senior High School in June 1975. The following September she entered The Pennsylvania State University and received a Bachelor of Science degree in Biological Sciences from that institution in November of 1978.

For the next three years she worked as a laboratory technician at Purdue University. After moving to Knoxville, Tennessee, she was employed at the University of Tennessee as a physiology technician until September of 1982. At that time she began graduate school at The University of Tennessee, Knoxville. There she completed the requirements for the Master of Science degree in Life Sciences in the area of physiology.