Effects of Histamine, Histidine and Imidazole Acetic Acid on Neurones of the Medulla Oblongata of the Cat

Histamine and some of its metabolites have been detected in various areas of the feline central nervous system (for ref. see[1]). It has been demonstrated that microelectrophoretically administered histamine, histidine and imidazole acetic acid (IAA) have mainly depressant actions on neurones of the cerebral cortex of the cat[2,3]. Furthermore, BRADLEY, HÖSLI and WOLSTENCROFT[4] reported that histamine depresses the firing of brain stem neurones. OBATA et al.[5] also observed a depression of spike discharges of Deiters neurones by IAA.

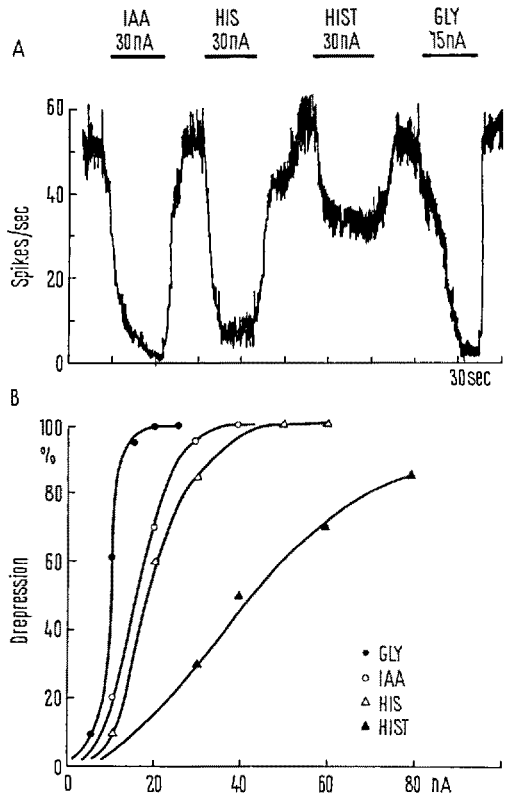
In the present investigation we have studied the effects of histamine, histidine and IAA on the spontaneous firing of neurones of the medulla oblongata of the cat. The action of strychnine on the depression caused by IAA was also investigated.

Experiments were carried out on 15 cats which had been decerebrated during nitrous oxide/halothane anesthesia. The methods used have been described in detail in a previous paper[6]. Action potentials were recorded extracellularly through the 4 M-NaCl containing barrel of a 6-barrel glass micropipette (3–6 μm tip diameter) from neurones of the medulla oblongata (1–5 mm rostral to the obex, up to 2 mm lateral to the midline and up to a depth of 5 mm). The following drugs were administered microelectrophoretically: Histamine dihydrochloride (Fluka, 0.5 *M*), L-histidine dihydrochloride (Fluka, 0.5 *M*), imidazole acetic acid hydrochloride (Calbiochem, 0.5 *M*), 1-methyl-4-imidazole acetic acid hydrochloride (Calbiochem, 0.5 *M*), 1,4-methylhistamine dihydrochloride (Calbiochem, 0.5 *M*) and glycine (Fluka, 0.5 *M*). The solutions were adjusted to pH 3-3,5 with HCl and ejected with cationic (+) current. Strychnine hydrochloride (British Drug Houses) was prepared as a 5 m*M* solution in 165 m*M* NaCl and ejected with cationic current.

Histamine, histidine and IAA depressed the firing of the majority of neurones tested. A comparison of these drugs on the same neurone revealed that IAA was usually a more potent depressant than histidine and histamine, although on some cells histidine and/or histamine were equally effective. When the action of glycine was compared with that of histamine and IAA on the same cell (42 cells), glycine was always a more effective depressant than the other two substances. A typical example of the depressant action of these substances is illustrated in Figure 1A. Glycine which was ejected with a current of 15 nA (10^{-9} A) caused a similar depression as IAA administered with a current of 30 nA. IAA was only slightly more potent than histidine but clearly more effective than histamine (ejected with the same current) on this cell. The order of relative potency of these drugs is also illustrated in the 'dose-response' curve (Figure 1B) which shows the relationship between various ejecting currents and the depression of firing (in %).

The time course of depression which often varied considerably between neurones, was usually slower for histamine than for IAA and histidine. The action of glycine was always faster in onset than that of the other substances (using equal ejecting currents). No desensitization to the depressant actions of IAA (6 cells) and histamine (3 cells) was observed when these drugs were applied repeatedly in short intervals. 1,4-methylhistamine dihydrochloride (MH) and 1-methyl-4-imidazole acetic acid hydrochloride (MIA) which have been tested on a few cells had also depressant actions, MH being more effective than MIA.

The action of strychnine on the depression caused by glycine, and IAA was studied on 11 cells in 6 cats. Electrophoretically administered strychnine (5 m*M* in 165 m*M* NaCl) always reversibly blocked the depressant action of glycine but did not affect the depression caused by IAA.



A) Comparison of the actions of glycine (Gly), imidazole acetic acid (IAA), histamine (Hist) and histidine (His) on the spontaneous firing of a neurone of the medulla oblongata. Firing frequency (spikes/sec, ordinate) is plotted against time (30 sec intervals, abscissa). Durations of drug ejection are represented by horizontal bars above the trace. Values of the ejecting currents in nA (10^{-9}A) are indicated above the bars.

B) 'Dose-response' curve obtained for the same neurone. Each point represents the maximal depression (in %) produced by Gly, IAA, His and Hist ejected with different currents (nA) for approximately equal periods.

1 J. P. GREEN, in *Handbook of Neurochemistry, Control Mechanisms in the Nervous System* (Ed. A. LAJTHA; Plenum Press, New York, London 1970), vol. 4, p. 221.

2 K. KRNJEVIĆ and J. W. PHILLIS, Br. J. Pharmac. *20*, 471 (1963).

3 J. W. PHILLIS, A. K. TEBÈCIS and D. H. YORK, Br. J. Pharmac. *33*, 426 (1968).

4 P. B. BRADLEY, L. HÖSLI and J. H. WOLSTENCROFT, Br. J. Pharmac. *29*, 121 (1967).

5 K. OBATA, K. TAKEDA and H. SHINOZAKI, Expl. Brain Res. *11*, 327 (1970).

6 L. HÖSLI and A. K. TEBÈCIS, Expl. Brain Res. *11*, 111 (1970).

A discussion of the results and the significance of these drugs for synaptic transmission will be deferred until this work is reported in detail.

Zusammenfassung. Mikroelektrophoretisch verabreichtes Histamin, Histidin und Imidazolessigsäure hemmen die Aktivität von Neuronen der Medulla oblongata der Katze. Strychnin, welches in reversibler Weise die hemmende Wirkung von Glycin blockiert, zeigt keinen Antagonismus zu Imidazolessigsäure.

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The Origin of Tourniquet Shock-Induced Cardiovascular Failure in Exogenous Hyperthyroidism

It is controversial whether the sudden cardiovascular collaps of hyperthyroid animals in shock is primarily due to myocardial or peripheral failure.

In exogenous hyperthyroidism the enlarged heart ejects more blood and is more efficient than the normal, euthyroid heart under basal conditions and during loading[1]. There are, however, indications that areas of relative hypoxia may exist in the hypertrophied myocardium of hyperthyroid animals. Marked tachycardia and increased oxygen requirement result in a non-uniform distribution of coronary blood flow, myocardial hypoxia and decreased contractile force[2]. This pattern could cause the sudden deaths of exogenous-hyperthyroid animals and may be the primary deteriorating factor in shock since susceptibility to shock is directly related to an increased metabolic rate of most organs[3] including the heart[4].

The following experiments were designed to differentiate between myocardial involvement and peripheral involvement as the primary deteriorating factors in the development of shock. Hyperthyroid animals were pretreated with either reserpine, a norepinephrine depleting agent or phenoxybenzamine, an α-blocking agent. The cardiovascular system was then challenged by unilateral or bilateral tourniquets on the hind limbs.

Material and methods. Male albino rats of the Sprague-Dawley Strain (Holzman) weighing 220 $\pm$ 15 g were used. The rats were made hyperthyroid by a daily s.c. injection during 14 days, of 20 µl/100 g of body weight of l-triiodothyronine (Cytomel: Smith, Klein & French Co.). The control animals received injections of solvent in the same volume to body weight ratio. Reserpine pretreatment consisted of a s.c. injection of Serpasil: Reserpine (Ciba Pharmaceutical Products, Inc.), 1 mg/kg body weight, 1 day before the tourniquet was applied. Phenoxybenzamine: Dibenzyline (Smith, Klein and French Lab.) 1 mg/kg of body weight, was given i.p. 1 h before tourniquet application. Tourniquet shock was produced by the ligation of the hind limb(s) of anesthetized animals (pentobarbital – 30 mg/kg i.p.) at the inguinal level, with a double rubber band kept in place for 5 h. Death was confirmed by electrocardiogram. Total body oxygen consumption was measured with a M.O.U.S.E. spirometer (Mod. 160, Custom Eng. & Dev. Co., St. Louis, Mo.). Blood pressure was recorded in the carotid artery by a Statham pressure transducer and the mean arterial blood pressure is expressed as diastolic pressure $+^1/_3$ of pulse pressure. The Student-*t*-test was used to determine the significance of the difference between two means. *P*-values less than 0.01 were accepted as significant.

Results and discussion. 5 h bilateral limb ischemia caused 100% mortality in eurythyroid rats (Table I). The survival time could be increased significantly by pretreatment with phenoxybenzamine but reserpine was completely ineffective. Similar results were seen with hyperthyroid animals having incresed cardiac work load (increased blood viscosity due to extravasation from the ischemic limbs) during the development of tourniquet shock. The animals died within a short time after the release of the tourniquets but again, phenoxybenzamine significantly lengthened the survival time.

Recent studies[5] fail to support the previous concept[6] that hyperthyroid animals are less resistant to shock as a

[1] M. BEZNÁK, Can. J. Biochem. Physiol. *40*, 1647 (1962).
[2] D. PIATNEK-LEUNISSEN and R. E. OLSON, Circulation Res. *20*, 242 (1967).
[3] A. G. B. KOVÁCH, L. TAKÁCS, A. MOHÁCSI, V. KÁLDOR and Z. KALMÁR, Acta physiol. hung. *11*, 181 (1957).
[4] G. G. ROWE, J. H. HOUSTON, A. B. WEINSTEIN, H. TUCHMAN, J. F. BROWN and C. W. CRUMPTON, J. clin. Invest. *35*, 272 (1956).
[5] H. S. MARGOLIUS and T. E. GAFFNEY, J. Pharmac. exp. Ther. *149*, 329 (1965).
[6] W. R. BREWSTER, jr., J. P. ISAACS, P. F. OSGOOD and T. L. KING, Circulation *13*, 1 (1956).

Table I. Bilateral limb ischemia: The effect of drugs on euthyroid and hyperthyroid rats

Treatment	Euthyroid			Hyperthyroid			
	No. of rats	Survival time (h)	Mortality (%)	No. of rats	Survival time (h)	Mortality (%)	Significant difference between Euthyroid-Hyperthyroid
Saline	11	11.2 $\pm$ 1.61	100	15	0.92 $\pm$ 0.24	100	$P < 0.01$
Reserpine	10	11.64 $\pm$ 1.24	100	14	0.85 $\pm$ 0.18	100	$P < 0.01$
Phenoxybenzamine	12	19.32 $\pm$ 2.84	83[a]	15	2.48 $\pm$ 0.45	100	$P < 0.01$

[a] 2 of 12 animals lived 7 days and were sacrificed.