464.5 INTERACTIONS OF TRICYCLIC ANTIDEPRESSANT DRUGS WITH HUMAN AND RAT MONOAMINE OXIDASE TYPE B. A.A. Reid*, J.L. Hill* and D.L. Murphy*. (Spon: H. Holloway). Lab of Clinical Science, National Institute of Mental Health, NIH 10/3D41, Bethesda, MD 20892.

Monoamine oxidase (MAO) exists as two isozymes, type A and B, which are both found in human and rat brain, while only MAO type B exists in human platelets. Tricyclic antidepressant drugs are primarily classed as monoamine uptake inhibitors, but they also act as weak reversible inhibitors of MAO in vitro, with a greater affinity for MAO type B. They inhibit the deamination of phenylethylamine and benzylamine, two MAO type B substrates, non-competitively and competitively, respectively.

We have further investigated the effects of tricyclic antidepressant drugs on the deamination of phenylethylamine and benzylamine by MAO type B, in vitro in human brain cortex, human platelet and rat brain preparations. These drugs inhibited MAO activity as expected, but, in addition, in human cortex and human platelet preparations a biphasic inhibitory response was observed when benzylamine was used as the substrate with 10^{-3} M imipramine and amitriptyline, two tertiary amine tricyclics, and an activation occurred with 10^{-3} M clomipramine, another tertiary amine tricyclic. The biphasic inhibitory pattern or activation was not reproduced when the secondary amine tricyclics, desipramine and desmethylclomipramine, or the secondary amine bicyclic antidepressant drug, fluoxetine, were studied or when phenylethylamine was utilized as the substrate or when rat brain was used.

Of the tricyclics which exhibited normal inhibition patterns, the same rank order of inhibition occurred among the drugs in both human tissues but not in the rat brain when phenylethylamine was used as the substrate, while with benzylamine the same inhibitory relationship was noted across all tissues. In general, the drugs inhibited the deamination of both substrates in the various tissues with the following potencies: rat brain > human platelet > human cortex ($p<0.05$). Furthermore, each tricyclic was a more potent inhibitor of phenylethylamine than benzylamine deamination ($p<0.01$), except for desmethylclomipramine which inhibited both substrates similarly. On the other hand, fluoxetine inhibited benzylamine deamination to a greater extent than phenylethylamine in human cortex ($p<0.01$) and tended to do so also in human platelet and rat brain.

These tricyclic-MAO interactional data suggest that rat and human MAO type B are not functionally identical, that secondary and tertiary amine tricyclics interact differently with MAO type B, that fluoxetine, a bicyclic antidepressant, interacts differently from the tricyclics, and also support other data that phenylethylamine and benzylamine are deaminated by different mechanisms.

464.6 COCAINE AND REGIONAL MONOAMINE UTILIZATION IN MOUSE BRAIN. M.G. Hadfield and C. Milio*, Neurochemistry Research Laboratory, Section on Neuropathology, Department of Pathology, Medical College of Virginia/Virginia Commonwealth University, Richmond, VA. 23298

Cocaine inhibits the uptake and enhances the release of central monoamines. This prolonges the activity of neurotransmitters at the synapse and may account for much of cocaine's action on the central nervous system. The present study was undertaken to see if cocaine produces selective changes in utilization of norepinephrine, dopamine and/or serotonin, depending on the brain region and neurotransmitter system examined.

In the present study, adult male ICR mice were given saline or 10 mg/kg cocaine i.p. 1/2 hr. before removal of the brains which were quickly frozen in liquid nitrogen. The olfactory bulbs (OB), prefrontal cortex (PC), striatum (ST), amaydaloid nuclei (AMY), hypothalamus (HT) and thalamus (TH) were dissected and extracted in acetate buffer containing ascorbate oxidase for HPLC analysis of monoamines and metabolites (Hadfield et al., J.Chromatogr. 369:449-453, 1986 and J. Liquid Chromatgr. In Press). Regional brain levels of the following compounds were measured: NE and its metabolite, 3, 4-dimethoxyphenylglycol (MHPG), DA and its metabolites, dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 3-methoxytyramine (3MT) as well as serotonin (5HT) and its metabolite, 5-hydroxyindoleacetic acid (5HIAA). Ratios of metabolite levels to those of their parent neurotransmitters were calculated in order to determine utilization of neurotransmitters. The following significant decreases were noted.

	OB	PC	ST	AMY	HT	TH
MHPG/NE				↓	↓	
DOPAC/DA		↓	↓	↓		
HVA/DA		↓		↓	↓	
3MT/DA		↓				
THIAA/5HT				↓	↓	↓

In all instances there was decreased utilization of neurotransmitter as indicated by the decrease in the metabolite/neurotransmitter ratios. However, the pattern was different depending on the neurotransmitter and the tissue. The noradrenergic system was altered in the AMY and HT while the serotonergic system was altered in the AMY, HT and TH. The DOPAC/DA ratios were altered in the PC. ST and AMY while the HVA/DA ratios were affected in the PC, AMY and HT. The 3MT/DA ratio was altered only in the PC. The greatest effects were noted in the prefrontal cortex, amygdala and hypothalamus, areas which have been related to various behavioral and emotional states. The direction of the changes will be discussed in terms of cocaine's mechanisms of action on the central nervous system and the pattern of changes to relevant clinical effects produced by cocaine.

464.7 EFFECTS OF SELECTIVE MAO-A INHIBITORS ON BRAIN BIOCHEMISTRY AND RESPONSES IN ANIMAL MODELS OF DEPRESSION. H.L. White, R.M. Norton*, F.E. Soroko* and B.R. Cooper. Department of Pharmacology, Wellcome Research Laboratories, Research Triangle Park, North Carolina 27709.

BW A616U and BW A70C are both reversible and selective inhibitors of monoamine oxidase-A (MAO-A). However, although BW A70C was at least 4-fold more potent than BW A616U as an MAO-A inhibitor, both in vitro and ex vivo, it was much less active as an antagonist of sedation in the tetrabenazine and Porsolt models of depression. The purpose of this study was to determine whether changes in brain levels of specific substrates or products of MAO could be correlated with behavioral responses in the animal models.

Inhibitors were administered orally to Sprague-Dawley male rats at various times before sacrifice. Brains were rapidly removed and immediately frozen to await biochemical testing. Biogenic amines and their metabolites were assayed in brain extracts using HPLC techniques. MAO-A and MAO-B were estimated in brain homogenates using [^{3}H] serotonin and [^{14}C] B-phenethylamine as substrates in a double-label radiochemical assay.

After 50 mg/kg p.o., both inhibitors produced similar elevations of major biogenic amines. Brain serotonin reached 134-142% of control, and norepinephrine, 120-127% of control, with maxima between 2 and 4 hr after dosing. Smaller, but significant elevations of dopamine also occurred (110-120% of control). MAO-A was inhibited by at least 80%, and no inhibition of MAO-B was observed with either compound. Other experiments showed similar patterns of tissue distribution for the two inhibitors.

The major difference between the two compounds was in levels of certain products of MAO. For example, DOPAC, a dopamine metabolite, was reduced to approximately 30% of control level after BW A616U administration, but was about 60% of control after BW A70C. Although the latter compound was the more potent MAO-A inhibitor, it produced weak and inconsistent results in the animal models.

We conclude that effects in the tetrabenazine and Porsolt models of depression by these MAO-A inhibitors are not simply related to elevated levels of brain serotonin, norepinephrine, or dopamine, but may involve more complicated interactions with brain monoamine systems.

464.8 EFFECTS OF ADRENALECTOMY ON THE 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA)-INDUCED DECREASE OF TRYPTOPHAN HYDROXYLASE ACTIVITY IN THE FRONTAL CORTEX AND HIPPOCAMPUS. M. Johnson*, L.G. Bush*, D.M. Stone*, G.R. Hanson and J.W. Gibb (SPON: F. Matsuo). Dept. Pharmacol. and Toxicol., University of Utah, Salt Lake City, UT 84112.

The administration of a single high dose of the psychoactive amphetamine analog, 3,4-methylenedioxymethamphetamine (MDMA), decreases brain 5-HT concentrations for up to 7 days (Schmidt et al., 1986). The changes occurring 7 days after drug treatment are accompanied with a decrease in synaptosomal 5-HT uptake, suggesting that neuronal damage has occurred (Schmidt, 1987). Several reports indicate that glucocorticoids affect the neuronal degeneration observed during aging or induced by the application of 3-acetylpyridine (Sapolsky, 1986). The purpose of this study was to determine whether glucocorticoids could be involved in the decrease of rat brain TPH activity after the administration of MDMA.

Male Sprague-Dawley rats were anesthetized with ketamine (175 mg/kg) and the adrenals were removed by dorsal incision. The animals were housed 3 per cage and the adrenalectomized rats received 0.9% saline in lieu of water. After 5 days, the rats were injected with 10 or 20 mg/kg MDMA (s.c.) and sacrificed 7 days later. TPH activity was determined according to Ichiyama et al (1970) and Sitaram and Lees (1978).

TPH activity in the frontal cortex remained unaffected 7 days after administration of 10 mg/kg of MDMA while the enzyme activity was decreased to 51% of control when a 20 mg/kg dose was used. Adrenalectomy had no effect on the MDMA-induced decrease of enzymatic activity in the frontal cortex. However, MDMA decreased the hippocampal TPH activity to 78% and 49% of control after a 10 and 20 mg/kg dose, respectively. Adrenalectomy prevented the decrease in TPH activity observed with the 10 mg/kg dose, and the decrease by the higher dose was significantly attenuated to 68% of control. These results suggest that glucocorticoids may contribute to the MDMA-induced long-term decrease in TPH activity observed in the hippocampus after a single dose; this response appears to occur in selected brain areas. (Supported by USPHS grants DA 00869, DA 04222 and Janssen Pharmaceutica Inc.)