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Reduction of Food Intake and Morphine Analgesia by Central Glybenclamide

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ROANE, D. S. AND N. E. BOYD. *Reduction of food intake and morphine analgesia by central glybenclamide.* PHARMACOL BIOCHEM BEHAV 46(1) 205-207, 1993.—Previous research has indicated the presence of a reciprocal relationship between food intake and opioid-mediated analgesia. We believe the cellular candidate most likely acting as a common mediator of both ingestive and nociceptive behaviors is the ATP-sensitive K^+ channel (K^+_{ATP}). This ion channel appears to be opened by mu and delta$_1$ opioid receptor agonists in the service of analgesia, and closed as cellular ATP availability rises. To further examine the role of the K^+_{ATP} in the relationship between feeding and opioid function, we administered 80 nmol of glybenclamide (a K^+_{ATP} antagonist) to male SD rats via the lateral ventricle. Chow consumption in the treated animals was significantly reduced over the following 48 h ($F = 2.62$, $p < 0.013$), with the peak effect (78% of control) occurring at 6 h. In the tail-flick test, 4 mg/kg morphine sulfate provided analgesia of 42.38 ± 8.4% and 18.89 ± 7.67% in vehicle and treated animals, respectively ($p < 0.05$, $n = 8$/group, one-tailed t-test). These results support the hypothesis that food intake and analgesia are reciprocally modulated through activity at the K^+_{ATP}.

Analgesia Nociception Food intake Appetite Energy balance Morphine
Glyburide Glybenclamide Metabolism Brain

A SUBSTANTIAL body of evidence has accumulated describing the role of the endogenous opioids in the regulation of food intake [see (8) for a representative review]. The general theme in these studies shows that agonists of mu and kappa opioid receptors increase food intake, while opioid receptor antagonists reduce food intake.

It has also been reported in recent years that alterations in food intake and energy balance affect opioid-mediated processes involved with nociception and analgesia. Alterations of animals' responsiveness to noxious stimuli occur concomitantly with alterations in total caloric intake (11), diurnal pattern of food intake (12), type of food (15), plasma glucose (17), brain glucose uptake and utilization (3), and, ultimately, glucose-driven brain ATP synthesis (18). It appears that factors that increase brain ATP synthesis reduce the analgesic potency of morphine, while factors that decrease brain ATP synthesis enhance morphine analgesia.

We feel that these previous studies provide ample evidence to suggest the existence of a reciprocal relationship between opioid-mediated processes and the regulation of food intake (i.e., not only do opioids affect food intake, but food intake subsequently affects opioid activity). We further speculate that there is a neuromolecular substrate common to some aspects of both food intake regulation and opioid analgesia, namely, the ATP-sensitive K^+ channel (K^+_{ATP}). This molecule seems to be a likely target for our studies because previous research suggests that this channel (identified by its sensitivity to sulfonylurea hypoglycemic agents) is opened by mu opioid agonists (13,14), and closed by increases in intracellular ATP concentrations.

In an attempt to test the hypothesis that the K^+_{ATP} is involved in the regulation of both food intake and opioid-mediated analgesia, we administered the K^+_{ATP} blocker, glybenclamide (a.k.a. glibenclamide, glyburide) into the lateral ventricles of albino rats and measured the subsequent effects on both behaviors.

METHOD

All animals were males of Sprague-Dawley descent, raised in the NLU vivarium. The animals were individually housed under standard conditions with a 12L : 12D cycle and were fed Purina rat chow throughout the experiments. The mean body weight (±SE) of the animals in the feeding study was 370.2 ± 5.8 g, while the mean body weight of the animals in the analgesia study was 359.8 ± 8.5 g. Each animal was fitted with an injection cannula directed at the lateral cerebral ventricle according to the method of Altaffer et al. (1). Glybenclamide (RBI, Natick, MA) was suspended (8 mg/ml) in a solution of 0.1% Tween 80. The suspension (5 μl) was administered to each test animal, while control animals received injections of the vehicle alone. Preliminary trials of ICV injections of glybenclamide suspended in 5% or 2.5% Tween 80, as previously reported in ICV mice injections [(14,19), respec-

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tively], produced barrel-rolling behavior in rats. The 0.1% Tween 80 vehicle injections exhibited no overt behavioral signs of toxicity.

In the feeding study, animals were divided into control and treatment groups on the basis of forming groups of equal body weights. Following the implantation of the cannulae, the animals were housed individually and allowed a minimum of 5 days to recover. Food cups were removed from the cages at 6:00 p.m. on the day preceding the injections. Between 1:00 and 2:00 p.m. all animals were injected, ICV with 5 μl of vehicle or glybenclamide (81 nmol) and the food cups were returned to the cages. The food cups were then weighed at 1, 2, 4, 6, 8, 24, 30, and 48 h following the injections. The food intake data, expressed as g/kg body weight, was analyzed by ANOVA with repeated measures.

In the morphine analgesia studies, 16 animals were implanted with cannulae and allowed 5–6 days to recover. On the last day of the recovery period, each animal was administered three or four control trials of the tail-flick procedure modified from D'Amour and Smith (5). The animals were then separated into glybenclamide and control groups based on establishing groups of equivalent mean tail-flick latencies. On the test day, each animal was injected ICV with 81 nmol glybenclamide or vehicle followed 15 min later by IP injection of 4 mg/kg morphine from a morphine sulfate salt preparation (NIDA, Drug Supply System, Rockville, MD). The animals were tested for analgesia with three rapid trials of the tail-flick test, beginning 30 min after the morphine injections. The third tail-flick value was used to calculate percent morphine analgesia based on the percent increase from the comparable predrug latency. A one-tailed Student's t-test was used to assess differences in morphine analgesia between glybenclamide and vehicle animals.

RESULTS

In the feeding study, there was a significant reduction in food intake in glybenclamide-injected animals during the 48-h period following administration of the drug (Fig. 1). This reduction was seen as a significant interaction between factors of time and drug ($F = 2.62$, $p = 0.013$). The main effect of the drug treatment did not reach statistical significance [$F = 3.23$, $p = 0.086$, using the type III mean square for individual (treatment) as an error term], due to the convergence of the data at the beginning and ending points of measurement.

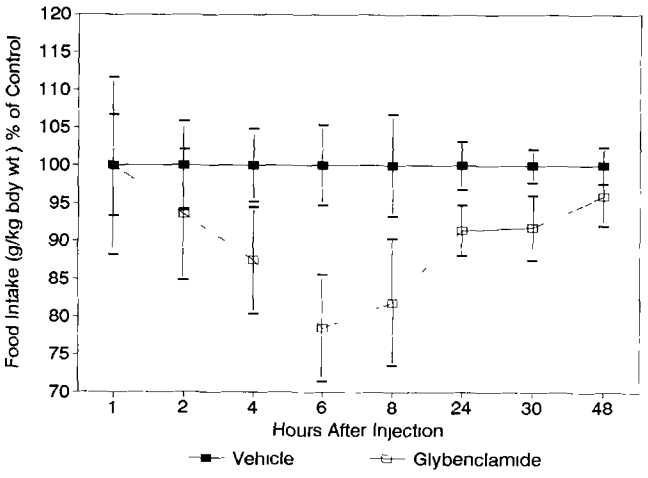

FIG. 1. Glybenclamide ICV produced a significant interaction between factors of time and drug ($F = 2.62$, $p = 0.013$). The main effect of the drug treatment did not reach statistical significance [$F = 3.23$, $p = 0.086$, using the type III mean square for individual (treatment) as an error term], due to the convergence of the data at the beginning and ending points of measurement.

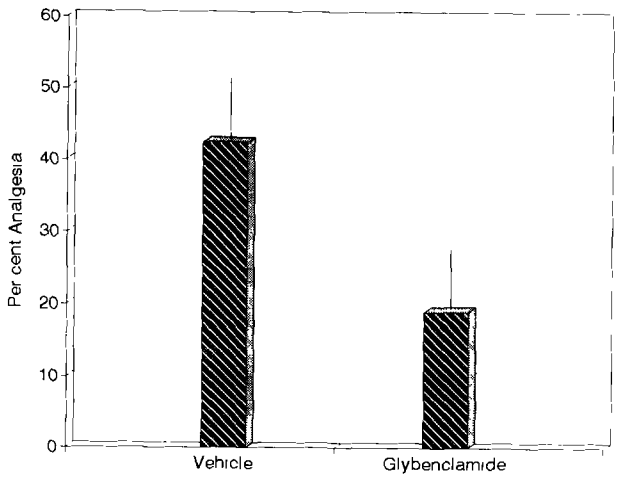

FIG. 2. The results of the tail-flick study showed that 4 mg/kg morphine sulfate provided analgesia of 42.38 ± 8.4% and 18.89 ± 7.67% in vehicle and treated animals, respectively ($p < 0.05$, n = 8/group, one-tailed t-test).

The results of the tail-flick study (Fig. 2) showed that 4 mg/kg morphine sulfate provided analgesia of 42.38 ± 8.4% and 18.89 ± 7.67% in vehicle and treated animals, respectively ($p < 0.05$, n = 8/group, one-tailed t-test).

DISCUSSION

The results of the morphine analgesia test are consistent with those previously reported using glybenclamide to functionally antagonize mu (14)- and delta$_1$ (19)-mediated analgesia in mice.

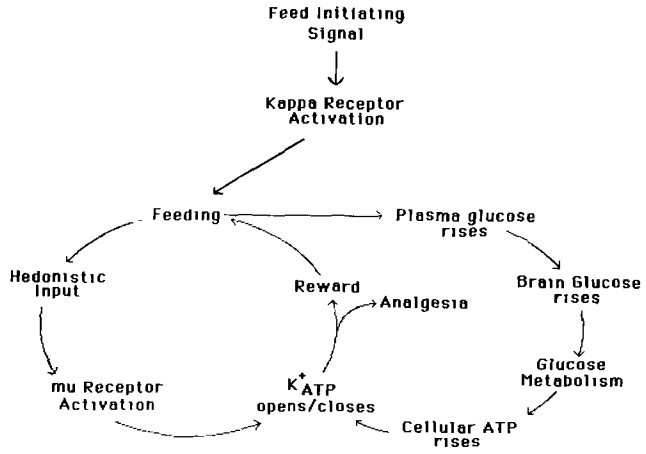

FIG. 3. The hypothetical relationship between opioid-mediated regulation of food intake and opioid-mediated antinociception with respect to the ATP-sensitive K^+ channel (see the Discussion section for further details).

The data from the feeding study are consistent with the prediction of our hypothesis, and are consistent with previous evidence regarding mu receptor involvement in the regulation of food intake (2,7).

Our hypothesis, shown schematically in Fig. 3, predicts that a drug such as glybenclamide, acting as an antagonist of the K^+_{ATP}, would decrease food intake and diminish morphine analgesia, as occurred in the current study. Further, this schematic is consistent with previous findings that have shown a) mu opioid receptors exert their effects by increasing K^+ conductance (13) through the K^+_{ATP} (14), b) a portion of the opioids' contribution to the regulation of food intake is mediated through the activation of mu-type receptors (2,6,9), c) processes contributing to increased synthesis of ATP interfere with morphine analgesia (16–18), and d) factors that hinder brain glucose metabolism enhance the potency of morphine (3,18).

In Fig. 3, we show, at the top, a "feed initiating signal" that, for the purposes of this discussion, we will not attempt to further identify. We will suffice it to say that some event does initiate a feeding signal, which, among many other potential events, leads to the release of central dynorphin and the subsequent activation of kappa opioid receptors; previous studies have indicated that kappa-preferring opioid peptides adiministered into the hypothalamus are more efficacious and potent than peptides preferring mu or delta receptors (6). Following stimulation of the kappa receptors, the animals begin food consumption. We assume that attendant with food intake are hedonic properties leading to a sensation of reward, which leads to further feeding. We suggest that this sensation of reward is supported by neural processes mediated through the activation of mu receptors by endogenous opioids released from neurons activated by peripheral alimentary afferents. In the molecular service of the reward sensation, mu receptors are stimulated, which leads to the opening of the K^+ channels (13), which are of the K^+_{ATP} type (14). As feeding continues, plasma glucose begins to rise and, subsequently, so does brain glucose. Presumably, as brain glucose rises, intracellular brain ATP synthesis and availability also rises. The increase in intracellular ATP facilitates closure of the K^+_{ATP} (4), antagonizing the mu receptor activation effect and hence diminishing the sensation of reward and food intake.

Along with these many assumptions, we further assume that both the phenomena of hedonically originated mu opioid agonism and ATP-mediated opioid antagonism generalize to regions of the brain involved in the opioid-mediated regulation of nociception. Hence, then we would expect that broad increases in intracellular brain ATP synthesis and availability would diminish the analgesic potency of mu agonists, while simultaneously diminishing food intake. Our current results indicate that this may be the case. Furthermore, our hypothesis is consistent with findings that show that self-reinforcing sweet solutions with low metabolic weight enhance resistance to noxious stimuli (10), while diets with high metabolic impact lower such resistance (15).

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