the α-receptor antagonist, phentolamine (125 μg i.c.v.), did not affect TRH or Ca^{++}-induced hypothermia but antagonized hypothermia provoked by NA. Although TRH is a tripeptide composed of pyroglutamic acid, histidine and prolineamide, none of these amino acids (0.1 μg, i.c.v.) produced effects similar to TRH. Thyroxine (0.25-1.0 μg, i.c.v.) caused a dose-related rise in temperature of slow onset (2 h) consistent with its known effect as a metabolic stimulant whereas thyrotropin (TSH) (0.2-0.8 i.u., i.c.v.) produced a gradual, sustained hypothermia which was unrelated to dose and which was not accompanied by an increase in respiratory rate.

It is concluded that the hypothermia produced in the cat by the i.c.v. injection of TRH is unrelated to its endocrine function and is not mediated by cerebral noradrenaline.

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References

CRANSTON, W.I., HELLON, R.F., LUFF, R.H. & RAWLINS, M.D. (1972). Hypothalamic endogenous noradrenaline and thermoregulation in the cat and rabbit. *J. Physiol.*, **223**, 59-67.

FELDBERG, W. & MYERS, R.D. (1963). A new concept of temperature regulation by amines in the hypothalamus. *Nature, Lond.*, **200**, 1325.

METCALF, G. (1974). TRH: a possible mediator of thermoregulation. *Nature, Lond.*, **252**, 310-311.

METCALF, G. & MYERS, R.D. (1975). Further evidence concerning the role of brain noradrenaline in mammalian thermoregulation. *J. Pharm. Pharmacol.* (in press).

MYERS, R.D. & VEALE, W.L. (1971). The role of sodium and calcium ions in the hypothalamus in the control of body temperature of the unanaesthetized cat. *J. Physiol.*, **212**, 411-430.

WINOKUR, A. & UTIGER, R.D. (1974). Thyrotropin Releasing Hormone: Regional distribution in rat brain. *Science*, **185**, 265-266.

Central hypertensive action of histamine in rats

L. FINCH & P.E. HICKS*

School of Studies in Pharmacology, University of Bradford, Bradford, W. Yorks. BD7 1DP

Intraventricular (i.c.v.) injection of histamine in cats has been shown to produce a short lasting rise in blood pressure, with an associated tachycardia (Trendelenburg, 1957; White, 1965; Sinha, Gupta & Bhargava, 1969). Similarly Brezenoff & Jenden (1969) were able to show a pressor response to intrahypothalamic injection of histamine in rats. However, Corrêa & Graeff (1969) and Jagiello-Wojtowicz (1973) failed to demonstrate the hypertensive response to i.c.v. histamine in rats.

In this study we have shown that i.c.v. administration of histamine elicits increases in blood pressure and heart rate in anaesthetized rats and we have examined possible mechanisms of action involved in these histamine-mediated cardiovascular changes.

Histamine (0.1-10 μg i.c.v.) caused a dose-related increase in blood pressure and heart rate in urethane-anaesthetized rats. Pretreatment with mepyramine (50 μg and 100 μg i.c.v.) produced a dose-related antagonism of the cardiovascular effects induced by a sub-maximal dose of histamine (1.0 μg i.c.v.). However pretreatment with metiamide, a histamine-H_2 receptor antagonist, in doses of 100 and 200 μg i.c.v., or procaine (300 μg i.c.v.) did not significantly modify the cardiovascular effects of histamine (1.0 μg i.c.v.) ($P > 0.05$).

Intraventricular administration of phentolamine (100 and 200 μg i.c.v.) caused a dose-dependent antagonism of the histamine-induced pressor effect, whilst peripheral administration of phentolamine (5 mg/kg i.v.) totally abolished this hypertensive response. Neither treatment significantly modified the positive chronotropic effect produced by histamine ($P > 0.05$).

6-Hydroxydopamine (3 x 250 μg i.c.v.) or mecamylamine (5 mg/kg i.v.) abolished both the pressor response and tachycardia to i.c.v. administered histamine, while atropine (100 μg i.c.v.) or propranolol (1 mg/kg i.v.) abolished the tachycardia without modifying the blood pressure rise. Acute bilateral vagotomy or adrenal demedullation failed to modify either cardiovascular change.

The results demonstrate that i.c.v. administration of histamine elicits blood pressure and heart rate increases in anaesthetized rats and are consistent with the view that centrally increased sympathetic nerve activity mediates these responses. Furthermore the central action of histamine appears to be mediated via histamine-H_1-receptors, although central adrenergic and cholinergic mechanisms also appear to be involved.

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References

BREZENOFF, H.E. & JENDEN, D.J. (1969). Modification of arterial blood pressure in rats following micro-injections of drugs into the posterior hypothalamus. *Int. J. Neuropharmac.*, 8, 593-600.

CORRÊA, F.M.A. & GRAEFF, F.G. (1969). Central mechanisms of the hypertensive action of intraventricular Bradykinin in the un-anaesthetized rat. *Neuropharmacology*, **13**, 65-75.

JAGIELLO-WOJTOWICZ, E. (1973). The central action of histamine (part I): The effect of intraventricular histamine on rat behaviour. *Pol. J. Pharmacol. Pharm.*, **25**, 503-510.

SINHA, J.N., GUPTA, M.L. & BHARGAVA, K.P. (1969). Effect of histamine and antihistaminics on central vasomotor loci. *Eur. J. Pharmac.*, **5**, 235-238.

TRENDELENBURG, U. (1957). Stimulation of sympathetic centres by histamine. *Circulation Res.*, **5**, 105-110.

WHITE, T. (1965). Peripheral vascular effects of histamine administered into the cerebral ventricles of anaesthetized cats. *Experientia*, **21**, 132-133.

An anticholinergic effect of general anaesthetics on cerebrocortical neurones

P.A. FORRESTER
(introduced by D.W. STRAUGHAN)

Department of Pharmacology, The School of Pharmacy, University of London, 29/39 Brunswick Square, London WC1N 1AX

The effect of general anaesthetics on the increase in neuronal firing rate produced by the iontophoretic application of acetylcholine and L-glutamate is controversial. Krnjević & Phillis (1963) observed a specific anticholinergic effect (see also Catchglove, Krnjević & Maretić, 1972). But a nonspecific decrease in the post-synaptic sensitivity to all chemical excitants has also been reported (Crawford, 1970; Crawford & Curtis, 1966). It seemed worthwhile therefore to try to eliminate these discrepancies and possibly throw light onto the mechanism of action of general anaesthetics. Rats were anaesthetized with urethane (2.2 g/kg). Electrodes were placed on the exposed cortical surface for ECoG. recording and multibarrelled glass micropipettes inserted into the underlying cortical tissue for recording of single neuronal action potentials and the application of drugs by iontophoresis using the standard techniques.

Under urethane anaesthesia the ECoG. appears as surface positive waves separated by quiescent periods, with the spontaneous activity of cortical neurones occurring during these waves in the ECoG. (Bindman, Lippold & Redfearn, 1964). Monitoring the ECoG. therefore gives a measure of the endogenous drive to the cortex. The iontophoretic application of either L-glutamate or acetylcholine to responsive cortical neurones caused firstly an increase in the number of action potentials falling within the ECoG. waves (presumably representing facilitation of endogenous drive—Forrester, 1975) and then, if the rate of iontophoresis was sufficiently high, evenly spaced action potentials between the ECoG. waves.

When a variety of central depressants (including barbiturates, halothane and benzodiazepines) were systemically administered a decrease in the frequency of the ECoG. waves resulted-without changes in blood pressure (Forrester & Gartside, 1975). Consequently iontophoretically induced excitations which were largely dependent upon the drive to the cortex were reduced. In 5 experiments with halothane (1-2%, inspired) and 8 experiments with thiopentone (5-10 mg/kg, i.v.) both L-glutamate and acetylcholine excitations of this type were reduced.

When thiopentone (5-10 mg/kg, 9 experiments), halothane (1-2%, 12 experiments) and diazepam (1.5-2.0 mg/kg, 10 experiments) were administered to animals where, in the control responses both acetylcholine and L-glutamate induced action potentials between the bursts, then the production of 'interburst action potentials' by acetylcholine was suppressed but those produced by L-glutamate were not.

Hence it is concluded that the general anaesthetics tested antagonize the depolarization of cortical neurones produced by the iontophoretic application of acetylcholine but not that produced by L-glutamate; although depending upon the conditions the increase in neuronal firing rate produced by L-glutamate can be reduced. These results, therefore, support the view that the anticholinergic effect of general anaesthetics may contribute to their anaesthetic effect (Krnjević, 1974).

References

BINDMAN, L.J., LIPPOLD, O.C.J. & REDFEARN, J.W.T. (1964). Relation between the size and form of