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BRIEF COMMUNICATION

Hyperthermia Following Self-Stimulation of the Median Raphe in the Rat

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MILIARESSIS, E. AND D. JACOBOWITZ. *Hyperthermia following self-stimulation of the median raphé in the rat.* PHARMAC. BIOCHEM. BEHAV. 4(4) 477–479, 1976. – Electrical self-stimulation (SS) in the median raphé of the rat but not in the locus coeruleus resulted in a dramatic rise of body temperature. This hyperthermia was facilitated by pretreatment with a inhibitor of serotonin uptake. The functional significance of the hyperthermia elicited by stimulation of the media raphé was discussed on the basis of the relationship between SS and primary reinforcers.

Self-stimulation Body temperature Median raphé Serotonin

SEROTONIN (5-HT) has received particular attention as a possible neurotransmitter in thermoregulatory mechanisms. Though considerable amounts of pharmacological studies have been performed in order to clarify its role (see review by Myers [6]), the conclusions have been limited by the relative non-specificty of drug treatment.

Limitations which result from the use of chemical agents could be partially circumvented by direct stimulation of specific serotonergic perikarya (raphé nuclei). Thus, electrical stimulation of caudal raphé in the rat was reported to induce a rise of body temperature [8]. We recently reported that stimulation of the median raphé is strongly rewarding and therefore results in a high self-stimulation behavior (SS). In addition, evidence was reported that this behavior is sustained by the activity of 5-HT containing neurons [4]. Therefore, the purpose of the present study was to investigate the question whether common nervous areas are involved in self-stimulation and hyperthermia elicited by stimulation of raphé nuclei.

METHOD

Bipolar electrodes (200 μm in dia.)were implanted stereotaxically in 31 male Sprague-Dawley rats (280 g) under anesthesia by inhalation of a mixture of oxygen and halothane. In 26 rats, the electrodes have been implanted to terminate their tip in the median raphé (nucleus centralis superior) while 5 animals received an electrode in the noradrenergic nucleus locus coeruleus. With the incisor bar 3 mm above the interaural line, stereotaxic coordinates for the locus coeruleus were 8.6 mm posterior to the bregma, 1.2 mm lateral to the midline, and 7.1 mm under the surface of the skull. Median raphé coordinates were respectively 6.0, 0 and 8.0 mm.

One week after surgery, rats were trained to self-stimulate intracerebrally by pressing a lever in a 23 × 33 × 28 cm transparent box. Each press delivered a 250 ms, 60 c/s sin. current. The intensity was adjusted individually for each rat during the first training trials in order to elicit a maximum frequency of presses without motor disturbances or apparent overexcitation (mean intensity, 47 ± 5.2 μa, rms). Following 10 days of stabilization of SS behavior, rats were allowed henceforth to self-stimulate only 1 hr per week, for 3 consecutive weeks. Rectal temperature was then recorded before and immediately after the SS periods. For a few animals, continuous records of temperature were recorded graphically. A few days following the completion of the above experiment, the effect of 3-(p-trifluoromethyl-phenoxy)-N-methyl–3-phenylpropylamine (Lilly 110140) on normal body temperature and changes of temperature during SS were tested according to the following procedure: the drug was injected IP 3 hr before a 60 min SS period. Rectal temperatures were recorded just before the injection, 3 hr after the injection (i.e., immediately preceeding the SS period) and just following SS. The same procedure was repeated on the same animals 3 times with 5,

10 and 20 mg/kg of Lilly 110140 respectively. All injections were separated by 3 days of rest. At the completion of the experiments, the animals were sacrificed and the brains sectioned in a cryostat and stained for histological verification of electrode placement.

RESULTS

One hr of SS in the median raphé (see elctrode location in Fig. 1) results in a 1.8 ± 0.14 C° increase in rectal temperature which represents a dramatic change. Increase of body temperature ranged from 1.1 to 5.0 C°. However, the majority of the animals showed changes varying between 1.5 and 2.5 C°. An individual record is graphically shown in Fig. 2. Changes in temperature following SS proved to be relatively stable as measured in 3 weekly tests. The dramatic change of temperature seems to rule out a nonspecific hyperthermia resulting from the body activity during SS. Furthermore, 1 hr of intense exploration in an open field situation, as measured in 8 of the experimental rats, resulted in only a slight temperature increase (mean, 0.59 ± 0.07 C°). In addition, rats self-stimulating in the locus coeruleus showed a 0.62 ± 0.01 C° increase in rectal temperature which is very close to that obtained following general body activity.

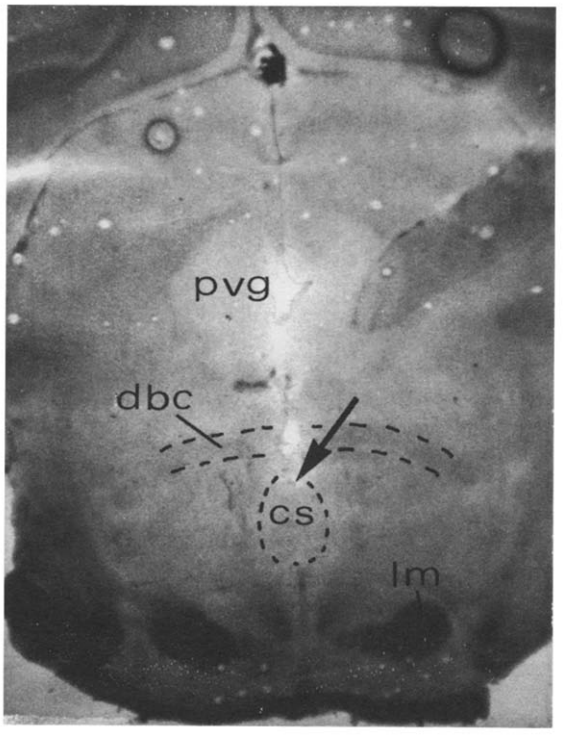

FIG. 1. Microphotograph showing a representative electrode placement in the median raphe of the rat. The tip of the electrode track is shown by an arrow. CS: nucleus centralis superior; dbc: decussation of brachium conjunctivum; lm: lemniscus medialis; pvg: substantia grisea centralis. (XII.5).

The pharmacological experiment performed in the present work was an attempt to test the hypothesis that changes in body temperature following SS in the median raphé result from the activity of 5-HT-containing neuronal elements. In this respect, the recent discovery of a highly specific inhibitor of serotonin uptake (Lilly 110140)

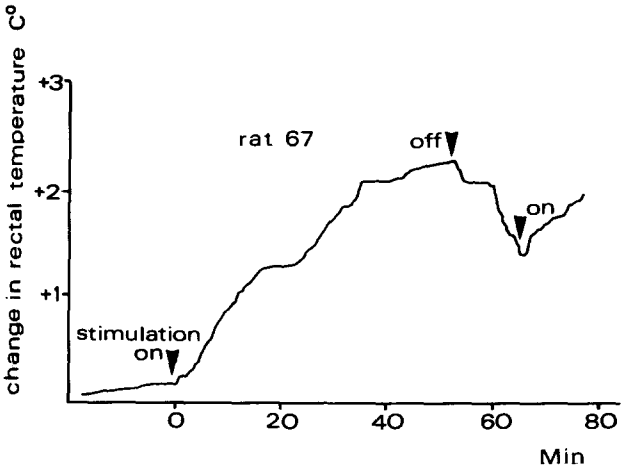

FIG. 2. Continuous record of rectal temperature during self-stimulation in the median raphé. Note the rapidity of changes that follow the onset and termination of the stimulation.

provides a useful tool [10]. Figure 3 shows the data obtained with this drug on a small group of 4 rats. Lilly 110140, alone, produces a dose-dependent decrease of rectal temperature (Fig. 3a) though a possible initial rise cannot be excluded since the temperature was recorded only 3 hr following injection of the drug. Figure 3b shows that in spite of its hypothermic effects, Lilly 110140 (at doses that do not effect SS) does not antagonize, but slightly facilitates the hyperthermic effect of median raphé stimulation (10 mg/kg Lilly 110140; $t = 2.28$; $df = 3$; $p = 0.10$).

Consistent changes in SS frequency following Lilly 110140 occur only with the highest dose of the drug (Fig. 3c). With this dose, median raphé SS is inhibited by 45%.

DISCUSSION

The present report shows that self-stimulation of the median raphé results in a dramatic rise of body temperature. Failure to observe the same phenomenon following self-stimulation in the locus coeruleus may suggest that the increase in temperature is not a common feature of SS behavior and that thermal changes may accompany rewarding neuronal activity elicited only by serotonergic stimulation. The present results confirm the data of Sheard and Aghajanian [8] obtained by forced stimulation of the median raphé. However, according to these authors, only the caudal part of raphé was involved in the hyperthermia phenomenon while both the anterior and lateral parts were not. In the present study the electrodes were located in the nucleus centralis superior in a relatively anterior position. However, since the location of the electrodes was not shown by the aforementioned authors, an accurate anatomical comparison is not possible. The opposite action on temperature between electrical stimulation of serotonergic neurons and administration of Lilly 110140 alone strongly supports the hypothesis that serotonin release mediates a mechanism which increases body temperature. In fact, Lilly 110140 produces a dose-dependent decrease of serotonergic turnover [1]. A decreased release of 5-HT from the terminals of the hypothalamus, an important thermoregulatory area, has also been observed [1]. Since the drug inhibits 5-HT reuptake and therefore, free amine accumu-

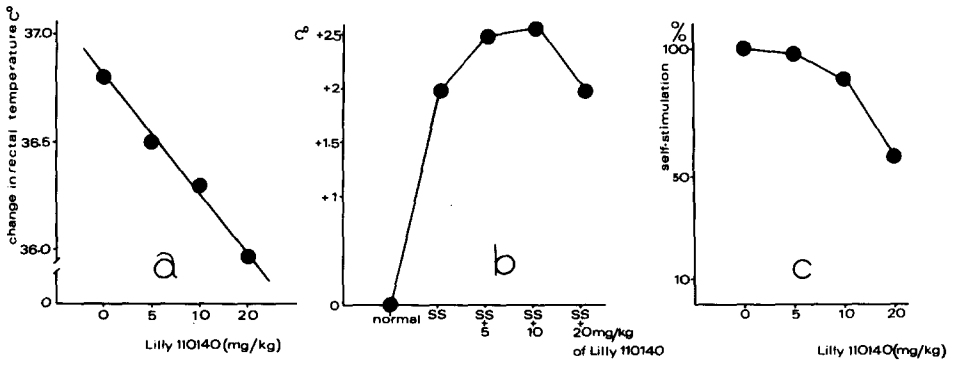

FIG. 3. (a) Mean rectal temperatures 3 hr following increasing doses of Lilly 110140. (b) Mean relative changes in rectal temperature following self-stimulation alone or in combination with increasing doses of Lilly 110140. (c) Mean percent of bar presses for self-stimulation following administration of Lilly 110140.

lates at the synaptic cleft, the inhibition of 5-HT neuronal activity probably represents a feedback regulatory mechanism. In agreement with this hypothesis is the fact that some of the tricyclic anti-depressant drugs which block the reuptake of serotonin produce an inhibition of firing in the midbrain raphé cells [9].

Lilly 110140, in spite of its hypothermic effects, does not antagonize but slightly facilitates the hyperthermia that results following raphé stimulation. This apparent discrepancy may mean, however, that the electrical stimulation of the median raphé disrupts and/or counteracts the regulatory mechanism and subsequently leads to an additional accumulation of amine at the synaptic level which results in a further rise in temperature.

The present report shows that positive reward is elicited by stimulation of raphé areas that activate a hyperthermic mechanism. The fact that p-chlorophenylalanine inhibits both positive reward [4] and hyperthermia [8] elicited by stimulation of median raphé suggest that a common serotonergic basis sustains the 2 phenomena. However, the possibility that 2 functionally independent systems are involved cannot be excluded. On the other hand, in view of the obvious reinforcing properties of temperature, the possibility that the 2 phenomena are functionally linked must be taken into consideration: primary reinforcers (food, water, sex) are believed to act via the self-stimulation system [7]. It is also known that stimulation of specific rewarding areas results in a breakdown of the normal regulatory mechanisms and leads to a hyperphagia [3], hyperdypsia [5] or hypersexuality [2]. Therefore, the hypothesis that the hyperthermia following self-stimulation results from an analogous mechanism with similar functional significance must be taken into consideration.

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