PARTICIPATION OF TWO TYPES OF BRAIN SEROTONIN RECEPTORS IN BODY TEMPERATURE REGULATION MECHANISMS IN RATS

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KEY WORDS: serotonin receptors; temperature regulation.

Injection of serotonin into the cerebral ventricles and cisterns and also into the hypothalamus gives rise to hypothermia in rats [1, 3-5, 7, 10]. In view of recently published data on the existence of two types of serotonin receptor (S_1 and S_2) in the brain, differing in their affinity for serotonin (5-HT) and its agonists and antagonists, and also in their dependence on guanine nucleotides and binding with adenylate cyclase [11, 12], the question of the type of 5-HT receptors mediating the action of 5-HT on body temperature has arisen. There are isolated data in the literature which can now be interpreted as evidence of participation of brain S_2 receptors in temperature regulation mechanisms [4]. No data on the role of S_1 receptors in body temperature regulation could be found in the literature.

The aim of this investigation was to study the role of central S_1 and S_2 receptors in the temperature-regulating effects of 5-HT.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 200-220 g, kept under standard animal house conditions. Drugs were injected into the lateral cerebral ventricle through previously (3-5 days before the experiment) implanted steel microcannulas: serotonin-creatinine sulfate (from Reanal, Hungary) in a dose of 20 μg, cyproheptadine (from Serva, West Germany) in a dose of 100 μg, Deliside (from Sandoz, Switzerland) in a dose of 0.5 μg, L-110 140 (from Eli Lilly, USA) in doses of 2, 10, and 50 μg. The solvent for serotonin was sterile isotonic NaCl solution, whereas for cyproheptadine and L-110 140 it was distilled water. Sterile isotonic NaCl solution or distilled water in a volume of 5 μl was injected into the control animals. L-110 140 also was injected intraperitoneally in doses of 10 and 15 μg/kg; animals receiving isotonic NaCl solution acted as the control.

During the experiments the rats were kept in open boxes measuring 30 × 20 × 20 cm at a temperature of 22.0 ± 1.0°C. The rectal temperature was measured by a transducer with sensitive element consisting of an MT-54 microthermistor, with an accuracy of ±0.1°C. Temperature was recorded on a multichannel KSP-4 potentiometer. The skin temperature was measured by means of a skin electrothermometer at the base of the tail.

To measure oxygen consumption the rats were placed in a chamber with a volume of 2 liters, through which air was pumped at the rate of 300 ml/min. The air leaving the chamber was led to an electrochemical oxygen analyzer [2]. The oxygen consumption was measured by comparing the oxygen concentration in the air before and after passing through the chamber containing the rat. The accuracy of analysis was 0.03 vol. % O_2 over the range from 17.9 to 20.9 vols. % O_2.

Recording of the rectal and skin temperatures and oxygen consumption of the rats began 60-90 min before injection of the drugs and continued for 60-90 min after injection.

At the end of the experiment methylene blue solution was injected into the rats through a cannula, after which the rats were decapitated and the brain removed, and entry of the substance into the cerebral ventricles was verified.

The data were subjected to statistical analysis by Student's t test.

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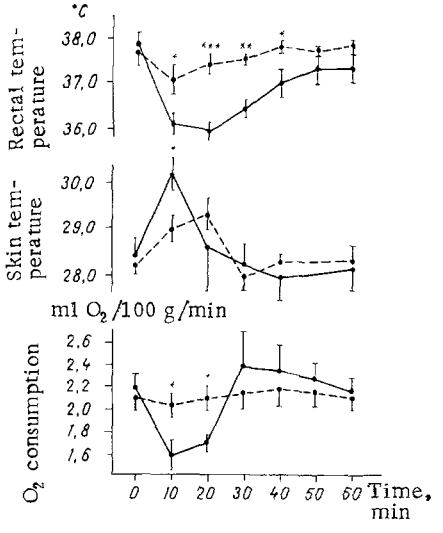

Fig. 1

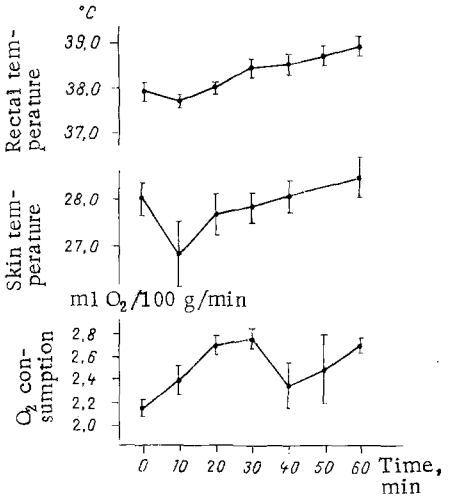

Fig. 2

Fig. 1. Changes in rectal and skin temperature and oxygen consumption of rats after intraventricular injection of 5-HT in a dose of 20 μg (continuous line) and the same dose of 5-HT 20 min after injection of 100 μg of cyproheptadine (broken line). Each point represents mean results of 4-6 experiments. 0) Time of injection of 5-HT. *P < 0.05, **P < 0.01, ***P < 0.001 compared with injection of 5-HT.

Fig. 2. Changes in rectal and skin temperature and oxygen consumption of rats after intraventricular injection of Deliside in a dose of 0.5 μg. Each point represents mean results of 4-6 experiments. 0) Time of injection of Deliside.

EXPERIMENTAL RESULTS

The initial body temperature of the rats with implanted microcannulas averaged 37.6 ± 0.2°C. Injection change in body temperature or oxygen comsumption fell and skin temperature rose compared with their initial values (Fig. 1). The results confirm observations [1, 5, 7] indicating that 5-HT, injected into the cerebral ventricles of rats, induces hypothermia, which is based on a decrease in heat production and (or) an increase in heat loss.

Cyproheptadine, a blocker of S_2 receptors [12], if injected into the cerebral ventricles caused no significant change in the body temperature or oxygen consumption of the rats. However, after preliminary injection of cyproheptadine, the hypothermic effect of 5-HT was considerably weakened (Fig. 1). Both the rise of skin temperature and the fall of oxygen consumption, induced by 5-HT, were blocked. The hypothermia arising after central injection of 5-HT is evidently linked with stimulation of brain S_2 receptors, leading to a decrease in heat production and an increase in heat loss from the body surface of the rats.

Unlike the S_2 receptors, for which a number of selective blockers are known, no substances with selective action of S_1 receptors are known. Nevertheless, experiments with Deliside, which acts on both types of receptors [12], can yield definite information on the effect of S_1 receptors on body temperature in rats.

When injected intraventricularly Deliside caused hyperthermia in rats. The oxygen consumption rose considerably (Fig. 2). The effect of injection of Deliside on oxygen consumption and body temperature was evidently connected with its stimulating action on S_1 receptors and not with blockade of S_2 receptors, for as experiments with cyproheptadine showed, S_2 receptor blockade did not change the rats' body temperature.

Compound L-110 140, which inhibits reassimilation of 5-HT [6, 13], when injected intraperitoneally in doses of 10 and 15 mg/kg, induced hypothermia in rats: The rectal temperature fell by 1.9 ± 0.6 and 2.3 ± 0.7°C respectively. These results confirm data [8, 9] showing that inhibitors of 5-HT reassimilation produce a hypothermic effect on intraperitoneal injection. However, in the present experiments when L-110 140 was injected into the lateral cerebral ventricle of rats, a hyperthermic response was found. The oxygen consumption increased and the skin temperature fell a little (Fig. 3). The effect of L-110 140 depended on

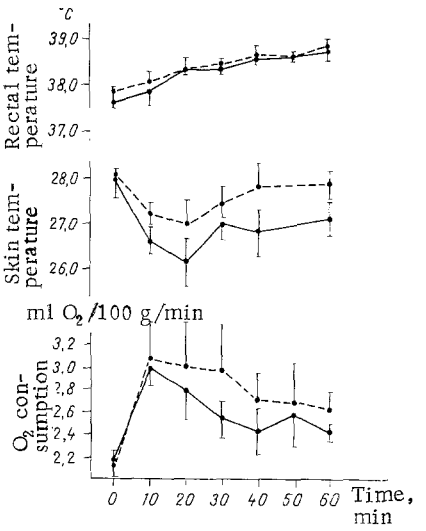

Fig. 3. Changes in rectal and skin temperature and oxygen consumption of rats after intraventricular injection of 10 μg of L-110 140 (continuous line) and the same dose of L-110 140 20 min after injection of 100 μg of cyproheptadine (broken line). Each point represents mean results of 4-6 experiments. 0) Time of injection of L-110 140. Differences between animals receiving L-110 140 with and without cyproheptadine not significant.

the dose of the drug. The hypothermic action of L-110 140 when injected intraperitoneally may perhaps be due, not to the central effect, but to the peripheral effect of the compound, which evidently predominates when this method of administration is used.

After preliminary injection of cyproheptadine the temperature reaction to centrally injected L-110 140 showed no significant change (Fig. 3). It can be postulated on the basis of these results that the hyperthermia induced by this compound was due to the action of 5-HT on S_1 receptors. The mechanism of development of hyperthermia through action on S_1 receptors is evidently based on increased heat production by the animals, for the oxygen consumption was increased after injection of both Deliside and L-110 140.

L-110 140, which increases the 5-HT concentration in the intersynaptic space, ought not to exhibit any selective action on one type of 5-HT receptor. However, the fact that L-110 140 is a substance with indirect action and that its effect can be exhibited only in synapses in which 5-HT is released into the intersynaptic space, must be taken into account. At a given environmental temperature S_2 receptors, which participate in temperature regulation, are not stimulated by 5-HT, for the blocker of S_2 receptors did not change the rats' body temperature and the effect of injection of L-110 140 was not blocked by cyproheptadine. Meanwhile the coincidence of the temperature effects of Deliside, a stimulator of S_1 receptors, and L-110 140 suggests that S_1 receptors are activated at a temperature of 22°C.

Stimulation of both types of brain 5-HT receptors thus had some effect on body temperature in rats. Stimulation of S_1 receptors leads to hyperthermia as a result of increased heat production. Stimulation of S_2 receptors causes hypothermia as a result of a decrease in heat production and an increase in heat loss from the body surface of the rats. S_1 receptors are evidently activated at an ambient temperature of 22°C, whereas S_2 receptors are not activated.

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COMPARISON OF DIRECT AND INDIRECT DETERMINATIONS OF THE SINUS NODE RECOVERY TIME

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High-frequency atrial stimulation is used in the diagnosis of the sick sinus syndrome [1, 5-7]. During atrial stimulation activity of the sinus node is considered to be suppressed and is not restored until a short time has elapsed after the end of stimulation [5, 6]. This time is called the sinus node recovery time (SNRT) and is regarded as an indicator of the functional capacity of the sinus node: In patients with a sick sinus syndrome SNRT is greater than normally. In clinical practice SNRT is determined indirectly from the atrial activity recovery time. Hence the great importance of the question of how correctly the atrial activity recovery time reflects the recovery time of the sinus node itself, how the sinus node functions during atrial stimulation, how the atrial activity recovery time depends on the character of activity of the sinus node during atrial stimulation with different frequencies. The investigation described below was devoted to a study of these problems.

EXPERIMENTAL METHOD

Experiments were carried out on the frog *(Rana temporaria)* heart. The sinus venosus was isolated together with the atria, unfolded to form a tissue slab, and placed in Ringer's solution, pH 7.2.

Electrical potentials were recorded by means of suction electrodes with a tip not more than 100 μ in diameter. The potentials were recorded on an ELKAR electrocardiograph. The atria were stimulated extracellularly by above-threshold square pulses 5 msec in duration from a "Physiovar" stimulator. The frequency of stimulation was higher than the spontaneous frequency of excitation of the preparation and was 37.5, 43, 50, 63, and 77 ± 4 beats/min. Stimulation at each frequency lasted 30-40 sec, after which the preparation was excited for 20-30 sec in its intrinsic rhythm.

The experimental results were analyzed by Student's t test.

EXPERIMENTAL RESULTS

In 11 experiments atrial stimulation was carried out as mentioned above. During atrial stimulation the imposed frequency was completely bound. In all experiments the sinus venosus continued to be excited during atrial stimulation (Fig. 1 and 2) but the frequency of its excitation varied depending on the frequency of atrial stimulation. The mechanism of changes in the frequency of the sinus venosus was examined previously [2].

During atrial stimulation at a frequency 20-30% higher than the intrinsic frequency of the preparation, the sinus venosus of all the preparations switched to the frequency of stimulation. An example of one such experiment is given in Fig. 1. The spontaneous frequency

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