It has been shown previously that sensitivity to ACh of the arterial muscle is low during both oestrus and dioestrus, although it becomes high during the course of pregnancy (Bell, 1968). The effect of chronic treatment of virgin animals with high doses of oestrogen (0·5 mg oestradiol i.m. per day) on responses of isolated perfused arteries to ACh was therefore investigated. It was found that following oestrogen treatment for 14 days or longer, the sensitivity of the arterial muscle to ACh was significantly increased.

It is concluded that the functionality of both pre- and postsynaptic components of this vasomotor system is determined by the levels of circulating oestrogenic hormones. The results emphasize the complex interaction which may exist between hormonal and nervous control of the female reproductive tract, as previously remarked for the adrenergic nervous system by Sjöberg (1968a, b).

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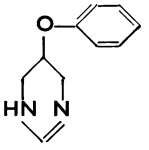
A new muscarinic agent: 1,4,5,6-tetrahydro-5-phenoxypyrimidine (AH 6405)

R. J. MARSHALL (introduced by R. T. BRITTAIN), *Department of Pharmacology, Allen & Hanburys Ltd., Ware, Herts*

Oral administration of 1,4,5,6-tetrahydro-5-phenoxy-pyrimidine (AH 6405) to rodents caused overt parasympathomimetic effects—for example, profuse lacrimation, salivation and urination. Intravenous injection of AH 6405 (0·01–1·0 mg/kg) into anaesthetized cats and dogs caused similar effects but unlike most other parasympathomimetic agents also caused a secondary pressor response after the initial vasodepression. Since there is evidence (Roszkowski, 1961; Franko, 1963) that certain muscarinic agents may produce a vasopressor response by stimulation of sympathetic ganglia, experiments were undertaken to investigate the possibility that AH 6405 possessed stimulant activity on autonomic ganglia.



AH 6405

In cats anaesthetized with chloralose, close-arterial injections of AH 6405 (2–10 μg/kg) to the superior cervical ganglion via the lingual artery caused dose-dependent contractions of the ipsilateral nictitating membrane. This action was not affected by pentolinium (1 mg/kg intravenously), but was abolished by section of the post-ganglionic sympathetic nerves or by previous close-arterial injection of atropine (0·1 μg/kg) or cocaine (0·1 mg/kg). Large intra-arterial doses of nicotine (0·1 mg/kg) had a biphasic effect on the response to AH 6405. Initially it blocked the action of AH 6405, but the response to AH 6405 soon returned even when the ganglion was

insensitive to nicotinic stimulants. After post-ganglionic nerve section, injection of higher doses of AH 6405 (50 μg/kg intra-arterially) produced a contraction of the nictitating membrane which could be blocked by atropine but not by cocaine. This effect indicated that AH 6405 stimulated peripheral muscarinic sites as well as those in sympathetic ganglia. In anaesthetized and spinal cats the vasodepressor and pressor responses to intravenous AH 6405 were reduced or blocked by atropine (0·1 mg/kg) but not by pentolinium (1 mg/kg). Essentially similar results have been reported for the muscarinic ganglion stimulants McN-A343 and AHR-602 (see Roszkowski, 1961; Franko, 1963; Jones, 1963).

In vitro AH 6405 was about 1/300 as active as acetylcholine as a stimulant of gastrointestinal smooth muscle of the rabbit and guinea-pig. These responses were blocked by atropine (2 ng/ml), but not by mepyramine (1 μg/ml). Surprisingly AH 6405 had a transient stimulant effect on guinea-pig isolated atria and typical muscarinic effects on this preparation have not been seen. It was also inactive on toad rectus abdominal muscle in concentrations up to 350 μg/ml.

AH 6405 has muscarinic effects on smooth muscles and sympathetic ganglia but not on heart muscle. It has no obvious nicotinic action on ganglia or amphibian skeletal muscle. AH 6405 may be useful in the characterization of muscarinic receptors.

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Circadian rhythm in plasma corticosterone concentration and pituitary adrenocorticotrophic response to stress in the betamethasone treated rat

J. R. HODGES and SUSAN MITCHLEY*, *Department of Pharmacology, Royal Free Hospital School of Medicine, London W.C.*1

Male rats were given betamethasone solution instead of drinking water over a 24 h period. The concentration of the solution (20 μg/ml) was adjusted on the basis of a series of preliminary experiments so that each rat received approximately 450 μg betamethasone/100 g. The circadian rhythm in plasma corticosterone concentration and the changes in the blood level of the steroid which occur in response to stress (exposure to ether vapour for 1 min) were studied at the end of betamethasone treatment and 1, 2 and 3 days afterwards. Both the circadian rhythm and the stress-induced rise in plasma corticosterone were abolished. Normal circadian rhythm returned within 1 day of withdrawal of the steroid, but the response to stress was not normal until 3 days after stopping the treatment. The effect on both the circadian and stress induced rise in plasma corticosterone was entirely due to the inhibition of corticotrophin release because the adrenal sensitivity to exogenous ACTH was unimpaired by the betamethasone treatment.

The final common pathway for ACTH release is known to be in the median eminence. Afferent nervous pathways to the hypothalamus control the circadian ACTH