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BRIEF COMMUNICATION

A Kappa Opiate Agonist, U50,488H, Enhances Energy Expenditure in Rats

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MANDENOFF, A., J. A. SEYRIG, D. BETOULLE, L. BRIGANT, J. C. MELCHIOR AND M. APFELBAUM. *A kappa opiate agonist, U50,488H, enhances energy expenditure in rats.* PHARMACOL BIOCHEM BEHAV **39**(1) 215–217, 1991.—The effect of U50,488H (a selective kappa opiate agonist) on oxygen consumption was measured in either resting and free-moving rats. In both states, U50,488H provokes an increase in oxygen consumption. In resting rats, the increase occurs at lower doses than in free-moving rats. The explanation could be that in the free-moving rats the drug results in an increase in energy expenditure, partially compensated by a decrease in activity.

Energy expenditure Oxygen consumption Opiates Kappa agonist U50,488H Rat

THE endogenous opiate system is known to be involved in energy balance. The most classic opiate agonist, morphine, belonging to mu opiate subsystem, has been reported to modify both food intake and energy expenditure. Morphine, injected peripherally at doses of 1 to 30 mg/kg or centrally, especially into the hypothalamic paraventricular nucleus, at the dose of 25 nmoles, increases food intake during the early daytime when rats are physiologically satiated by the important nighttime food intake or in rats satiated by a "satiation period" before food intake tests (3, 11, 15, 16, 18). In fasted rats or during the early nighttime, a peripheric morphine injection decreases food intake at doses as low as 1.0 or 0.05 mg/kg (11, 14, 15, 18).

In rats, β-endorphin, a mixed delta and mu endogenous opiate, centrally injected (ICV) at the beginning of the dark period, at the dose of 30 μg, decreases sucrose intake in stress-induced hyperphagia (2).

The effect of morphine on energy expenditure has been studied only during light time. Peripherally injected morphine decreases energy expenditure measured by oxygen consumption in rats (5.0 or 15.0 mg/kg) (20) or by metabolic weight loss in mice (2.0 to 60.0 mg/kg) (8); centrally injected in preoptic anterior hypothalamus (1.0 to 10 μg), it decreases oxygen consumption for 10 minutes after injection in rats (20). It has been suggested that such a decrease in oxygen consumption could be provoked by a decrease in the locomotor activity (13, 17, 19). However, this explanation remains controversial.

Morphine, injected peripherally or centrally, which does not only decrease locomotor activity but increases it, still results in a decrease of oxygen consumption in mice (7,8) or rats (5,6). Opiate agonists belonging to kappa opiate systems have also been reported to modify both food intake and energy expenditure. Kappa opiate agonists such as bremazocine or ketocyclazocine peripherally injected induce an increase in food intake during daytime (15,16). Ketocyclazocine or MR 2033, like morphine, induce a decrease in food intake either during nighttime or in fasted rats (14,15). The highly selective kappa opiate agonist U50,488 H (12) peripherally injected is reported to induce an increase in daytime food intake lasting at least one hour at doses 0.3 to 3 mg/kg (SC) (10) or 4 hours at 2.5 mg/kg (SC) (9), but a decrease in 24-hour food intake (9). In contrast to morphine, U50,488H increases energy expenditure for 3 hours as measured by the metabolic weight loss method in mice (8). The aim of the present study was to evaluate the effect of U50,488H on energy expenditure by the measure of oxygen consumption: for short times in resting animals and continuously (180 min) in free-moving rats.

METHOD

Male Wistar rats were housed at 23 ± 2°C with a 12-hour light/dark cycle and with free access to water and food (chow Extra Labo M25). Oxygen consumption was measured in each rat

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individually during the light period in a closed underwater circuit respirometer at 29°C after one hour of adaptation and, subsequently in two different situations.

Short Time Measures (1) (About 15 Min) (Experiment 1)

Resting oxygen consumption is determined by measuring the time necessary to consume 20 ml of oxygen. The rat was continuously observed and only the measures during which it remained standing still were taken into account. Twenty-four rats were tested twice in random order without food or water, after a subcutaneous injection of isotonic saline or of U50,488H. Groups of 6 rats were used for each dose of the drug (1.0, 3.0, 6.0, 10.0 mg/kg).

Three-Hour Measures (Experiment 2)

Fifteen rats with access to water, but without food, were tested in a respirometer monitored by an on-line computer recording the volume of oxygen consumed, whatever the activity. The results were obtained every minute and the mean of ten consecutive measures were reported, during 180 minutes.

Expression of Results and Statistical Analysis

Oxygen consumption was expressed as mean ± sem ml of oxygen consumed per hour, per cm^2 of body surface calculated using Benedict's formula: cm^2 of surface = $9.1 \times$ (g body weight 2/3).

Experiment 1. Student's paired *t*-test was used to compare oxygen consumption measured after injection of U50,488H with oxygen consumption after saline injection. The dose dependence of oxygen consumption was evaluated using linear regression analysis.

Experiment 2. Two-way variance analysis with repeated measures was used to assess the effect of U50,488H on total oxygen consumed in the course of 3 hours. One-way variance analysis was used to compare oxygen consumption recorded for every ten minutes in the 3 groups studied: saline, U50,488H (6.0 mg/kg) and U50,488H (10.0 mg/kg).

RESULTS

Experiment 1 (Fig. 1)

In resting animals basal oxygen consumption measured after injection of a low dose (1 mg/kg) of U50,488H (0.8765 ± 0.0104 ml $O_2/h/cm^2$) was not significantly different from that measured without drug (0.8851 ± 0.0104 ml $O_2/h/cm^2$). At higher doses, U50,488H induced an increase in oxygen consumption [3.0 mg/kg: 0.9241 ± 0.0164, $p<0.02$; 6.0 mg/kg: 0.9688 ± 0.0168, $p<0.001$; 10.0 mg/kg: 0.9896 ± 0.0089 ml/$O_2/h/cm^2$, $p<0.001$ (mean ± sem)]. The relationship between oxygen consumption and doses of U50,488H was linear ($y = 0.012 x \pm 0.0882$) with a correlation coefficient $r = .96$ ($p<0.001$).

Experiment 2 (Fig. 2)

In free-moving rats, oxygen consumption of rats injected with 6.0 mg/kg of U50,488H, measured continuously over 3 hours, was not significantly different from that of saline-injected rats. At the dose of 10.0 mg/kg, U50,488H induced an increase in oxygen consumption between 20 and 110 minutes after injection and an increase in global cumulated oxygen consumption measured for 3 hours ($p = 0.006$).

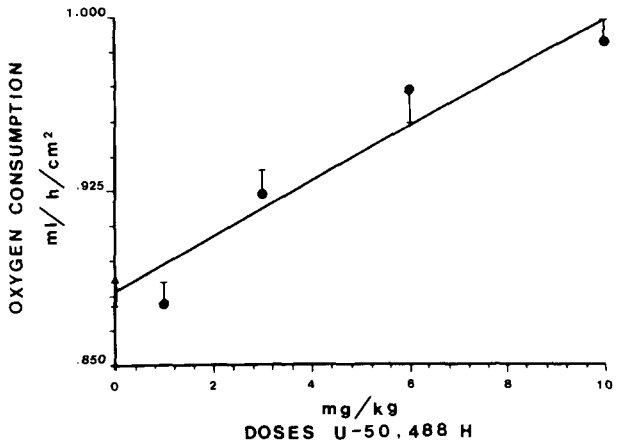

FIG. 1. Dose-response curve of the effect of U50,488H (1.0, 3.0, 6.0, 10.0 mg/kg) on oxygen consumption measured acutely in resting rats. Results are expressed as mean of ml $O_2/h/cm^2$ of body surface ± sem.

DISCUSSION

The present data show that the kappa opiate agonist, U50,488H, induces an increase in oxygen consumption. 1) In resting rats, this effect is dose dependent from 3 to 10 mg/kg. 2) In free-moving rats, it occurs only at the dose of 10 mg/kg. Such an increase was reported and the proposed explanation was that it was partially or totally related to an increase in activity. In mice, such an explanation is wrong since it has been shown that U50,488H injected subcutaneously induces a dose-dependent decrease in locomotor activity measured between 20 and 40 minutes after injection (21). In rats, the effects on activity are more controversial: U50,488H at the dose of 0.3 mg/kg SC does not increase food intake but does not modify physical activity. At 3.0 mg/kg, U50,488H induces an increase in food intake but a decrease in locomotor activity, rearing, grooming and an "increase in inactivity" (10). In no case has an increase in physical activity been reported. Our experiment provides a direct argument against the relation between the activity and the increase in energy expenditure, since such an increase occurs in a dose-dependent manner, in animals permanently observed and at standstill. One intriguing feature is that U50,488H at the dose of 6 mg/kg increases resting oxygen consumption but has no significant effect on oxygen con-

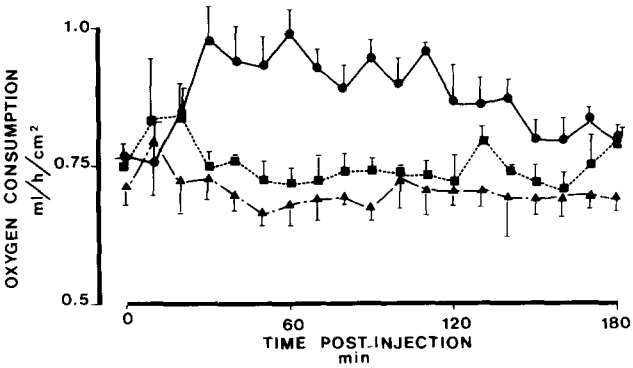

FIG. 2. Effects of U50,488H (6.0, 10.0 mg/kg) on oxygen consumption measured continuously for 3 hours in free-moving rats. Results are expressed as mean of ml $O_2/h/cm^2$ of body surface ± sem: saline (▲), U50,488H 6 mg/kg (■); U50,488H 10 mg/kg (●).

sumption measured continuously in free-moving rats. A possible explanation is that the increase in energy expenditure could be partially compensated by a decrease in activity. At 10 mg/kg the effect of U50,488H on oxygen consumption in free-moving rats would be more potent than its effects on locomotor activity.

Thus the kappa opiate agonist, U50,488H, induces an increase in energy expenditure, which is independent from its effect on physical activity. This effect could be specifically mediated by kappa opiate receptors since it has been shown that the increase in metabolic weight loss induced by U50,488H is suppressed by the kappa opiate antagonist Mr2266 (8). To know whether endogenous kappa opiates are physiologically involved in the control of energy expenditure needs further investigations.

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