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SIMILARITY OF THE BEHAVIORAL EFFECTS OF QUIPAZINE AND LSD IN CATS. M. E. Trulson*, J. W. Brandstetter* and B. L. Jacobs. Univ. of Texas-Dallas, Richardson, TX 75080 and Princeton Univ., Princeton, NJ 08544.

Administration of quipazine (0.5 to 5.0 mg/kg, i.p.) to cats elicited a number of behaviors, such as limb flicking, abortive grooming, investigatory and hallucinatory-like behaviors, which we have previously proposed as an animal behavior model for studying the actions of LSD and related hallucinogens. Of these behaviors, the limb flick has proven to be the most sensitive and reliable index of hallucinogenic activity. Quipazine produced a dose-dependent increase in limb flicking, from a saline baseline of virtually 0 to a peak of 29.7 flicks/hr, which is similar to the peak behavioral effect of LSD. The behavioral effects of 5 mg/kg of quipazine persisted for 4 to 6 hrs, which is somewhat shorter than that observed following LSD administration. When a second 5 mg/kg dose of quipazine was readministered 24 hrs later, the behavioral changes were not significantly different from those observed after the initial dose. This latter finding is in sharp contrast to the nearly complete tolerance that develops to LSD following a single injection. In summary, the behavioral effects of quipazine in cats are very similar to those observed following LSD, except that no tolerance occurred following repeated administration of quipazine. The present data are consistent with preliminary findings by other investigators indicating that quipazine induces hallucinations in humans.

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EFFECTS OF d-LYSERGIC ACID DIETHYLAMIDE (LSD), 2,5-DIMETHOXY-4-METHYLAMPHETAMINE (DOM), PENTOBARBITAL (PB) AND METHAQUALONE (MQ) ON CONFLICT BEHAVIOR IN CONTROL AND 5,7-DIHYDROXYTRYPTAMINE (5,7-DHT)-TREATED RATS. R.L. Commissaris*, W.H. Lyness* and R.H. Rech. Dept. of Pharmacology & Toxicology, Michigan State Univ., East Lansing, MI 48824.

The present study examined the role of central 5-hydroxytryptamine (5HT) neuronal systems in the effects of LSD, DOM, PB and MQ on punished and unpunished responding. Thirsted rats were trained in a conditioned suppression paradigm (Ford et al., Psychopharmacology, 65: 197-204, 1979). PB and MQ produced large (300-500%) increases in punished responding, and at higher doses, decreased water intake (unpunished responding). The hallucinogens produced only moderate (25-75%) increases in punished responding, yet a similar depression of unpunished responding. Destruction of 5HT neurons by i.c.v. 5,7-DHT per se produced little change in punished or unpunished responding in control sessions. This destruction of 5HT neurons also had no effect on the punishment-releasing or sedative effects of PB or MQ. The punishment-releasing effects of the hallucinogens, however, were blocked by this destruction of 5HT neurons. Furthermore, the capacity of the hallucinogens to decrease water intake was significantly potentiated by the neurotoxin pretreatment. These data demonstrate that the effects of LSD and DOM on conditioned suppression are different from those of PB and MQ, and that this difference may be due to the extent of 5HT involvement in the effects of these agents. (Supported by NIDA grant DA-01836.)

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EFFECTS OF 5-HYDROXYTRYPTAMINE (5-HT) ANTAGONISTS, METHERGOLINE, CINANSERIN, AND BC-105, ON THE DISRUPTION OF OPERANT BEHAVIOR IN RATS FOLLOWING ADMINISTRATION OF HALLUCINOGENS. D.J. Mokler*, R.L. Commissaris* and R.H. Rech. Dept. of Pharmacology & Toxicology, Michigan State Univ., E. Lansing, MI 48824.

The present study examined the antagonism of disruption of fixed ratio 40 (FR-40) operant responding in rats following administration of the indolealkylamine hallucinogen d-lysergic acid diethylamide (LSD) and the phenethylamine 2,5-dimethoxy-4-methylamphetamine (DOM). Adult male rats were food deprived and trained to press a bar for food reinforcement. Both LSD and DOM, when administered i.p. immediately prior to the session, produced a dose-dependent disruption of FR-40 behavior characterized by a decrease in the number of reinforcements associated with an increase in pausing. This study examined the effects of methergoline (1.0 mg/kg, 180 min pretreatment), cinanserin (20 mg/kg, 80 min pretreatment) and BC-105 (1.0 mg/kg, 80 min pretreatment). These antagonists blocked the disruption of FR-40 operant behavior produced by hallucinogens with different efficacies for the two hallucinogen classes. At the doses used, methergoline, cinanserin, and BC-105 alone produced an increase in reinforcements and a decrease in pausing. These data further suggest that the effects of the hallucinogens on operant behavior are mediated through 5-HT systems and that there are differences in the mechanism(s) of action between the indolealkylamine and the phenethylamine hallucinogens. (Supported by NIDA grant DA-01836.)

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VASCULAR EFFECTS OF THE SEROTONERGIC ANTAGONIST R 41 468. J.M. Van Nueten* and P.M. Vanhoutte. Dept. of Pharmacology, Janssen Pharmaceutica, B-2340 Beerse, and Dept. of Medicine, University of Antwerp, B-2610 Wilrijk, Belgium

Experiments were performed to determine the vascular effects of 3-[2-[4-(fluorobenzoyl)-1-piperidinyl]ethyl]-2,4(1H,3H)-quinazolinedione (R 41 468), a novel antagonist of $5HT_2$ serotonergic receptors. R 41 468 caused a dose-dependent inhibition of the contractile responses to 5-hydroxytryptamine (5-HT) of isolated rat caudal, canine basilar, carotid, coronary and gastrosplenic arteries and canine saphenous veins; the compound had no agonistic properties. In the rat caudal artery, R 41 468 abolished the amplifying effect of low concentrations of 5-HT on alpha-adrenergic activation. In the canine saphenous vein, R 41 468 did not affect the prejunctional inhibitory effect of 5-HT on adrenergic neurotransmission. In the perfused guinea-pig stomach, R 41 468 depressed or even reversed the vasoconstrictor effect of 5-HT. In the perfused kidney of normotensive and spontaneously hypertensive (SH) rats, the compound antagonized vasoconstrictions caused by 5-HT. R 41 468 caused greater reductions of aortic blood pressure in awake SH rats than in control rats. These experiments demonstrate that R 41 468 is a potent antagonist of the vasoconstrictor, but not of the vasodilator effects of 5-HT, which helps explain its antihypertensive properties.

CHOLINERGIC PHARMACOLOGY (182–183)

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ACETYLCHOLINE SYNTHESIS AND RELEASE IN HUMAN PLACENTA: EFFECTS OF (2-BENZOYLETHYL) TRIMETHYLAMMONIUM CHLORIDE, 4-(1-NAPHTHYLVINYL)PYRIDINE, AND HEMICHOLINIUM-3. Steven M. Leventer* and Peter P. Rowell* (SPON: T.G. Scharff). Dept. of Pharmacology and Toxicology, University of Louisville, Louisville, KY 40292

The existence of two of the components of a cholinergic system, acetylcholine (ACh) and choline acetyltransferase (ChAc), has been established in human placenta. We have shown that in incubated human placental mince, both tissue ACh levels, and the amount of ACh released, increase linearly with time. The addition of the ChAc inhibitors (2-benzoylethyl) trimethylammonium chloride (BETA), 4-(1-naphthylvinyl) pyridine (NVP), or the choline uptake inhibitor hemicholinium-3 (HC-3), leads to dose-dependent inhibition of the increase in tissue ACh levels without affecting ACh release. In addition, the metabolic fate of ^{3}H-choline added to the incubation medium was studied. After incubation and subsequent extraction, tritiated compounds were separated by high voltage electrophoresis. ^{3}H-ACh increased from 195±42 cpm/g at 2 min to 1736±243 cpm/g at 45 min, while ^{3}H-choline increased from 898±86 cpm/g to 1217±140 cpm/g over the same time period. The addition of BETA or NVP led to dose-related inhibition of the increase in ^{3}H-ACh without affecting ^{3}H-choline levels. These results suggest that choline uptake is not the rate-limiting step in the synthesis of ACh in human placenta.

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ACETYLCHOLINE IN HUMAN TERM PLACENTA: EFFECTS OF DISSECTION, PREINCUBATION AND (2-BENZOYLETHYL)TRIMETHYLAMMONIUM ON TISSUE LEVELS. Frank Welsch and Donald B. Stedman*. Dept. of Pharmacol. & Toxicol., Mich. State Univ., East Lansing, MI 48824.

Fragments of villous tissue were pooled in Earle's solution without (E) or with 100 μM physostigmine (EP). Total acetylcholine (ACh) tissue content was determined immediately following dissection (57±11 nmoles/g, mean ± S.E., n=5, range 23-80 in E; 92±10 nmoles/g, mean ± S.E., n=5, range 56-113 in EP bathing medium). Portions (≈500 mg) were then preincubated for 60 min at 37°C in 20 ml of E or EP, and ACh levels were now 177±14 nmoles/g (mean ± S.E., n=11, range 100-245) and not different under both incubation conditions. To other preincubated tissue were added 5 ml of E without or with (2-benzoylethyl)trimethylammonium (BETA, final 0.09, 0.3 and 3 mM), a stable choline acetyltransferase (ChAc) inhibitor. Tissue ACh was determined 40, 50 and 60 min after BETA exposure. These time points were chosen to coincide with those of placental amino acid uptake (aau) measurements in a parallel study. The aim was to explore temporal correlations between inhibition of ChAc by BETA, reduction of aau and placental ACh levels. Just as ChAc and aau were inhibited in a BETA concentration dependent manner (Rowell and Sastry, J. Pharmacol. Exp. Ther., in press; Welsch et al., Placenta, in press), so was the ACh tissue content reduced at corresponding time points. These findings support the hypothesis that the human placental cholinergic system may regulate transport functions in the trophoblast. (Supported by NIH grant HD07091.)