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Effects of Hyperprolactinaemia on Core Temperature of the Rat

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DRAGO, F. AND S. AMIR. *Effects of hyperprolactinaemia on core temperature of the rat.* BRAIN RES BULL 12(4) 355–358, 1984.—The effects of endogenous hyperprolactinaemia (HPRL), as induced by pituitary homografts under the kidney capsule, on core temperature (T_c) was investigated in rats before and after the application of restraint stress. HPRL was accompanied by a significant decrease in T_c of freely moving rats, as observed for four days after pituitary homografts. HPRL-induced hypothermia was totally reversed by intraperitoneal (IP) injection of naloxone. In normoprolactinaemic (NPRL) rats, IP administration of naloxone caused a small but significant decrease in T_c and attenuated rise in temperature following the application of restraint stress. After application of restraint stress, T_c of HPRL rats raised to the level of unstressed NPRL rats. However, HRPL rats injected IP with naloxone showed no increase in T_c after restraint stress application. The effects of HPRL on T_c seem to involve an opioid component, and support the concept of a role played by stress hormones of hypophyseal origin in the control of T_c.

Hyperprolactinaemia Core temperature Naloxone Restraint stress

THE hormones of pituitary gland play a major role in adaptive responses to stress. Among others, prolactin (PRL) is released by the pituitary gland in response to various stressor stimuli [16] and can affect adaptive behaviors, such as grooming [5] and avoidance behavior [7]. These effects seem to involve opioid transmission, as peripheral injection of the opiate receptor antagonist naloxone inhibits them [6].

Thermoregulatory changes, that follow the application of stressor stimuli, can also be caused by opiate drugs and endogenous opioids. In particular, depending on the dose, intracerebroventricular (ICV) administration of β-endorphin can elicit a rise or fall in the core temperature (T_c) of the rat [1,10]. Hypothermia has often been described after ICV administration of low doses of β-endorphin [14]. This effect is totally abolished by peripheral administration of naloxone. However, naloxone it-self produces a dose-dependent hypothermia in unstressed rats and attenuates or prevents the stress-induced rise in T_c [20].

The present experiments were carried out in order to evaluate the effects of PRL on T_c of the rat, before and after the application of restraint stress. The experimental model was represented by rats with endogenous hyperprolactinaemia (HPRL), as induced by pituitary homografts under the kidney capsule. These homografts secrete very high amount of PRL and little, if any, of the other pituitary hormones [15]. They, hence, maintain plasma PRL at high levels and allow to avoid continuous administration of the hormone. Furthermore, we used restraint stress because it is constantly followed by an hyperthermic response, that has been called "emotional hyperthermia" [20]. Another aim of the present experiments was the study of a possible involvement of opioid transmission in the effects of HPRL on T_c of the rat. This has been investigated by injecting naloxone to HPRL and normoprolactinaemic (NPRL) animals.

METHOD

Animals

Male rats of an inbred Wistar strain, weighing 220±20 g, were used throughout all the experiments. The animals were housed 5 in a cage under a 12-hr constant light-dark cycle (lights on between 8.00 and 20.00) and at a constant 21°C room temperature. Commercial animal food and water were available ad lib.

Surgery

A number of rats were subjected to a surgical operation consisting of the implantation of two adenopituitaries of similar strain animals under the kidney capsule, according to the method described elsewhere [22]. Control animals received the implantation of a piece of smooth muscle only. These surgical operations were performed under ether anaesthesia.

Drugs

Naloxone hydrochloride (Endo Laboratories) was dissolved in saline and injected intraperitoneally (IP). Control animals received a similar injection of saline only.

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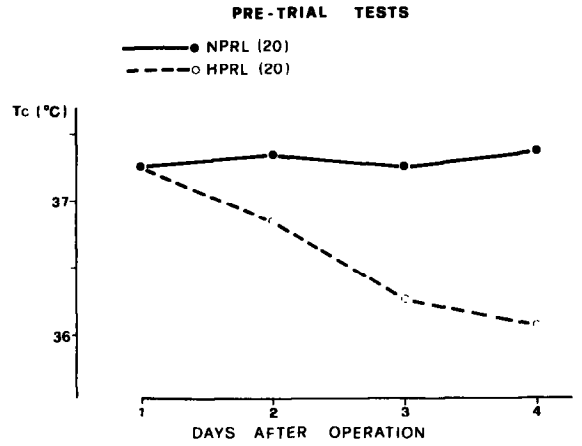

FIG. 1. Time-course of T_c in HPRL and NPRL rats as measured in the pre-trial tests for four days after pituitary homografts. Values are mean (S.E.M. are omitted). In parentheses the number of animals for each experimental group. For statistical differences see the text.

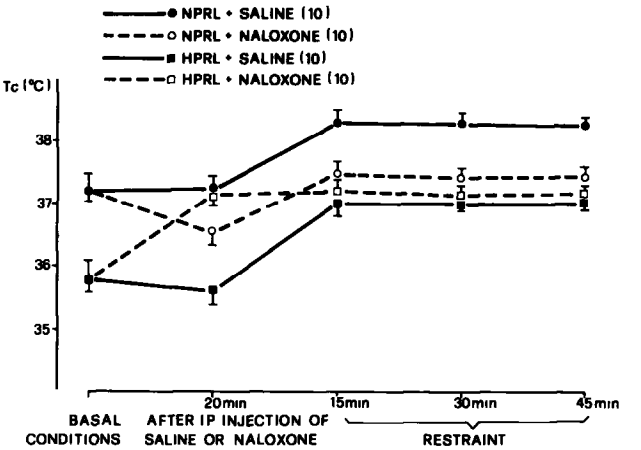

FIG. 2. Changes in T_c of HPRL and NPRL rats after IP injection of naloxone or saline and application of restraint stress. Values are mean±S.E.M. In parentheses the number of animals for each experimental group. Animals were subjected to a measurement of T_c under basal conditions and successively injected IP with naloxone (1 mg/kg) or saline. Twenty min later, T_c was again measured and the rats were subjected to restraint stress. Measurements of T_c were performed 15, 30 and 45 min after restraint stress was initiated. For statistical differences see the text.

Temperature Measurements

T_c was measured at selected times by inserting a thermistor (Yellow Springs Telethermometer, model 46, accuracy±0.1°C) 6 cm into the rat's rectum. The thermistor was held in place for about 30 sec until a stable temperature was read from the telethermometer. Ambient temperature was controlled between 20–22°C. All temperature measurements were performed in the morning, between 9.00 and 15.00.

Experimental Design

Both HPRL (homografted) and NPRL (control) rats were subjected to a daily measurement of T_c, starting on the day after operation. Animals were removed from their cage only for temperature measurements and were immediately returned to the cage. Temperature measurements for these pre-trial tests were performed for four days with freely-moving animals. On the fifth day, HPRL and NPRL animals were randomly divided into two sub-groups of 10 rats each. Immediately after temperature measurement (with freely-moving animals), the rats were given an IP injection of naloxone (1 mg/kg) or saline and returned to their cage. Twenty min later, T_c was again measured with freely-moving animals. The rats were successively subjected to restraint stress by placing them in cylinders (diameter: 5 cm; length: 18 cm) made of Plexiglas. The thermistor was inserted immediately and temperature measurements were read just after 15, 30 and 45 min after beginning of restraint.

At the end of experimental procedures, all animals were killed by decapitation and trunk blood was collected for PRL radioimmunoassay (RIA). Plasma PRL levels were measured according to the method described by Niswender *et al.* [17], with six serial 1:2 dilutions, using NIAMDD rP-1 rat-PRL as standard.

Statistical Analysis

Statistical analysis was made using an analysis of variance (ANOVA) with replication, and the Student's t-test, two tailed. A probability level of 0.05 or less was accepted as significant difference.

RESULTS

Plasma PRL levels of all homografted rats appeared to be significantly higher than those of sham-operated controls (88.7 ng/ml, n=20, vs. 19.7 ng/ml, n=20, $p<0.01$, Student's t-test, two tailed).

T_c of HPRL and NPRL rats, as measured in the pre-trial tests for four days after operation, is shown in Fig. 1. HPRL animals exhibited a gradual decrease in T_c as compared to NPRL rats, $F(3,152)=13.07$, $p<0.01$, ANOVA with replication.

Figure 2 shows the results concerning the effects of IP injection of naloxone or saline and of restraint stress on T_c of HPRL and NPRL rats. Twenty min after IP administration of naloxone, T_c of NPRL animals appeared to be slightly but significantly lower than that of NPRL saline-treated rats ($p<0.05$, Student's t-test, two tailed). Furthermore, IP injection of naloxone to HPRL rats was followed by a rise in T_c to a level similar to that of NPRL saline-treated animals. When restraint was applied, T_c of NPRL saline-treated rats showed a significant rise that was kept during all restraint period. The application of restraint stress of NPRL naloxone-treated rats was followed by a small increase in T_c. ANOVA with replication revealed a significant difference within group in NPRL naloxone-treated rats for all three T_c measurements during restraint stress, $F(1,72)=5.54$, $p<0.05$. However, the level of T_c of NPRL naloxone-treated rats was significantly lower during all restraint period than that of NPRL saline-treated animals, $F(3,72)=5.44$, $p<0.05$, ANOVA with replication). T_c of HPRL saline-treated rats increased significantly after restraint stress was applied, $F(1,72)=4.13$, $p<0.05$, ANOVA with replication. However, the level of T_c

of HPRL saline-treated rats was significantly lower during all restraint period than that of NPRL saline-treated animals, $F(3,72)=6.77$, $p<0.01$, ANOVA with replication). T_c of HPRL naloxone-treated rats did not show any change in all three measurements during restraint stress, keeping a level significantly lower than that of NPRL saline-treated rats, $F(1,72)=5.76$, $p<0.05$, ANOVA with replication.

DISCUSSION

The present results show that HPRL induces hypothermia in unstressed freely-moving rats. This effect seems to involve opioid transmission, as IP injection of the opiate receptor antagonist naloxone, despite of its hypothermic effect in NPRL unstressed rats, leads to a normalization of T_c in HPRL animals. PRL can indeed affect opioid transmission in the brain. Endogenous HPRL is accompanied by changes in opioid concentration of various brain areas [19]. Furthermore, PRL-induced behavioral effects such as enhanced grooming, facilitated acquisition of active avoidance behavior and reduced responsiveness to electrical footshock, are inhibited by peripheral administration of naloxone or naltrexone [6]. Thus, it is possible that brain opioid transmission is also involved in HPRL-induced hypothermia. It is worth mentioning that ICV injection of β-endorphin can also, depending on the dose, elicit a fall in T_c of the rat [14]. However, hypothermia induced by naloxone has occurred in the present experiments and in others [20]. Furthermore, peripheral injection of naloxone inhibits hypothermia induced by ICV administration of β-endorphin [14]. These data, taken together, suggest that multiple opiate receptors are probably involved in the control of thermoregulation of the rat.

A role played by monoamine neurotransmitters in morphine-induced hypothermia has recently been pointed out [2]. In particular, 5-hydroxytryptamine and norepinephrine seem to participate as central mediators of morphine-induced hypothermia. Furthermore, ICV injection of either 5-hydroxytryptamine or norepinephrine or dopamine is followed by a fall in body temperature of the rat [13]. Thus, HPRL-induced hypothermia may also involve monoamine transmission in the brain. It is worth mentioning that short-term HPRL (five days after pituitary homografts) is accompanied by numerous changes in the steady-state concentration and turnover of dopamine and norepinephrine of various brain areas [12]) which might mediate HPRL-induced hypothermia. However, as in the present experiments only the opiate receptor antagonist naloxone and no dopamine or norepinephrine receptor antagonist was used, an involvement of these monoamine neurotransmitters in HPRL-induced hypothermia remains hypothetical. The parallelism between PRL and morphine in the multiple mediation of their hypothermic effect by opioid and monoamine transmission seems to be an interesting phenomenon.

As an alternative, HPRL may induce hypothermia via an increase in plasma corticosterone levels. In fact, augmented concentrations of plasma corticosterone have been described in animals with endogenous HPRL [4], and corticosterone may exert antipyretic effects [25]. However, this hypothesis is not in agreement with the finding that HPRL-induced hypothermia is inhibited by peripheral administration of naloxone, unless the antipyretic effect of corticosterone also involves opioid transmission.

The present results also show that application of restraint stress, causing hyperthermia in NPRL saline-treated rats, is followed by a small increase in T_c of NPRL naloxone-treated animals and fails to change T_c of HPRL rats given an IP injection of the drug. These results are consistent with others showing that naloxone, when administered prior to stress induction, can attenuate or prevent stress-induced rise in temperature [20,21]. When, however, naloxone is administered after stress is applied, it fails to modify stress-induced hyperthermia [20]. Furthermore, hypophysectomy restores the inhibiting effect of naloxone on stress-induced hyperthermia even if stress is applied after the drug injection [20]. Thus, the pituitary gland may mask the effects of naloxone on T_c because of the stress-induced release of hormones influencing thermoregulation [8]. This should be the case also for PRL, as this hormone is massively released by the pituitary gland in response to various stressor stimuli [16].

A number of hormones released by the pituitary gland in response to stressor stimuli exert behavioral effects for the adaptation of the subject to environmental changes. In particular, adaptive behavior is influenced by ACTH [23], α-MSH [23], β-endorphin [18], vasopressin [24], and PRL [7]. It is of great interest that all these hormones, besides behavioral effects, cause also hypothermia [3, 9, 14]. They can, hence, mediate the hypothermia occurring after application of certain types of stressor stimuli [11].

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