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Food Intake: Opioid/Purine Interactions[1]

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WAGER-SRDAR, S., A. S. LEVINE AND J. E. MORLEY. *Food intake: Opioid/purine interactions.* PHARMACOL BIOCHEM BEHAV **21**(1) 33–38, 1984.—The exogenous opioids butorphanol tartrate (BT) and ethylketocyclazocine (EKC) have been reported to stimulate feeding in rats. In this study we evaluated the effects of purines (known to suppress feeding) and the adenosine antagonist, caffeine, on opioid induced feeding. Adenosine and inosine significantly suppressed BT and EKC induced feeding at various doses and time points. Caffeine enhanced food consumption was suppressed by various doses of naloxone, but was not suppressed by adenosine or inosine. Although caffeine itself induced further feeding, it did not enhance BT induced food consumption. Adenosine and inosine failed to suppress BT induced feeding when 12.5 mg/kg of caffeine was administered to the rats suggesting blockade of the adenosine receptor by caffeine. In contrast to 12.5 mg/kg caffeine, high dose caffeine (50 mg/kg) suppressed BT induced feeding over a 4 hour time period. Adenosine (50 mg/kg) and inosine (50 mg/kg) injected one hour after injection of BT and caffeine (50 mg/kg) reversed the suppressive effect of high dose caffeine in BT induced feeding. These studies indicate that opioid induced feeding can be suppressed by adenosine and inosine. Also, caffeine can reverse the suppressive effect of adenosine and inosine on feeding and vice versa. Naloxone's suppression of caffeine enhanced food consumption indicate that at least part of caffeine's effect on food intake may be mediated through an opioid mechanism.

Opioids Naloxone Purines Caffeine Food intake

PURINES are putative neurotransmitters that are involved in the regulation of a number of physiological functions both centrally and peripherally [4]. Capagrossi *et al.* [6] found that adenosine and inosine, when administered peripherally, could suppress food intake in rats. Our group found that both adenosine and inosine administered peripherally suppressed food intake in rats under a number of conditions, whereas when administered centrally, only adenosine was effective in suppressing food intake [19,28]. Animals to which adenosine had been administered centrally exhibited exploratory and grooming behavior related to food intake, but did not eat, suggesting that suppression of food intake was not due to the sedative effects of adenosine [28]. It has been suggested that adenosine may play a role in central actions of opioids [42,44].

Administration of endogenous and exogenous opioids results in feeding in sated animals whereas opioid blockade by naloxone suppresses food intake (see [34] for a review) [20, 26, 27, 29]. Recently it has become apparent that there are a number of opioid receptors and that opioid agonists bind preferentially to one receptor [43,46]. There is a good deal of evidence that kappa receptor agonists, such as ketocyclazocine and butorphanol tartrate may be more potent enhancers of feeding than other classes of opioid agonists [16, 18, 29, 32] and that the endogenous kappa receptor ligand, dynorphin [7,45] may play a central role in the initiation of feeding [27, 29, 30]. In the present study we investigated the interactions of opioids, purines and their antagonists on feeding behavior.

GENERAL METHOD

Food consumption was studied using 300 male Sprague-Dawley rats (body weight 100–175 g) housed in temperature and light controlled rooms (12 hour light/dark cycle). All drugs and vehicle were administered peripherally by injection either intraperitoneally (IP) or subcutaneously (SC) as specified in each study. Drugs used were butorphanol tartrate (Bristol Laboratories), ethylketocyclazocine (Sterling-Winthrop Research Institute), naloxone (Dupont Laboratories, Inc.), caffeine (Sigma Chemical Company), adenosine (Sigma Chemical Company) and inosine (Sigma Chemical Company). Vehicles are as described for individual experiments. Immediately after injections, the animals were replaced in their home cage. In the case of several injections, the time elapsed between injections is specified for the individual studies. All experiments were done between 8:00 and 9:00 hours (second and third hours of light period). A Latin Square experimental design was used. Data was analyzed by ANOVA followed by the least significant difference test. All results are expressed as mean±S.E.M.

EXPERIMENT 1

Ethylketocyclazocine (EKC) and butorphanol tartrate (BT) are kappa opioid agonists which stimulate food intake and the purines adenosine and inosine suppress feeding. The purpose of this study was to examine whether purines and opioids interact in feeding behavior.

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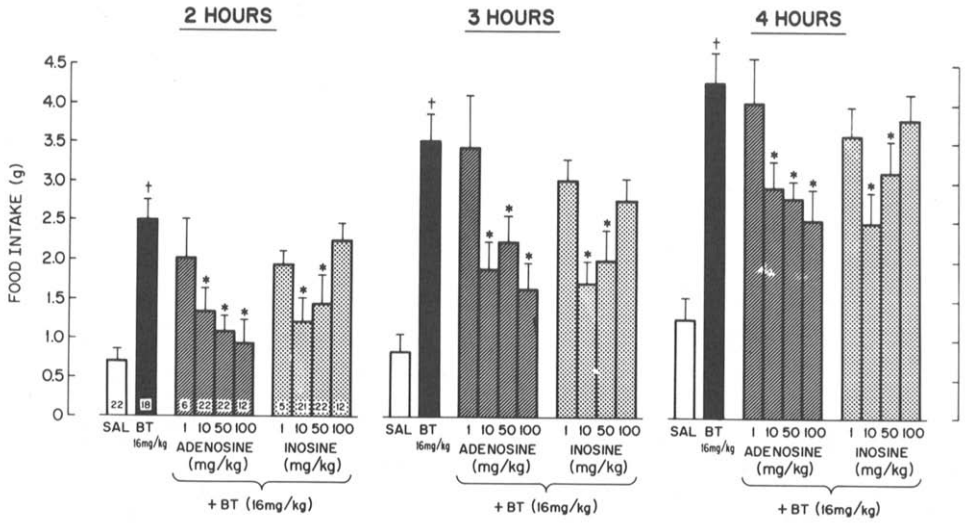

FIG. 1. Effect of butorphanol tartrate (BT) on food intake and the effects of adenosine and inosine on BT induced food intake. At 2 hr: $F(9,152)=3.94$, $p<0.01$; 3 hr: $F(9,152)=4.84$, $p<0.01$; 4 hr: $F(9,152)=5.82$, $p<0.01$. †Compared to saline ($p<0.05$), *compared to BT only ($p<0.05$).

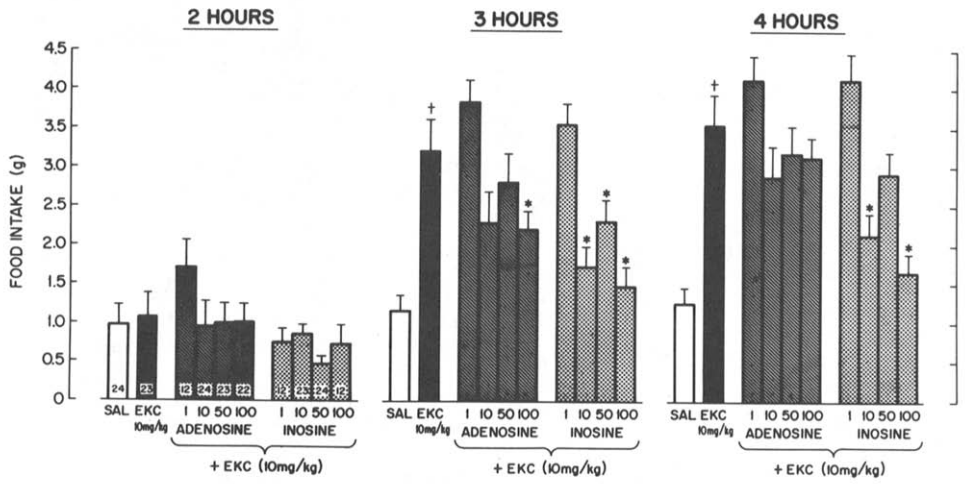

FIG. 2. Effect of ethylketocyclazocine (EKC) on food intake and the effects of adenosine and inosine on BT induced food intake. At 2 hr: $F(9,189)=1.58$, N.S.; 3 hr: $F(9,189)=6.61$, $p<0.01$; 4 hr: $F(9,189)=7.41$, $p<0.01$. †Compared to saline ($p<0.05$), *compared to EKC alone ($p<0.05$).

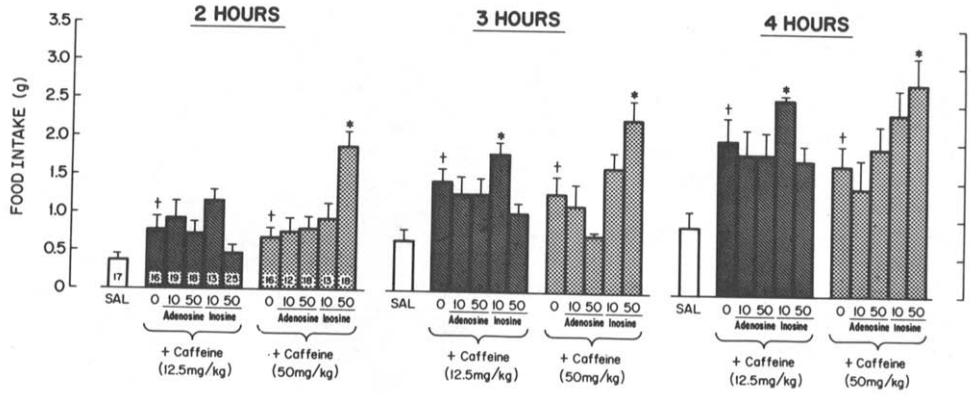

FIG. 3. The effect of caffeine on food intake and the effect of adenosine and inosine on caffeine induced food intake. At 2 hr: $F(10,181)=3.45$, $p<0.01$; 3 hr: $F(10,181)=5.23$, $p<0.01$; 4 hr: $F(10,181)=4.27$, $p<0.01$. †Compared to saline ($p<0.05$), *compared to caffeine alone.

Method

BT (16 mg/kg) (in BT buffer (1 liter): 3.3 g citric acid, 6.4 g sodium citrate and 6.4 g sodium chloride) or EKC (10 mg/kg) (in alkaline saline, pH 9.5) were injected subcutaneously (SC), followed by a second injection of adenosine or inosine (1.0, 10, 50 or 100 mg/kg) (saline, pH 9.5) intraperitoneally (IP) one hour later. This one hour delay was chosen since BT and EKC do not generally increase food intake during the first hour, probably due to sedation and we have previously shown that the duration of the action of purines is short (approximately 2 hours) [19]. Measured quantities of food in the form of pellets (Purina Lab Chow) were presented to the animal at the time of the second injection and food consumption was measured at 2, 3 and 4 hours from the time of the BT or EKC injection.

Results and Discussion

Butorphanol tartrate administered peripherally increased food consumption at all time points compared to the saline control group (Fig. 1). Adenosine (10, 50 and 100 mg/kg) decreased BT induced food consumption throughout the study (Fig. 1). Inosine (10 mg/kg and 50 mg/kg doses) suppressed food consumption throughout the experimental period (Fig. 1). Ethylketocyclazocine induced food consumption compared to the saline control at 3 and 4 hours post-injection (Fig. 2). Adenosine (100 mg/kg) suppressed EKC induced feeding at the 3 hour time point whereas inosine suppressed EKC feeding at 3 (10, 50 and 100 mg/kg) and 4 hours (10 and 100 mg/kg) (Fig. 2). Thus, both BT and EKC induced food consumption and the purines, adenosine and inosine suppressed feeding by BT and EKC. In the case of purines it appears that BT induced feeding is suppressed by similar doses of purines as those required to reduce starvation induced feeding [6,19].

EXPERIMENT 2

It has been reported that caffeine (1,3,7 trimethylxanthine) increases food consumption at low doses and suppresses food intake at high doses [23]. The methylxanthines, including caffeine, have been shown to be adenosine receptor antagonists [9,12]. The purpose of this experiment was to investigate whether caffeine's stimulatory effect on feeding on mediated through the purines.

Method

Caffeine (12.5 mg/kg and 50 mg/kg) in 0.1% ethanol-saline vehicle was injected SC. Adenosine or inosine (10 mg/kg and 50 mg/kg) were injected IP one hour after the caffeine injection, as caffeine is longer acting than the purines [23]. Measured quantities of food in the form of pellets (Purina Lab Chow) were presented to the animal at the time of the second injection and food consumption was measured at 2, 3, and 4 hours from the time of the caffeine injection.

Results and Discussion

Caffeine (50 and 12.5 mg/kg) enhanced food consumption at all time points (Fig. 3). Adenosine did not suppress the caffeine induced food intake (Fig. 3). Inosine (10 mg/kg) further enhanced the caffeine (12.5 mg/kg) induced food intake at 3 and 4 hours (Fig. 3) and inosine (50 mg/kg) enhanced the caffeine (50 mg/kg) induced food intake at all time points (Fig. 3).

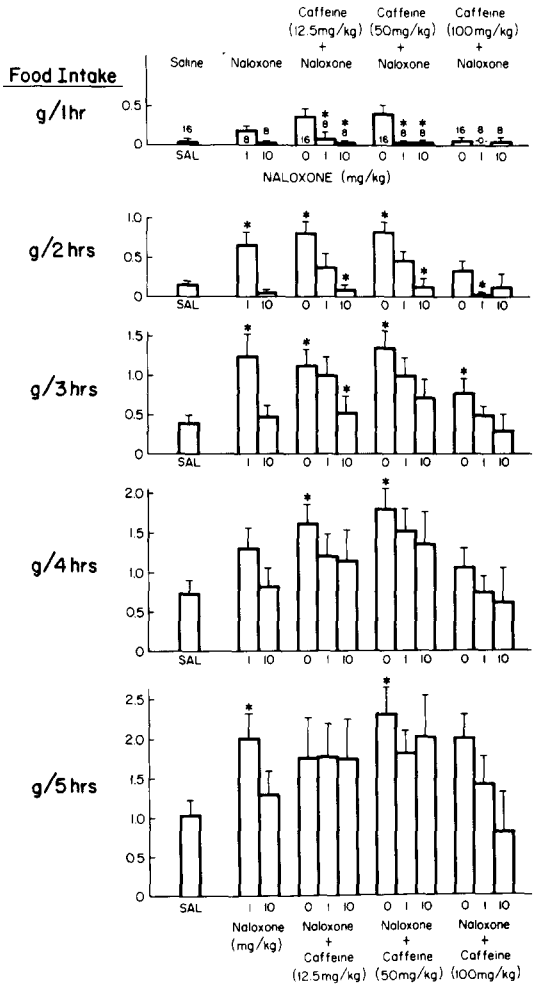

FIG. 4. The effect of caffeine on food intake and the effect of naloxone on caffeine induced food intake. At 1 hr: $F(11,115)=3.91$, $p<0.01$; 2 hr: $F(11,115)=5.09$, $p<0.01$; 3 hr: $F(11,115)=3.16$, $p<0.01$; 4 hr: $F(11,115)=2.00$, $p<0.05$; 5 hr: $F(11,115)=1.39$, N.S. †Compared to saline ($p<0.05$), *compared to caffeine alone ($p<0.05$).

It has been hypothesized that the central stimulatory actions of caffeine may be due at least in part to antagonism of the central adenosine receptor [8, 9, 12]. The data from the present study indicate that adenosine and inosine do not antagonize the enhancement of feeding stimulated by caffeine. This suggests that caffeine's stimulatory effect on feeding is either independent of purine effects or that caffeine is more avidly bound to the adenosine receptor and is not displaced by the adenosine. Inosine acts in an additive or synergistic fashion with caffeine and further stimulates food intake.

EXPERIMENT 3

The methylxanthines have been found to antagonize the analgesic effects of morphine and the endogenous opioids [5,14] which suggest that the methylxanthines may be involved in opioid actions. Naloxone, an opioid antagonist, decreases food intake in rats in response to a number of feeding stimulants [3, 15, 20, 25, 31, 33, 40, 41]. To determine if the food intake stimulatory action of caffeine might be

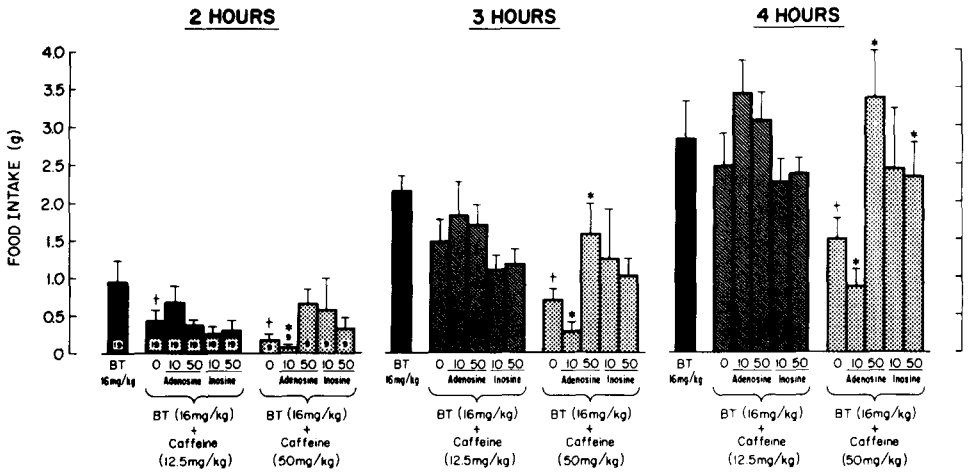

FIG. 5. The effect of caffeine and caffeine plus adenosine or inosine on butorphanol tartrate induced feeding. At 2 hr: $F(10,157)=1.83$, N.S.; 3 hr: $F(10,157)=2.40$, $p<0.05$; 4 hr: $F(10,157)=2.49$, $p<0.05$. †Compared to BT alone ($p<0.05$), *compared to BT plus caffeine.

mediated through the opioids we tried antagonizing this effect with naloxone.

Method

Caffeine (12.5, 50 and 100 mg/kg) was injected SC and this injection was followed within 60 seconds by naloxone (1.0 mg/kg and 10 mg/kg) injected IP. Measured quantities of food in the form of pellets (Purina Lab Chow) were presented to the animals at the time of the second injection and food consumption was measured at 1, 2, 3, 4, and 5 hours.

Results and Discussion

Caffeine (12.5 mg/kg) enhanced food consumption at 2, 3 and 4 hours and caffeine (50 mg/kg) enhanced food consumption at 2, 3, 4 and 5 hours (Fig. 4). In contrast, caffeine (100 mg/kg) only enhanced food consumption at 3 hours. Naloxone (1 mg) suppressed caffeine-induced feeding during the first hour, whereas naloxone (10 mg/kg) suppressed the stimulatory effect of caffeine (12.5 mg/kg) at 1, 2 and 3 hours and caffeine (50 mg/kg) at 1 and 2 hours. Many of the effects of naloxone have been attributed to their ability to antagonize the activity of the endogenous opioid system [37]. The suppression of caffeine enhanced food consumption by naloxone suggests that opioids may be involved, at least indirectly, in the stimulatory action of caffeine on food intake.

EXPERIMENT 4

In the final study, we looked at the effects of opioids, purines and caffeine, administered in combination, on food consumption. In the previous three experiments, we looked at opioid-purine interaction, purine-caffeine and caffeine-opioid interaction through the opioid antagonist, naloxone. The purpose of this study was to observe whether caffeine would stimulate food intake more effectively in combination and what the effects administration of adenosine and inosine would have on the food intake response elicited by these compounds. We have previously shown that the purines suppress the food intake stimulation of both caffeine and the exogenous opioids, BT and EKC.

Method

Butorphanol (16 mg/kg) and caffeine (12.5 mg/kg or 50 mg/kg) were injected SC with injections spaced 60 seconds apart, followed by a second injection of adenosine or inosine (10 and 50 mg/kg), IP, one hour later. Measured quantities of food in the form of pellets (Purina Lab Chow) were presented to the animal at the time of the second injection and food intake was measured at 2, 3 and 4 hours from the time of the initial injection.

Results and Discussion

Butorphanol tartrate induced feeding is suppressed by caffeine (50 mg/kg) at three and four hours (Fig. 5). Adenosine (50 mg/kg) in combination with butorphanol tartrate (16 mg/kg) and caffeine (50 mg/kg) increased food intake in comparison to BT and caffeine (50 mg/kg) at all time points. Inosine (50 mg/kg), BT (16 mg/kg) and caffeine (50 mg/kg) increased food consumption at 4 hours in comparison to BT and caffeine (50 mg/kg). This study indicates that the BT stimulated food intake can be suppressed by the methylxanthine, caffeine. How this effect is obtained is unclear as caffeine alone is stimulatory to food consumption behavior and appears to be mediated through the opioids. Adenosine and, to a lesser extent, inosine reversed the caffeine-induced suppression of opioid induced food consumption suggesting that caffeine/purine interactions did occur in this study.

GENERAL DISCUSSION

The regulation of food intake is a complex process involving a large number of satiety, inhibitory and aversive factors [24]. To the already long list of interactions that modulate feeding behavior, it now appears that we can add the opioid-purinergic interaction. Numerous studies have shown that food intake can be stimulated by exogenous and endogenous opioids [18, 21, 27, 29, 36]. It appears that dynorphin (an endogenous opioid peptide) is involved in stimulating feeding [29,30]. Dynorphin activates the kappa receptor [29,30] which seems to be the principal feeding receptor in

TABLE 1

SUMMARY OF THE INTERACTIONS OF PURINES, OPIOIDS AND CAFFEINE ON FEEDING BEHAVOR

	Adenosine	Inosine	Caffeine	Naloxone
Alone	ND	ND	↑	ND
BT	↓↓	↑	↑*	ND
EKC	↓	↓↓	ND	ND
Caffeine	0	↑	ND	↓

*This effect was antagonized by adenosine and inosine.
ND=not done in present study.
BT=butorphanol tartrate.
EKC=ethylketocyclazocine.

the central nervous system [29,30]. EKC, a preferential kappa agonist, and butorphanol tartrate, a kappa-sigma agonist, have both been shown to markedly stimulate food intake [28,29]. The purines, adenosine and inosine, suppress this opioid induced feeding when administered peripherally. Whether this suppression is due to an interaction at the opioid receptor or mediated through the adenosine receptor is unclear. Since inosine does not bind to the adenosine receptor and inosine behaves differently in feeding behavior compared to adenosine, it is unlikely that inosine is exerting its effects via the adenosine receptor.

It has been reported that inosine may be the endogenous ligand of the central benzodiazepam receptor [1, 38, 39] as it has been reported that inosine antagonizes pentylenetetrazol-evoked seizures. The benzodiazepines may play a role in appetite regulation as they have been found to enhance spontaneous food intake [11], tail pinch induced feeding [24] and it initiates feeding in a sated animal [11, 40 41]. Our group has found that inosine administered peripherally can suppress diazepam induced feeding, food deprivation induced feeding, insulin induced feeding and spontaneous nocturnal feeding [19]. At this time, it is unclear whether inosine suppresses feeding through the diazepam receptor or if it is converted to adenosine via the purine salvage pathway and suppresses food intake through adenosine's action.

Wu *et al.* [44] and Stone and Perkins [42] have reported that some of the central action of the opioids might be mediated by adenosine [8, 42, 44]. Ginsborg and Hirst reported that both morphine and adenosine can inhibit neurotransmitter release [13]. Perkins and Stone found that aminophylline, a methylxanthine which is an adenosine antagonist, brought about a rapid and reversible blockade of the inhibitory responses of morphine [35] on single neurons. We found in this study that naloxone, a specific opioid antagonist, could inhibit caffeine's stimulation of food intake. In examining the evidence of interaction between the opioids, purines and methylxanthines it would appear that the purines and opioids influence feeding behavior through a purinergic-opioid interaction. At this time it can not be discounted that caffeine and the purines effect feeding behavior independent of the opioid system through a lipostatic effect. The lipostatic theory of appetite regulation suggests that the level of free fatty acids can modulate appetite [17,22]. It has been shown that adenosine is antilipolytic [10] and caffeine is lipolytic [2]. Adenosine, which is produced in adipose tissue and released from it, may serve as a signal to appetite regulatory centers in the hypothalamus [6]. When we combined two appetite stimulators, BT and caffeine, the net effect was a suppression of feeding which was reversed by adenosine. In this combination, adenosine appears to be disinhibiting the suppression of the opioid-caffeine interaction and allowing the stimulatory effect of one or both of these compounds to be exerted.

Table 1 summarizes the results obtained in the series of experiments conducted by us. These results clearly highlight the antagonistic effects of purines on opioid induced feeding. It further shows that the caffeine-induced feeding requires an intact opioid feeding system (the effect is reversed by opioid blockade). The ability of adenosine to block caffeine-induced feeding and the enhancement seen after inosine suggests that these two purines produce their appetite suppressant effects through different mechanisms. A comparison of the peripheral and central effects of adenosine and inosine in our laboratory has led us to similar conclusions [19,28]. Finally, we are left with the conundrum that two appetite enhancers, BT and caffeine, when combined lead to a decrease in feeding. This observation deserves further investigation. Overall, our data are compatible with the theory that purines modulate opioid induced feeding.

ACKNOWLEDGEMENT

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