cycloheximide (CYCLO) were administered at low doses (0.5 μl.) into seven structures of the brain (brainstem, septum, hippocampus, amygdala, thalamus, caudate nucleus, and nucleus accumbens septi). Across drugs, amnesia only resulted when drugs were administered into the hippocampus, amygdala, and caudate. ANI and CYCLO always affected retention similarly, while AMPT and DDC showed some differences in anatomical substrate related to relative dopaminergic or noradrenergic innervation. The most important substrate difference was that when AMPT or DDC were applied to the pontine brain stem they caused amnesia, while neither ANI nor CYCLO given into the same area affected retention. This is the region of the brain where cytoplasmic synthesis of DA and NE occurs.

Synthesis of DA and NE in other regions of the brain occurs via mitochondrial synthesis and depends on transported enzymes into the synaptic terminals. Neither ANI nor CYCLO have been found to interfere with mitochondrial protein synthesis. In an effort to determine whether neurotransmitter interaction with its synaptic receptor has an effect on long-term memory, 41 different drug treatments affecting catecholamine (principally, DA and NE) or acetylcholine interaction with their receptors were studied. The results can be summed up as follows: Regardless of the specific mechanism, drug treatments which lead to an increase in the interaction of the neurotransmitter and its receptor improved retention, while decreases in such interactions lead to amnesia. Direct stimulation of the receptors resulted in improved retention, while receptor antagonists yielded amnesia. All drugs in this series of experiments were administered after training and 1 week prior to testing retention. The investigator and his group feel that evidence points to a short-term memory based on synaptic receptor activation and a long-term memory conversion of this receptor activation by protein.

Rate-Dependent and Stimulus Control Effects of Drugs

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Purpose: It is hypothesized that drugs exert rate-dependent effects on behavior via their stimulus properties. The stimulus properties of drugs might also be responsible for the decrements in stimulus control over behavior which several drugs produce. According to the investigator, if the basis of at least some of the behavioral effects of a given drug is that it alters the stimulus situation and thus disrupts the environmental control of behavior, then other (nondrug) stimuli should produce similar effects. In addition, animals given chronic drug treatment until they develop behavioral tolerance should show similar behavioral changes when the drug treatment is halted. The investigator is conducting laboratory studies to test these ideas, which he feels may help to explain a great number of the effects of many psychoactive drugs.

Subjects: Rats are the main subjects of this study. Experiments with pigeons are also planned.

Method: Animals are trained to perform various tasks, such as brightness discrimination or key press for food under different schedules of response and reinforcement. The effects of different drugs (such as LSD, amphetamine, and scopolamine) on performance are compared. In some studies, the effects of drug removal and of the introduction of irrelevant stimuli are compared with the effects of representative psychoactive agents. A differential reinforcement of interresponse times procedure is used to examine whether the amount of drug-induced change in behavior is related to the difficulty of a behavioral test or to the degree of behavioral control generated by the test procedure.

Results: Rats showed a decrease in fixed-interval (FI) response rate at LSD doses of 0.32 mg/kg and above, but not at lower doses. This drug exerted little influence on the overall pattern of FI responding. In comparison, amphetamine produced a rate-dependent disruption of the FI response pattern without much change in overall rate over the range of test doses (0.5 to 2.0 mg/kg). These studies demonstrated a lack of correspondence between the effects of the two drugs. Studies of the effect of changing from drug to nondrug state showed that switching from pretest injections of 1.0 mg/kg d-amphetamine to placebo could produce rate-dependent alterations in FI responding. Rats trained to respond on a two-key brightness discrimination showed greater drug effects on performance when the discrimination was difficult than when it was easy, when either scopolamine or d-amphetamine was used as the test compound. LSD produced no disruption of discrimination performance under either condition.

Central Drug and Lesion Studies of Feeding Behavior

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