# Society for Neuroscience

# ABSTRACTS

## Volume 7

## 11th Annual Meeting
## Los Angeles, California
## October 18–23, 1981

66.1 OLFACTORY BULBECTOMY AND CHRONIC AMITRIPTYLINE TREATMENT. W.A. Jesperger* and J.S. Richardson. Depts. of Pharmacology and Psychiatry, University of Saskatchewan, Saskatoon, Sask., S7N 0W0.

Bilateral abalation of olfactory bulbs produces a number of behavioral and biochemical changes that are normalized by chronic antidepressant therapy. We have used this preparation as an animal model of depression to examine the biochemical events associated with chronic treatment with the tricyclic antidepressant (TCA), amitriptyline (AMI). Recent investigations have shown that chronic treatment with TCA's will result in a decrease in the density of high affinity binding sites for the beta-adrenergic antagonist $^{3}$H-dihydroalprenolol ($^{3}$H-DHA) and the TCA, $^{3}$H-imipramine in several regions of the brain. We have investigated the binding of these two ligands to brain membranes from sham and bulbectomized male Sprague Dawley rats that have received either saline or AMI for 28 days (10 mg/kg i.p.) followed by a 5 day drug free period. Behavioral testing (stepdown passive avoidance and emotionality rating) was conducted after the 5-day drug washout period. The animals were then sacrificed, trunk blood was collected and the brain was excised and dissected. Regions dissected out and investigated were the hypothalamus, midbrain, hippocampus and pons medulla.

Olfactory bulbectomy resulted in an increase in the number of trials for acquisition of the stepdown passive avoidance task, increased irritability scores and elevated 11-hydroxycorticosteroid levels, all of which were returned to near sham values by AMI treatment. Membrane preparations from sham-operated amitriptyline treated animals exhibited a decreased binding for the beta-adrenergic antagonist $^{3}$H-DHA relative to that of saline treated shams. Lesioned-saline treated animals did not show any significant decrease in the binding of $^{3}$H-DHA relative to saline treated shams nor did the AMI treated lesioned animals exhibit any altered binding relative to that found in saline treated lesioned animals. Chronic treatment with amitriptyline resulted in a decrease in binding for $^{3}$H-imipramine in sham-operated animals. Binding studies of $^{3}$H imipramine in bulbectomized subjects are in progress.

These studies suggest that olfactory bulbectomy indirectly or directly alters the noradrenergic response potential to chronic AMI treatment.

66.2 STUDIES ON THE EFFECTS OF INTRAVENTRICULAR INFUSIONS OF (-)-NICOTINE ON BEHAVIOR MAINTAINED UNDER FIXED RATIO SCHEDULES, W. J. DeNoble* and L. Carroll*. Behavioral Pharmacology Laboratory, Philip Morris Research Center, Richmond, VA 23261.

Intraventricular infusion of (-)-nicotine produces a prostration syndrome that is prevented by intraventricular pretreatment with derivatives of nicotine but not by anticholinergic drugs (Abood et al., 1979). Present studies investigated 1) intraventricular infusions of (-)-nicotine on behavior maintained under fixed ratio (FR) schedules of food reinforcement, 2) effect of repeated infusions and, 3) effect of nicotinic-cholinergic antagonists on prostration.

In exp. 1 eight male albino rats, each implanted with a cannula in the lateral ventricle were maintained under FR 16 until response rates were stable (<10% variance in responses/sec for 5 consecutive sessions). Sessions were two consecutive 15-min periods with a 5-min time-out (TO) in between. All infusions were separated by 5 days. Rats were first infused with saline (5ul) and repetitive 15-min sessions were run until response rate was at preinfusion levels. Latency to complete the first FR following infusions was recorded. Next, rats were infused with 5ug of (-)-nicotine. This was repeated with the rats maintained under FR 32 and 64. In exp 2 (N=6) rats were maintained under FR 32 and tested as follows: 1) saline infusion, 2) (-)-nicotine (10ug) 3) saline/precession injection (sc) of mecamylamine HCL (0.05, 1.5 and 3.0) or hexamethonium Cl (0.5, 1.0, 1.5 mg/kg/sc) 4) (-)-nicotine/precession injection of the antagonists, and 5) (-)-nicotine retest.

Results of exp 1 showed that latency to complete the first ratio under FR 16 following a saline infusion was $\bar{X}$ = 0.8 min (.04 SE) whereas the latency following (-)-nicotine was $\bar{X}$ = 10.9 min (1.6 SE). Latencies were inversely related to FR size (FR 16, 11.0 min (7.6 SE), FR 32, 7.7 min (1.5 SE), FR 64, 4.3 min (0.9 SE). To determine if this inverse relationship was due to repeated (-)-nicotine infusions independent of the FR schedule the rats in exp 1 were tested with (-)-nicotine twice under FR 32. No significant difference was found between the latencies. Latency following a 10ug infusion of (-)-nicotine (exp 2) was $\bar{X}$ = 13.0 min (1.4 SE). Mecamylamine had no effect during saline infusions, however, it did produce a dose dependent decrease in the latency following a (-)-nicotine infusion (0.05, 1.5 and 3.0 mg/kg/sc; latency = 6.8, (1.2 SE), 2.0, (0.7 SE), 0.6, (0.1 SE) min. Hexamethonium injections had no effect. These results suggest that: 1) duration of the effect of intraventricular infusions of (-)-nicotine extended beyond the observed prostration, 2) duration of suppression varies as a function of the FR size, 3) there is a lack of tolerance with repeated infusions and 4) mecamylamine but not hexamethonium antagonized the effects of (-)-nicotine on FR responding suggesting that the effects are mediated by central nicotinic-cholinergic receptors.

66.3 THE EFFECTS OF STRYCHNINE, 5-METHOXY-N,N-DIMETHYLTRYPTAMINE AND CLONIDINE ON ACOUSTIC AND ELECTRICALLY-ELICITED 'STARTLE' RESPONSES IN THE RAT. R.L. Commissaris* and M. Davis (SPON: M. Bowers). Dept. Psychiat., Yale Univ. Sch. Med., New Haven, CT 06508.

Although many neuropharmacological agents have been shown to alter the acoustic startle response, the site(s) of action for many of these agents has not been defined. This study used electrical stimulation within the startle circuit in combination with selected drug treatments as a technique to localize the site(s) of action for these agents.

Previous work has suggested that the primary acoustic startle circuit in the rat is: auditory nerve, ventral cochlear nucleus, nuclei of the lateral lemniscus, nucleus reticularis pontis caudalis (RPC), spinal interneuron, lower motor neuron, muscles. Electrical stimulation of sites within this circuit produces a response similar to the acoustic startle response (Gendelman and Davis, Neurosci. Abstr. 5: 494, 1979). In the present study male rats (350-400 g) received bilateral, single-pulse (100 μA per electrode, 1 msec duration) stimulations of the RPC alternating with acoustic noise bursts (115-db, 4-20 kHz band-width, 90 msec). The interstimulus interval between the two types of stimuli was 10 sec. Both acoustic and RPC-elicited 'startle' responses were measured for forty minutes following intraperitoneal administration of strychnine (1.0 mg/kg), 5-methoxy-N,N-dimethyltryptamine (5-MeODMT; 4.0 mg/kg), clonidine (80 μg/kg) and saline. These drugs were chosen because previous studies in which they were injected directly into the lumbar region of the spinal sub-arachnoid space (intrathecal administration) have indicated that their excitatory (strychnine, 5-MeODMT) and inhibitory (clonidine) effects on acoustic startle are mediated at least in part through the spinal cord (i.e., "downstream" from the RPC). As expected, strychnine and 5-MeODMT increased and clonidine decreased acoustic startle. Consistent with the spinal actions of these agents in modulating acoustic startle, RPC-elicited 'startle' was also increased by strychnine and 5-MeODMT and decreased by clonidine.

These results indicate that the 'startle' elicited by electrical stimulation of the RPC can be altered by treatments which act in the spinal cord to modulate acoustic startle. Furthermore, these results suggest that the 'startle' response produced by electrical stimulation of various sites within the acoustic startle circuit may be used to elucidate the site(s) of action for agents which modulate the acoustic startle response in the rat.

Supported by NSF Grant DNS-78-017421; USPHS Grant MH-00004, MH-14459, and the State of Connecticut.

66.4 COCAINE POTENTIATES KETAMINE-INDUCED LOSS OF RIGHTING REFLEX AND SLEEP TIME. Christine VanderWende, Marie T. Spoerlein and Judy Lapello*. College of Pharmacy, Rutgers-The State University, Box 789, Piscataway, N.J. 08854.

Ketamine has dissociative anesthetic properties and unlike the parent compound, phencyclidine (PCP), is still used as an anesthetic in the human. However, it does have post anesthetic sequelae which resemble the psychotomimetic effects of PCP. Because of these mind-altering effects, ketamine has now gained acceptance as a street drug. There is the potential that ketamine will be used in combination with other drugs such as cocaine, amphetamine and caffeine which are at times used as adulterants of ketamine powders. We have found that cocaine modifies ketamine induced loss of the righting reflex and sleep time.

Cocaine caused a shift to the left of the dose-response curve of ketamine for the loss of righting reflex in a dose-dependent manner. Cocaine administered simultaneously with ketamine reduced the $ED_{50}$ to 48(30-76) and 86(61-120) mg/kg when given in doses of 30 and 15 mg/kg, respectively, as compared to 115 mg/kg in the ketamine controls. Sleep time with 150 mg/kg of ketamine was significantly increased by 56% when administered simultaneously with 30 mg/kg of cocaine. This effect of cocaine was not a generalized effect with CNS depressants since cocaine had no effect on loss of righting reflex or sleep induced by pentobarbital, phenobarbital or hexobarbital. Conversely, Metrazol (55 mg/kg) antagonized ketamine sleep as would be anticipated for a CNS stimulant.

Since ketamine has a cocaine-like effect on catecholamines (CA), we examined the possibility that CA systems may underlie the cocaine potentiation of ketamine. Mice were treated with alpha-methyl-p-tyrosine (=MPT), 400 mg/kg, to deplete the CA's. At various times after the pretreatment, the cocaine effect was again reexamined. Although the sleep time with ketamine (100 mg/kg) was significantly increased with =MPT itself, the administration of cocaine had no further effect on sleep. Thus, the effect of cocaine was blocked by =MPT. Attempts to further study the CA involvement using adrenergic and dopaminergic receptor modifying drugs were more difficult to interpret. Generally DA agonists increased while DA blockers antagonized the effect of cocaine, although they, in themselves, potentiated ketamine. The results with alpha and beta agonists and antagonists were less clear.