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Stereoselective Effects of Opiate Agonists and Antagonists on Ingestive Behavior in Rats

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LOWY, M. T., C. STARKEY AND G. K. W. YIM. *Stereoselective effects of opiate agonists and antagonists on ingestive behavior in rats.* PHARMAC. BIOCHEM. BEHAV. **15**(4)591–596, 1981.—In male Sprague Dawley rats, the (−)-isomer of the opiate antagonist GPA 1843 (β-9-methyl-5-phenyl-2-allyl-2′-hydroxy-6, 7-benzomorphan) produced dose-related decreases in nocturnal feeding and of hyperphagias induced by 2-deoxy-D-glucose (2-DG; 400 mg/kg) and 24 hr food deprivation (FD). The hyperphagia induced by insulin (10 U/kg) was not significantly decreased by GPA 1843. In contrast, comparable doses of the (+)-stereoisomer, GPA 1847, had no effect on nocturnal, 2-DG or FD hyperphagia. In addition, hyperphagia and hyperdipsia were observed following administration of the opiate agonist levorphanol, but not its stereoisomer, dextrorphan. Thus, the effects of these agents on consummatory behavior are mediated by a stereospecific interaction with opiate receptors, which further indicates that endogenous opiate peptides are involved in the expression of these opiate-related hyperphagias.

Stereospecific opiate antagonism Endogenous opioids Opiate feeding and drinking

RECENT evidence suggests that endogenous opiate peptides (EOP) are involved in the regulation of food intake. Genetically obese rats (fa/fa) and mice (ob/ob) have elevated pituitary levels of β-endorphin [27], although a direct causal connection has not been established [39]. Centrally injected EOP [13,19], as well as systemically administered opiate agonists [23,51] increase feeding. Opiate antagonists, such as naloxone, attenuate various consummatory behaviors [5, 6, 7, 8, 10, 20, 32, 33, 40, 49] including the overeating of the genetically obese rodents [27]. We have reported that naloxone produces a dose-dependent attenuation of various types of induced feeding including 2-deoxy-D-glucose (2-DG), food deprivation (FD), night, tail pinch (TP), but not insulin hyperphagia [24]. The finding that acute stress releases pituitary β-endorphin, as well as adrenocorticotrophic hormone (ACTH) [14], is in consonance with the possibility that these opiate-related hyperphagias are in part mediated by the activation of an EOP pathway. Indeed, dexamethasone, a synthetic glucocorticoid which inhibits the synthesis and stress-induced release of pituitary β-endorphin and ACTH [38,41], produces a feeding profile similar to that seen in naloxone-treated rats [26].

A major criterion for demonstrating opiate receptor mediation is stereospecificity [12]. This has been demonstrated in studies concerning receptor binding [34], analgesia [17], drinking behavior [8] and thermoregulation [46]. The facilitory effect of opiate antagonists on electrical stimulation-induced acetylcholine release in the guinea-pig myenteric plexus-longitudinal muscle preparation is stereoselective in nature, since the (−)-isomer of β-9-methyl-5-phenyl-2-allyl-2′-hydroxy-6,7-benzomorphan HCl (GPA 1843) had an effect similar to naloxone, whereas the (+)-isomer (GPA 1847) was inactive [47]. The relative potencies of the (−)-and (+)-isomers with respect to naloxone were 0.06 and 0.001, respectively. The (−)-isomer, GPA 1843 has no morphine-like agonist activity, whereas the (+)-isomer, GPA 1847 has a low amount of morphine-like agonist activity [47]. In addition, it has been demonstrated that these two isomers have stereoselective effects *in vivo*, as GPA 1843, but not GPA 1847, antagonize morphine induced antinociception [21].

Thus, the main objective of this study was to use the GPA 1843/47 stereoisomers to determine if the attenuation of opiate-related eating by opiate antagonists [24] is mediated via a stereospecific interaction with opiate receptors. In this regard, opiate-induced eating has been observed following chronic administration of the (−)-opiate agonist levorphanol, but not the (+)-isomer dextrorphan [46]. We report similar results following single doses of this stereoisomeric pair of opiate agonists.

METHOD

Male Sprague Dawley rats were purchased from Murphy Breeding Laboratories (Plainfield, IN) and housed individually in metal cages (25×21×20 cm) at least ten days prior to testing. The rats had free access to water and Wayne Lab Blox placed on the cage floor. Illumination was on a 12/12 hr schedule with light onset at 8:00 hr. Room temperature was maintained at 23–26°C. All feeding and drinking tests were

conducted in the home cage of the rat. Animals were handled and given saline injections in three preliminary sessions to accommodate them to the experimental procedure.

An initial group of 34 rats (340–400 g) were utilized in the studies with the GPA 1843/47 stereoisomers. Each experimental group consisted of 6 rats, except for the GPA 1843 40 mg/kg group which had only 4 rats. Each experiment had a non-stimulated control saline injected group and a stimulated feeding (2-DG, FD, nocturnal, insulin) group, as well as 3 or 4 groups of feeding rats treated with increasing doses of a stereoisomer. The (−)-isomer, GPA 1843, was administered in doses of 0.1, 1.0, 10.0 and 40.0 mg/kg, while the doses of the (+)-isomer, GPA 1847, were 0.1, 1.0 and 10.0 mg/kg. Our small supply of these isomers limited our use of the 40 mg/kg dose. The stereoisomers were injected subcutaneously 10–15 min prior to the induced hyperphagia. The 2-DG, insulin and FD feeding tests were initiated 2–3 hr into the light cycle, when food intake is low. Nocturnal food intake was monitored from 20:00–22:00 hr. Daytime 2 hr food intake was stimulated by either 24 hr FD (water present) or subcutaneous administration of 400 mg/kg 2-DG (U. S. Biochemical Co., Cleveland, OH) or 10 U/kg insulin (Illetin U-100, Eli Lilly and Co.). The seven feeding tests were separated by a minimum of 7 days and conducted in the following order: 2-DG, FD, insulin and nocturnal. The 1843 isomer was generally tested first. After each experiment rats were randomly reassigned to different experimental groups.

An additional 42 male Sprague Dawley rats (400–520 g) housed and maintained as described above were utilized to examine the effect of levorphanol and dextrorphan tartrate on 3 hr daytime feeding and drinking in non-food and non-water deprived rats. Six rats were randomly assigned to one of seven experimental groups (1 control plus 3 doses of each isomer). Various doses (0.33, 1.0 and 3.0 mg/kg) of each isomer or the saline vehicle were injected subcutaneously and subsequent 3 hr food and water intake measured.

All drugs were dissolved in 0.9% sterile saline immediately before injection. Doses are expressed as the salt form. All injections were given subcutaneously in a volume of 1 ml/kg, except for the 40.0 mg/kg dose of GPA 1843 which was injected in a 2 ml/kg volume. Food intake was measured to the nearest 0.1 g by subtracting spillage collected on paper towels and uneaten food from the premeasured supply. Water intake was measured to the nearest ml using calibrated Richter drinking tubes.

Statistical significance was assessed by analysis of variance (ANOVA). When comparing the response between two isomers in the same feeding condition (i.e., 2-DG), data was expressed as a percentage of the stimulated feeding group and then assessed by ANOVA. When ANOVA indicated an effect of drug administration, post hoc comparisons were made using the Newman-Keuls procedure. For the regression analysis, food intake at each dose of GPA 1843 was expressed as a percentage of the control feeding response. The ED50 and 95% confidence interval (C.I.) were then calculated by regression analysis of the log dose-response curves. The slopes were compared to assess deviation from parallelism between the dose-response curves [9].

RESULTS

As seen in Fig. 1A and 1B, 2-DG (400 mg/kg) administration to non-deprived rats resulted in a nine- to eleven-fold increase in daytime intake of lab chow. A 2-way ANOVA (treatment × test day) revealed that this increase of 2 hr food

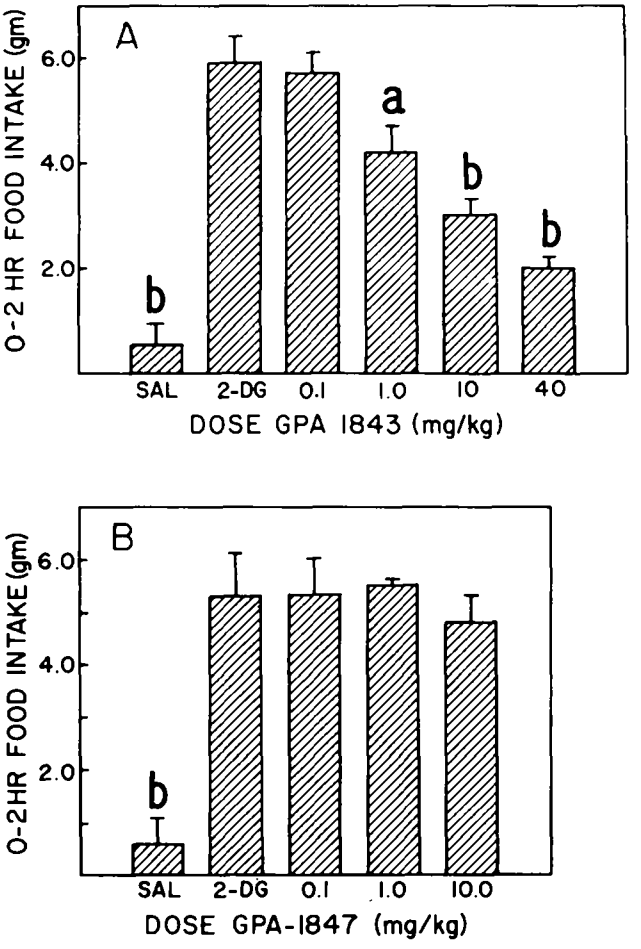

FIG. 1. Stereospecific reduction of 2-DG-induced hyperphagia by the opiate antagonist, GPA 1843 (A), but not by its stereoisomer GPA 1847 (B). The isomers were injected 10 min prior to 2-DG (400 mg/kg) injection. Bars represent mean daytime intake of rat chow in g (+S.E., n = 4–6). a=$p<0.05$; b=$p<0.01$ vs 2-DG stimulated feeding group.

intake by 2-DG was significant, $F(1,20)=78.90$, $p<0.01$; and that this response did not vary between test days, $F(1,20)=0.30$, $p>0.5$. The interaction was not significant, $F(1,20)=0.40$, $p>0.5$. A 2-way ANOVA (isomer × dose) using percentage values indicated a significant effect of isomer, $F(1,30)=11.04$, $p<0.01$, and dose (0.1, 1.0 and 10.0 mg/kg), $F(2,30)=3.96$, $p<0.05$, but not the interaction, $F(2,30)=2.03$, $p>0.1$. One-way ANOVA revealed an effect of drug administration for the 1843 isomer, $F(4,23)=16.2$, $p<0.01$, but not the 1847 isomer, $F(3,20)=0.2$, $p>0.8$, with post hoc comparisons indicating that the 1.0, 10.0 and 40.0 mg/kg dose of GPA-1843 significantly (minimum $p<0.05$) decreased 2-DG stimulated food intake by 30, 50, and 66%, respectively.

The compensatory food increase resulting from 24 hr FD is illustrated in Fig. 2A and 2B. A 2-way ANOVA (treatment × test day) revealed that 24 hr FD increased food intake 8–15 times above non-FD rats, $F(1,20)=203.8$, $p<0.01$; and that this response did not vary between test days, $F(1,20)=0.1$, $p>0.7$. The interaction was not significant, $F(1,20)=0.5$, $p>0.5$. A 2-way ANOVA (isomer × dose) using percentage

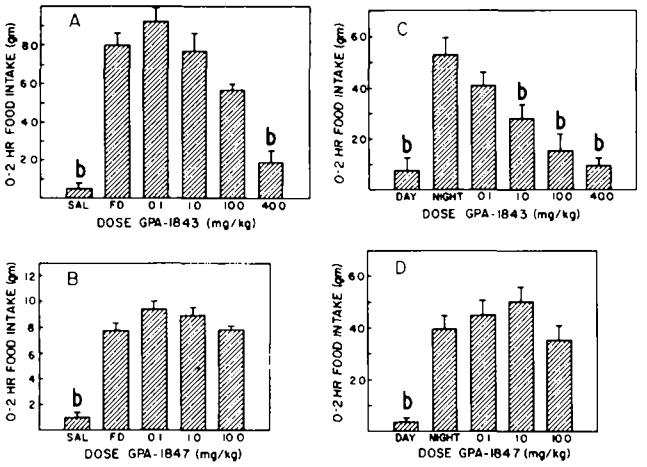

FIG. 2. Stereospecific reduction of deprivation-induced (A) and nocturnal (C) hyperphagia by the opiate antagonist, GPA 1843, but not by its stereoisomer GPA 1847 (B, D). The isomers were injected 10 min prior to presentation of food (A, B) or darkness (C, D). Bars represent mean intake of rat chow in g (+S.E., n=4–6). a=$p<0.05$; b=$p<0.01$ vs appropriate stimulated feeding group (FD, night).

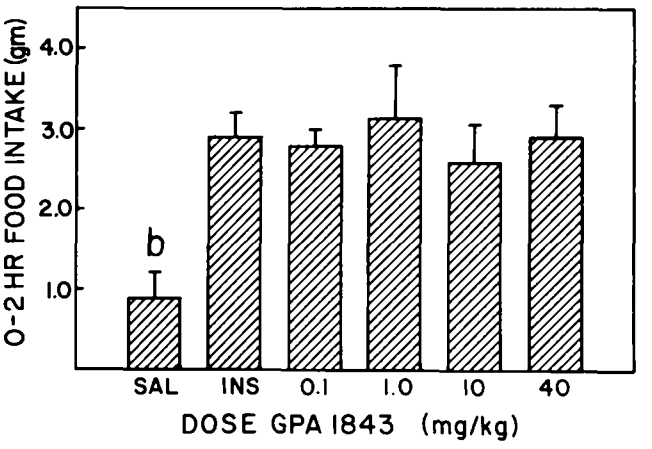

FIG. 3. Lack of an effect of the opiate antagonist, GPA 1843, on insulin-induced feeding. GPA 1843 was injected 10 min prior to insulin (10 U/kg) administration. Bars represent mean daytime intake of rat chow in g (+S.E., n=6). b=$p<0.01$ vs insulin group.

values indicated a significant effect of isomer, $F(1,30)=8.1$, $p<0.01$, and dose, $F(2,30)=8.31$, $p<0.01$, but not the interaction, $F(2,30)=1.04$, $p>0.3$. One-way ANOVA revealed an effect of drug administration for the 1843 isomer, $F(4,23)=14.6$, $p<0.01$, but not for 1847, $F(3,20)=2.15$, $p>0.1$. The 40.0 mg/kg dose of GPA 1843 decreased ($p<0.01$) food intake by 78%.

The expected elevated night food intake of the nocturnally feeding rats is illustrated in Fig. 2C and 2D. A 2-way ANOVA (treatment × test day) revealed that rats consumed 7–13 times as much food during the 2 hr night test period compared to daytime, $F(1,20)=59.5$, $p<0.01$. This response did not vary between test periods, $F(1,20)=3.0$, $p>0.05$, and the interaction was not significant, $F(1,20)=0.8$, $p>0.6$. A 2-way ANOVA (isomer × dose) using percentage values indicated a significant effect of isomer, $F(1,30)=28.6$, $p<0.01$; and dose $F(2,30)=4.6$, $p<0.05$, but not the interaction, $F(2,30)=1.04$, $p>0.3$. One-way ANOVA revealed an effect of drug administration for 1843, $F(4,23)=9.5$, $p<0.01$, but not 1847, $F(3,20)=1.28$, $p>0.3$. Post hoc comparisons indicated that the 1.0, 10.0 and 40.0 mg/kg dose of GPA 1843 significantly ($p<0.01$) decreased nocturnal feeding by 47, 70 and 85%, respectively.

Selected aspects of the regression analysis of the three resultant dose-response curves are presented in Table 1. The large regression components of the dose-response curves indicate that GPA 1843 reduced the hyperphagia induced by 2-DG, FD and night in a dose-dependent manner ($p<0.01$). Although the slopes of the individual dose responses varied (line 3), these differences were not significant; the F value (*df* 2,60) calculated for the slopes component in the regression analysis of these three dose-response curves was only 1.44. Since deviation of these curves from parallelism was not significant, the ED50's and 95% C.I. were estimated using the calculated common slope (-2.36×10^{-2}. Note that the 3 ED50 values are similar to each other, with nocturnal feeding being the most sensitive to the anorexic effect of GPA 1843.

The effect of GPA 1843 on insulin-induced feeding is presented in Fig. 3. One-way ANOVA indicated a significant effect of treatment, $F(5,28)=3.98$, $p<0.01$. Post hoc comparisons revealed that insulin significantly ($p<0.01$) increased food intake 3.4 times above control values. In contrast to the other types of induced hyperphagias, GPA 1843 had no significant ($p>0.2$) effect on insulin feeding.

The differential effect of the opiate agonist stereoisomers, levorphanol and dextrorphan, on 3 hr daytime food intake in non-FD, non-water deprived rats is illustrated in Fig. 4A. A 2-way ANOVA (isomer × dose) revealed a significant effect of isomer, $F(1,30)=14.07$, $p<0.001$, but not for dose, $F(2,30)=1.21$, $p>0.3$, or the interaction, $F(2,30)=2.05$, $p>0.1$. Subsequent 1-way ANOVA indicated an effect of levorphanol, $F(3,20)=4.3$, $p<0.01$, but not dextrorphan, $F(3,20)=0.6$, $p>0.6$, administration. The 1.0 mg/kg dose of levorphanol produced a two-fold increase ($p<0.05$) in daytime 3 hr food intake while dextrorphan (0.33–3.0 mg/kg) had no significant effect on feeding. In these same rats, the isomers had a similar stereoselective stimulatory effect on water intake (Fig. 4B). A 2-way ANOVA (isomer × dose)

TABLE 1

SELECTED ASPECTS OF REGRESSION ANALYSIS OF GPA-1843 DOSE-RESPONSE CURVES

	2-DG	FD	Night-Time
Regression F(1,21)	53.2*	37.8*	21.4*
r df=21	0.85*	0.81*	0.72*
Slope ($\times 10^{-2}$)	3.08	−2.08	−2.24
ED50† (95% C.I.)	5.8 (2.6–12.8)	8.6 (3.5–21.2)	1.7 (1.2–3.3)

*$p<0.01$.

†Calculated using common slope of -2.36×10^{-2}. Other values based on individual regression analysis.

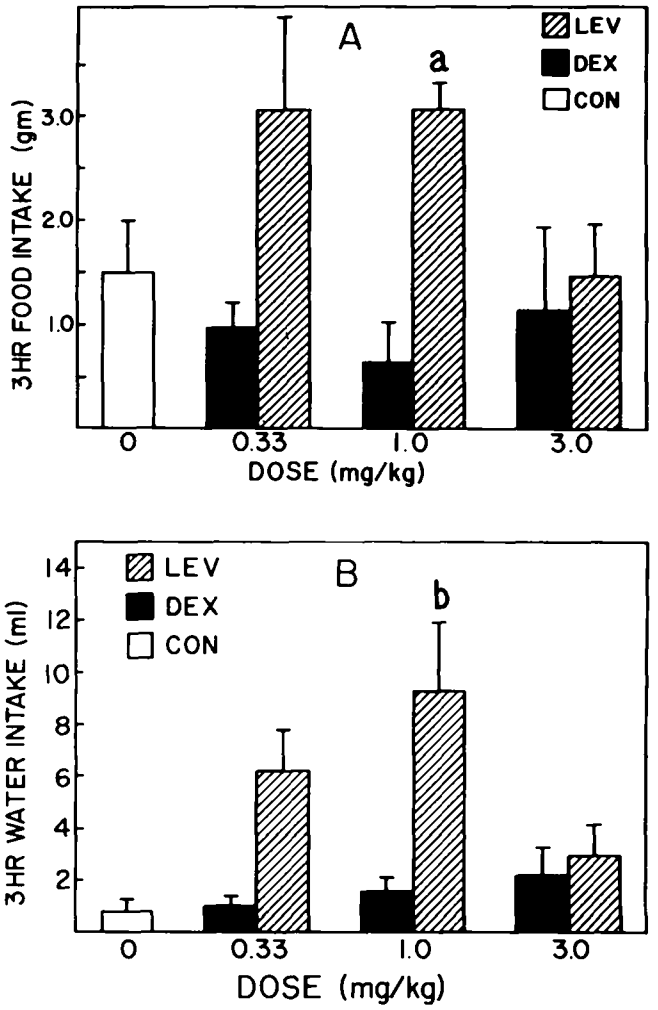

FIG. 4. Stereospecific increase in (A) feeding and (B) drinking by levorphanol but not dextrorphan. Bars represent mean daytime intake of rat chow (g) or water (ml) (±S.E., n=6). a=$p<0.05$; b=$p<0.01$ vs appropriate control group.

revealed a significant effect of isomer, $F(1,30)=13.64$, $p<0.01$, but not dose, $F(2,30)=1.99$, $p>0.1$, or the interaction, $F(2,30)=2.23$, $p>0.1$. One-way ANOVA indicated an effect of levorphanol, $F(3,20)=4.2$, $p<0.05$, but not dextrorphan, $F(3,20)=0.58$, $p>0.6$, administration. The 1.0 mg/kg dose of levorphanol produced a maximum elevenfold increase ($p<0.01$) in water consumption. Rats injected with the 3.0 mg/kg dose of levorphanol appeared cataleptic, which may have hindered the development of a larger feeding and drinking response.

DISCUSSION

The observed selective attenuation by the opiate antagonist, GPA 1843 [47] of nocturnal feeding and of the hyperphagia induced by 2-DG and FD confirms previous reports of the suppressive effect of opiate antagonists on these opiate-related hyperphagias [5, 7, 10, 24, 40]. The ineffectiveness of GPA 1847, the inactive stereoisomer of GPA 1843 [47], indicates that the anorexic effect of opiate antagonists is mediated by a direct stereospecific interaction with opiate receptors. The lack of effect of GPA 1843 on insulin-induced feeding confirms our previous report obtained with naloxone [24]. In these feeding studies, both GPA compounds showed little evidence of increasing food consumption, which is in line with their previously demonstrated low agonist actions in the guinea pig ileum [47]. This stereospecific anorexic effect of the GPA compounds agrees with their previously reported stereospecific reduction of morphine analgesia [21]. It appears that the suppressant effects of naloxone on ingestive behavior are likely not due to conditioning a taste aversion [33,49]. Thus the anorexic effect of GPA 1843 is probably not due to making the rats sick. It is possible that GPA 1843 has additional aversive properties which naloxone does not possess. However, GPA 1843 did not attenuate insulin-induced feeding, which indicates that the rats were capable of ingesting food.

The increased feeding observed in rats treated acutely with the opiate agonist, levorphanol, but not dextrorphan, similarly suggests that the opiate-induced hyperphagia is mediated via a stereospecific interaction with an opiate receptor. Similar results have been reported for rats given multiple injections of these opiate agonists [46]. Our results also demonstrate an identical stereospecific effect on stimulated water intake in rats treated with these two agents. The suppressive effect of opiate antagonists on salt-induced drinking is also mediated by a stereospecific interaction with an opiate receptor [8].

The reduction of nocturnal feeding and 2-DG and FD induced hyperphagia by GPA 1843 and by naloxone is in line with the earlier suggestion of opiate involvement in stress-related eating [24,32]. 2-DG, a glucose antimetabolite, produces intracellular glucoprivation [48] accompanied by increases in corticosteroids, and nociceptive levels [2,45]. The 2-DG analgesia is not affected by high doses (20 mg/kg) of naloxone [3], yet is reduced in morphine tolerant rats [42]. Tolerance develops to the analgesic, but not hyperphagic properties of 2-DG [1]. The other two opiate-sensitive hyperphagias, night and FD-induced feeding, are also associated with elevations in corticosteroid and nociceptive levels [4, 22, 31, 37]. Interestingly, the analgesia produced by FD is reversed by naloxone administration [28] or by access to food [29]. However, since FD and nocturnal feeding can be viewed as physiological, adaptive processes, endogenous opioids may be involved not only in genetic obesity [27,39] and stress-induced eating [24,32] but also in the regulation of normal feeding behavior [11,29]. Consequently, deficits in the opiate feeding system could be expected to result in pathological anorexic states. Indeed, anorexic tumor-bearing rats displayed an identical feeding profile as naloxone and dexamethasone treated rats, suggesting that a deficit in an EOP system was involved in the anorexia of these rats [25].

One unsolved question concerns the identity of the EOP involved in feeding. Margules' initial report suggested that pituitary β-endorphin may be involved in the etiology of genetic obesity [27]. However, a temporal analysis of obesity development in the ob/ob mice demonstrated that pituitary β-endorphin levels did not correlate with increases in body weight [39]. Instead, body weight gain was correlated with elevations of LEU-enkephalin levels of the pars nervosa. Still, several findings suggest that the role of pituitary β-endorphin is worth further study. First, acute stress releases large amounts of β-endorphin into the peripheral circulation [14]. Second, dexamethasone, in a regimen that abolished the stress-induced release (foot shock) of pituitary β-endorphin [38], also selectively reduced the opiate-related, but not insulin or daytime feeding [26]. Third, 2-DG (but not insulin)-induced hyperphagia is accompanied by a 2-fold in-

crease in plasma β-endorphin levels [50]. However, FD produced no change in pituitary β-endorphin levels, while hypothalamic levels were decreased [11]. In addition, gastrointestinal tract β-endorphin levels increased with food deprivation [35]. Thus, multiple EOP systems may be involved in the various types of induced hyperphagias.

The attenuation by naloxone of TP and other stress-related hyperphagias in rats suggests that opiate antagonists may be anorexic agents selective for stress-induced eating [24,32]. It is known that obese subjects overeat in response to stress [15, 30, 44] and that caloric ingestion has an anti-anxiety effect in the obese [36]. In rats the ingestion of food inhibits the pituitary-adrenal response to stress [16]. Naloxone administration does decrease subjective reports of appetite in normal volunteer subjects [18]. However, further clinical studies are necessary to determine if naloxone can decrease caloric intake. Thus, the results of the present study and others indicate that EOP may be involved in the regulation of both normal and pathological feeding states.

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