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The Role of Serotonergic System in Body Temperature Regulation

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Summary

Results indicate that vascular responses to temperature stimulation are predominantly impaired in animals with 5-HT deprivation. A hypothesis is therefore raised that the 5-HT system participates in body temperature regulation in such a way asto link the regulatory output with vasomotor pathways. The 5-HT system in the spinal cord has been shown to inhibit the afferent transmission of temperature signals. Therefore, depletion of 5-HT does not prevent sensory transmission, at least at the spinal cord level.

Key words

Thermoregulation – Vascular responses – Serotonin

Intracerebroventricular injection of monoamines generally alters body temperature. In the rabbit, intracerebroventricular injection of the 5-hydroxytryptamine (5-HT) causes hypothermia, and noradrenaline (NA) causes hyperthermia (Cooper *et al.* 1965). Iontophoretic application of monoamines to temperature sensitive neurones in the hypothalamus has revealed that 5-HT activates warm sensitive neurones and inhibits cold sensitive neurones (Hori and Nakayama 1973). NA in turn activates cold sensitive neurones and inhibits warm sensitive neurones. These neurophysiological data support the idea that the action of 5-HT is hypothermic and that of NA is hyperthermic. However, 5-HT microinjected into the rostral part of the preoptic area and anterior hypothalamus (PO/AH) causes hyperthermia, whereas 5-HT in the remainder of PO/AH induces hypothermia (Komiskey and Rudy 1977). Further, 5-HT injected into the subarachnoid space of the spinal cord causes hyperthermia in the animal species in which intracerebroventricular injection of 5-HT induces hypothermia (Lopachin and Rudy 1982). In this species, intrathecal NA causes hypothermia, while intracerebroventricular NA causes hyperthermia. Therefore, it is yet difficult to determine whether 5-HT and NA are hypothermic or hyperthermic. Monoaminergic systems in the brain and spinal cord possess heterogeneity concerning body temperature regulation. We evaluated the role of the serotonergic system in each effector mechanism of body temperature regulation. Further, effects of the microinjection of 5-HT on the responses of dorsal horn neurones in the spinal cord to temperature stimulation were observed in order to examine the participation of the descending 5-HT system in the afferent transmission of temperature signals.

Autonomic responses to thermal stimulation in 5-HT-deprived rabbits

The aim of these experiments was to evaluate the role of 5-HT system in each effector mechanism of body temperature regulation. Vasomotor and metabolic responses to temperature stimulation were observed in rabbits pretreated with 5,7-dihydroxy-

tryptamine (5,7-DHT) and lysergic acid diethylamide (LSD).

1. The Effect of 5,7-Dihydroxytryptamine (5,7-DHT) on 5-HT Content

Rabbits were pretreated with 5,7-DHT (300 g/kg with 0.1 % ascorbic acid) injected intracisternally. The 5-HT content of the brain and spinal cord regions was determined by high performance liquid chromatography. The content of 5-HT was significantly reduced in all brain regions examined (Nagai *et al.* 1985). The reduction of the 5-HT content was already significant one day after 5,7-DHT treatment, and was still proceeding 7 days after the treatment. For the experiments, animals one day and 7 days after 5,7-DHT treatment were used.

2. Vasomotor Responses to Warm Stimulation

Vasomotor responses of the ear skin and renal arteries to warm stimulation of the spinal cord were observed in rabbits anaesthetized with sodium pentobarbital. In control animals, spinal cord warming simultaneously induced vasodilatation of the ear artery and vasoconstriciton of the renal artery, a typical response pattern to warm stimulation (Iriki and Nagai 1981). In animals pretreated with 5,7-DHT, vasomotor responses in the ear skin and renal arteries were both abolished (Nagai *et al.* 1985).

LSD, especially in low doses, has been reported to inhibit the firing of presynaptic 5-HT neurones *via* autoreceptors in a reversible manner (Haigler and Aghajanian 1977). Intraperitoneal injection of LSD, 40–50 μg/kg, inhibited the vasodilatatory response of the ear skin artery to spinal cord warming (Nagai and Iriki 1985). The vascular response was restored 60–100 min after LSD injection.

These results indicate that impairment of the 5-HT system abolishes the vascular responses to warm stimulation. The patternized response of the vasculatures to warm stimulation, i.e. vasodilatation of the ear skin artery and vasoconstriction of the renal artery, is subserved by concomitant changes in the activity of sympathetic neurones (Iriki and Nagai 1981). A possible explanation for the abolition of the response pattern is that the descending transmission of the signals from the regulatory centre for body temperature to the sympathetic preganglionic neurones, which influence the vascular tone, is impaired by 5-HT deprivation.

3. Vasomotor and Metabolic Responses to Cold Stimulation

In conscious rabbits, body-core cooling was employed, and core temperature, ear skin temperature and metabolic rate were determined at the onset of shivering and at maximum shivering (Nagai *et al.* 1986). Experiments were performed at a neutral ambient temperature, 20 °C. Shivering was still induced by body-core cooling in the animals pretreated with 5,7-DHT. The core temperature and metabolic rate at the onset of shivering and at maximum shivering did not differ between control and 5,7-DHT-treated animals. The most obvious difference was that the vasoconstrictor response of the ear skin artery to cooling was strongly inhibited in the animals pretreated with 5,7-DHT. We also applied body-core warming, and observed that thermal panting was induced in 5,7DHT-treated animals as in the controls. As in the case of warm stimulation, the vascular response to cold stimulation was predominantly inhibited in 5,7-DHT-treated animals. The fact that shivering and panting were still induced in 5,7-DHT-treated animals as in the controls suggests that the afferent transmission of temperature signals is not impaired by 5-HT deprivation.

4. Metabolic Responses to NA and Propranolol

In conscious animals, the effects of NA (500 mg/kg, s.c.) and propranolol (4 mg/kg, s.c.) on the metabolic rate were investigated at a neutral ambient temperature, 20 °C. NA increased the metabolic rate, and propranolol decreased it. There were no significant differences in the metabolic responses between control and 5,7-DHT-treated animals, although the metabolic rate of 5,7-DHT-treated animals tended to be slightly higher than that of control animals. These results show that non-shivering thermogenesis (NST) through adrenergic receptors is not significantly influenced by 5-HT depletion with 5,7-DHT.

Table 1

Effects of microiontophoretic injection of monoamines (MA)on the responses of spinal cord neurones of the urethane-anaesthetized rat to somatic stimulations.

	Tactile	Joint flexion and extension	Scrotal warming	Total
	16	12	7	35
MA application	11	10	4	25
MA effective	5	4	4	13
5-HT +	0	1	0	1
5 -HT -	1	1	4	6
NA +	1	0	0	1
NA -	2(1)	2	0	4(1)

In total, 35 units were identified. In 25 out of 35 units, application of both 5-HT and NA was successfully performed. In 13 out of these 25 units, 5-HT or NA effectively modified the neural responses. 5-HT+: 5-HT enhanced the response. 5-HT-. 5-HT inhibited the response. NA+: NA enhanced the response. NA-. NA inhibited the response. Parentheses show that monoamines did not influence the response of the neurone but influenced the resting firing rate.

Effects of microiontophoretic injection of 5-HT on responses of dorsal horn neurones in rats

It is well known that the afferent transmission of nociceptive signals in the spinal cord is inhibited *via* the descending serotonergic system (Carstens *et al.* 1981, Yezierski *et al.* 1982).

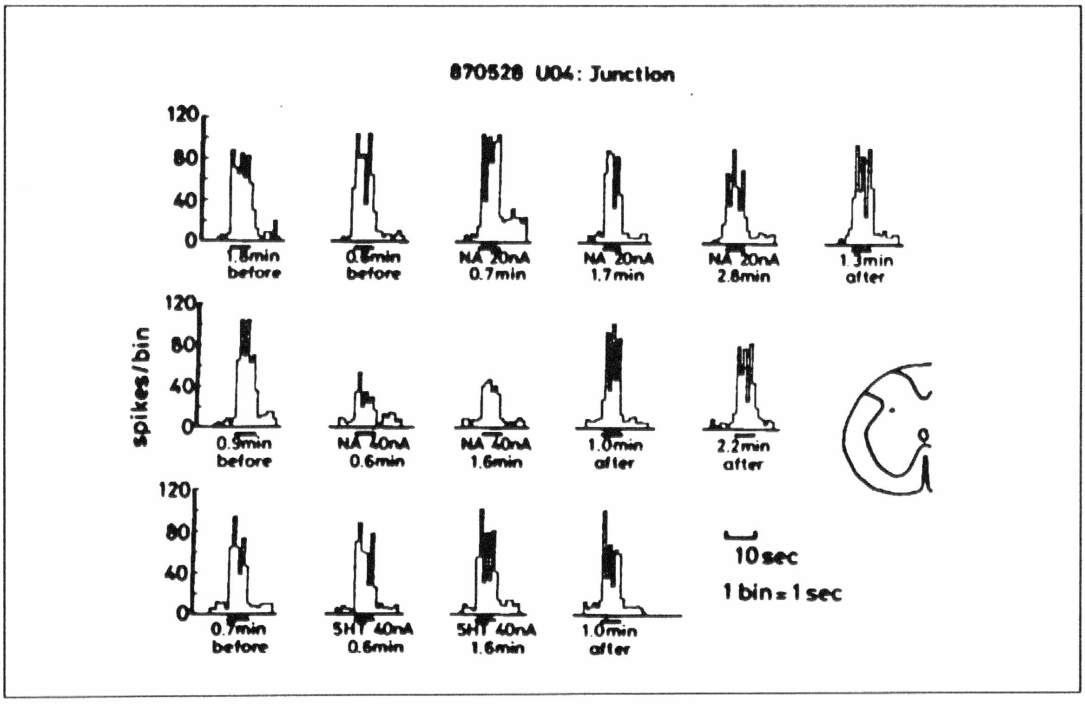

Fig. 1
Unit response of spinal cord neurone to joint flexion and extention in urethane-anaesthetized rat. NA inhibited the response in a dose-dependent manner, but 5-HT had no effect on the response.

We examined the effect of microiontophoretic application of monoamines on the responses of dorsal horn neurones to somatic stimulations of the hind limb of urethane-anaesthetized rats. Dorsal horn neurones were

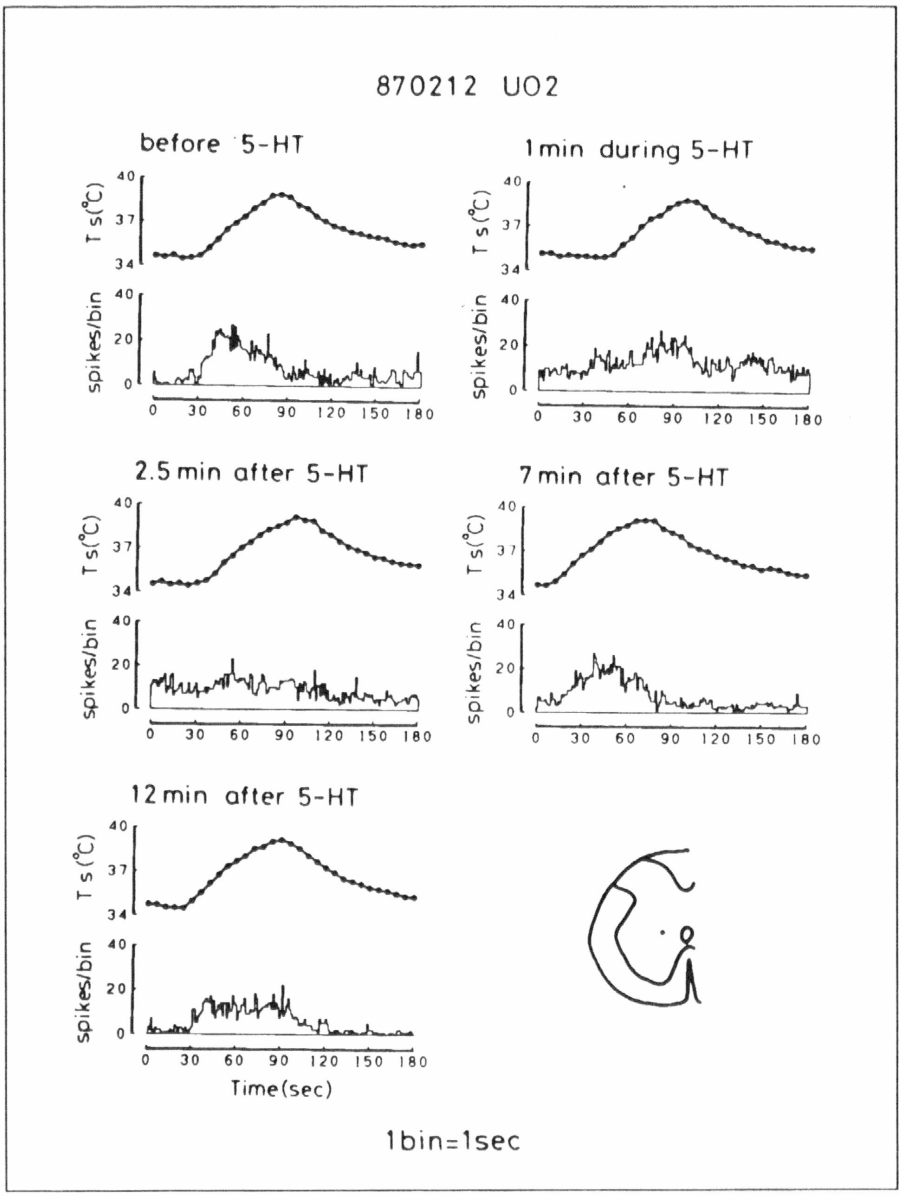

Fig. 2
Unit response of spinal cord neurone to warm stimulation of the scrotal skin in urethane-anaesthetized rat. 5-HT inhibited the response in a reversible manner. Ts: temperature of the scrotal skin.

explored in the spinal cord at the L6 – S1 level. The results are summarized in Tab. 1. In dorsal horn neurones which responded to tactile stimulation and flexion and extention of joints, serotonin possessed no effect, or inhibitory or excitatory effect on the responses. Fig. 1 shows that the response of dorsal horn neurones to flexion and extension was inhibited by NA in a dose-dependent manner but not influenced by 5-HT. On the contrary, in neurones which responded to warm stimulation of the scrotal skin, 5-HT always inhibited the response, whereas NA had no effect. Fig. 2 shows an example in which 5-HT inhibited the response of a neurone to scrotal warming. Inhibitory effect of 5-HT on the

temperature response was apparent 1 min after the onset of 5-HT application and lasted 5 min after the application had ceased. In this neurone, 5-HT increased baseline firing rate at the same time: 5-HT cut off the thermal input to this neurone on one hand, but activated the neurone itself on the other hand. Therefore, this neurone probably became more sensitive to inputs with other qualities by 5-HT. In this case, the serotonergic system in the spinal cord serves as a switching mechanism for sensory inputs or weight constant for the transmission of sensory signals with different qualities. The neurone shown in Fig. 2 was located deeper in the spinal gray matter. It is therefore uncertain whether this neurone is spinothalamic, has a sensory function, or whether it is an interneurone belonging to the local segmental circuitry.

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