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A BEHAVIORAL AND PHARMACOLOGICAL STUDY OF THE
HISTAMINERGIC AND CHOLINERGIC SYSTEMS

BY

Michael C. Gerald

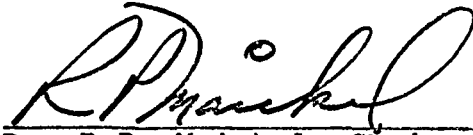
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A Behavioral and Pharmacological Study of the
Histaminergic and Cholinergic Systems

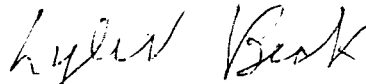
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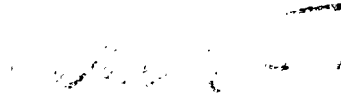
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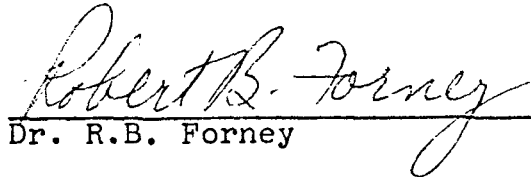
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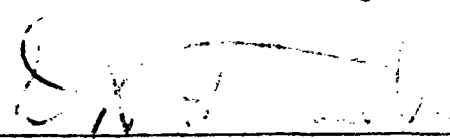
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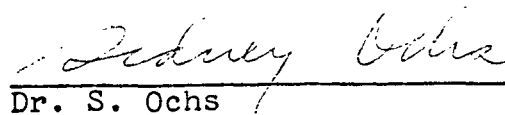
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SUMMARY

A comparison has been made of the histaminergic and cholinergic systems, both pharmacologically and behaviorally, seeking both overlapping and divergent properties.

A more precise study was undertaken of the nature of the dose-response and time-response course of water intake, following administration of carbachol into the lateral hypothalamus of water-satiated rats. With increasing concentrations, there was a linear increase in water intake, with a concurrent displacement of the time for peak activity to the right.

Histamine, administered in the same anatomical site as carbachol, was shown to stimulate water intake in both deprived and water-satiated rats. The water intake decrement seen with atropine and methapyrilene in deprived rats was reversed with histamine; conversely, methapyrilene was able to prevent histamine stimulation of water intake in satiated rats. The water intake of deprived rats was effectively reduced following peripheral administration of both tertiary and quaternary cholinergic stimulants and blockers. Log-dose response curves of the tertiary cholinergic blockers indicated mutual parallelism; the relative molar potency for both tertiary and quaternary blockers was scopolamine > atropine > homatropine, with the quaternary blockers more potent than the tertiary at the lowest dose. A carryover effect was seen with methylatropine in both normal and desalivate rats.

The effectiveness of the quaternary cholinergic compounds strongly suggests the presence of peripheral components in thirst-induced water consumption in the rat that are cholinergically receptive.

A wide chemical spectrum of antihistamines was found to be effective in reducing thirst-induced water consumption. Mutually parallel dose-response curves among these agents were demonstrated, which were also parallel to those seen with the tertiary cholinergic blockers. This is highly suggestive of a common mechanism of action between the 2 drug classes.

Intraventricular administration of histamine caused an initial depression of avoidance responses in a continuous avoidance situation, followed by a return to normal rates of responding or stimulation. With subsequent histamine administration, tolerance developed to this depression. Whereas tertiary cholinergic blocking agents evoked consistent stimulation of response rates, their quaternary, N-methyl analogs were without effect. In general, those antihistamines possessing the most potent anticholinergic properties were shown to be most effective in disrupting normal reinforcement withdrawal behavior.

Atropine and methylatropine effectively prevented oxotremorine lethality; the antihistamines were found to potentiate this lethality linearly with the dose of antihistamine employed. Almost all antihistamines tested antagonized oxotremorine-induced hypothermia in mice at 25⁰, whereas in rats at 4⁰, those antihistamines with the greatest anti-

cholinergic potency appeared most effective.

Bromodiphenhydramine, diphenhydramine, cyproheptadine and chlorcyclizine potentiated hexobarbital sleeping time, with the first 2 compounds prolonging it directly proportional to the dose of antihistamine used.

To date, literally volumes of experimental literature have been devoted to an attempt to elucidate the role of norepinephrine and serotonin in the brain, with but modest results; only a few scant pages have been relegated to histamine. The time for greater interest in brain histamine and behavior is long overdue.

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