The Hypothermic Effect of Eserine in the Rat

V. M. VARAGIĆ, MILENA ŽUGIĆ, and T. KAŽIĆ

Department of Pharmacology, Faculty of Medicine, Belgrade 11.000 and Drug Factory "Zdravlje", Leskovac 16.000, Yugoslavia

Received April 22, 1971

Summary. In rats kept under ordinary laboratory and living conditions the intravenous injection of eserine regularly produced a dose-dependent hypothermic effect. Neostigmine produced variable responses including both hyperthermia and hypothermia. The effect of eserine is most probably due to an activation of central cholinergic processes. The finding that the hypothermic effect of eserine was blocked by atropine and not by methylatropine indicates both the central origin of the effect and the implication of muscarinic receptors in it. Propranolol did not affect the response to eserine, but alpha-receptor blocking agents (phenoxybenzamine, phentolamine), if injected in sufficiently high doses, blocked it. All the adrenergic blockers, particularly the alpha-receptor blockers, were found to produce pronounced hypothermia by themselves.

Eserine was also found to produce a dose-dependent decrease in the oxygen consumption. This effect is most probably crucial for the hypothermic response to eserine, because this substance also produced hypothermia at ambient temperatures close to thermal neutrality. It is supposed that eserine, by activating central cholinergic synapses, produces an inhibition of thermogenesis.

In animals kept in cages with warm bases (29—37°C) eserine produced hyperthermia. This effect was blocked by neither propranolol nor atropine, and it is most probably produced by fasciculations.

Key Words: Eserine — Thermoregulation — Adrenergic Mechanisms — Cholinergic Mechanisms.

Several investigators have shown that cholinomimetic substances can produce hypothermia in the rat and the mouse (Lomax et al., 1969; Meeter, 1969; Friedman and Jaffe, 1969). This effect was observed after injection of these substances either intravenously or into the rostral hypothalamus. After studying cholinergic and adrenergic interactions in the thermoregulatory centers of the rat, Lomax et al. (1969) suggested that temperature regulation involves a cholinergic link in the rostral hypothalamus. These authors suggested that catecholamines may play a role in the control of body temperature by changing the degree of polarization of these cholinergic neurons. The role of noradrenaline in the central control of body temperature in the rat is also the subject of several other papers (Gordon et al., 1966; Corrodi et al., 1967; Feldberg
Eserine has been known to produce adrenergic effects in the rat (Varagić, 1955; Varagić et al., 1967; Mršulja et al., 1968; Stamenović and Varagić, 1970). An initial activation of the central cholinergic mechanisms is supposed to precede the activation of adrenergic mechanism (Varagić et al., 1968). It was therefore of interest to study the action of eserine on temperature regulation in the conscious rat.

Methods

White rats (160 to 220 g) of either sex were used in these experiments. Food and water were left to all animals ad libitum. In the animal quarters the temperature was kept between 24 and 26°C. In the laboratory in which the experiments were performed the ambient temperature always ranged from 19 to 25°C. The experiments were performed in autumn, winter and early spring. In order to minimize the circadian fluctuations in rectal temperature, all experiments were performed between 9 a.m. and 3 p.m. The rectal temperature was measured by using either YSI thermistor probes, models 401 and 402 (Yellow Springs Instrument Co.), or a Hartman-Brown Fe-Const. thermocouple. The probes and the thermocouple were inserted into the rectum to a depth of 4—6 cm. The animals were kept in small rat cages during the experiment. The temperatures measured by thermistor probes were monitored on a recorder (“Physiograph four” E & M Instruments Co.).

In a separate series of experiments the animals were also kept in small cages, but the rat holder base was heated with a rat holder temperature control unit (E & M Instruments Co.); the plate on which the animals were placed was heated to 29, 35, 37, or 39°C. A separate series of experiments was performed at an ambient temperature of 29—30°C (“hot room”). The temperature in this room was thermostatically controlled and kept within this range. For the purpose of adaptation the animals were kept in this room for 18 days before the experiment.

The oxygen consumption was measured with a closed system in which a respirometric chamber was immersed in a thermostatically controlled bath at 20°C. Details of this method are described by Giaja (1953). With this method the oxygen consumption is continuously recorded.

All drugs were dissolved in pyrogen-free distilled water and injected intravenously into the tail vein, except phenoxybenzamine (dissolved in propylene glycol) which was injected intraperitoneally.

The following substances were used: eserine salicylate, neostigmine methylsulphate, atropine sulphate, atropine methyl nitrate, (±)-propranolol hydrochloride (Inderal®, ICI), d-tubocurarine chloride, phenoxy benzamine hydrochloride and phentolamine methansulphonate (Regitin®, CIBA).

Results

Hypothermic Effect of Eserine

The intravenous injection of eserine in doses ranging from 50 to 200 μg/kg was found to produce a hypothermic effect. This effect was manifested by a decrease in rectal temperature ranging from 0.5 to