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Effects of 2% Sodium Chloride Imbibition on Various Opiate Related Hyperphagic Conditions

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BRYANT, H. U., M. T. LOWY, P. V. MALVEN, T. D. STEELE AND G. K. W. YIM. *Effects of 2% sodium chloride imbibition on various opiate related hyperphagic conditions.* PHARMACOL BIOCHEM BEHAV **23**(3) 391–395, 1985.— Dynorphin is one of the most potent appetite stimulants among the endogenous opioids. In this study, we describe the anorexic effects of 5 days of forced 2% NaCl drinking in rats, a regimen which depletes vasopressin as well as dynorphin in the neurohypophysis. Feeding induced by direct activation of kappa-opioid receptors with ketocyclazocine was unaffected by the NaCl regimen. However, 2% NaCl imbibition reduced 2-deoxy-D-glucose (2-DG) induced feeding by 65% and spontaneous nocturnal feeding by 38%. Feeding subsequent to 24 hour food deprivation was not decreased. Naloxone-resistant hyperphagia induced by insulin and spontaneous daytime feeding were also not reduced. The combination of naloxone (3.0 mg/kg) and the NaCl regimen produced an additional 50% reduction in 2-DG induced feeding and an extra 40% decrease in nocturnal feeding. Naloxone, given with 2% NaCl to food deprived animals, retained its appetite suppressing activity, indicating that the NaCl regimen did not deplete the endogenous opioid which mediates food deprivation hyperphagia. These results demonstrate that 2% NaCl imbibition suppresses certain opioid mediated hyperphagias. However, the failure of 2% NaCl to affect all of the naloxone-sensitive types of feeding and the independence of naloxone-sensitive and NaCl-sensitive components suggests that NaCl drinking does not deplete dynorphin in the brain areas which mediate opiate-sensitive hyperphagias.

Dynorphin Ketocyclazocine Naloxone 2-Deoxy-D-glucose Food deprivation 2% NaCl imbibition Insulin

THE regulation of food intake is an intricate balance of both central and peripheral components. There is substantial evidence from both pharmacological and biochemical investigations that the endogenous opioids (EO) are involved in the complex control of feeding behavior [7, 20, 27]. The exact EO involved in these opioid mediated hyperphagias remains unidentified. The kappa opiate receptor plays an important role in opiate-induced feeding [13,19] and the endogenous kappa receptor ligand, dynorphin [3], is one of the EO implicated in the regulation of both normal and pathological ingestive behavior [22,23]. Dynorphin, which is nearly 700 times more potent than leucine-enkephalin in certain *in vitro* assays [5], is a very potent stimulant of appetite [16]. The highest concentrations of dynorphin are found in the paraventricular nucleus and other hypothalamic structures [26] where microinjections of norepinephrine induce feeding [11,14].

Dynorphin and vasopressin are co-localized in the neurosecretory magnocellular neurons of the hypothalamus and neurohypophysis [26]. Following the forced consumption of a 2% NaCl solution, Hollt *et al.* found a parallel depletion of both vasopressin and dynorphin in the neurointermediate lobe of the pituitary [6]. While pituitary dynorphin is probably not involved in the control of food intake, if a similar depletion of dynorphin occurs in brain areas associated with feeding, such a NaCl regimen may have suppressant effects on hyperphagias mediated by endogenous dynorphin. Therefore, the objective of this series of experiments was to study the effects of the forced imbibition of 2% NaCl on various feeding paradigms.

The goal of the first part of this study was to determine if NaCl-induced anorexia could be attributed to effects other than dynorphin depletion. Therefore, we investigated whether the feeding deficits resulting from NaCl drinking affected the ability of the kappa agonist, ketocyclazocine, to elicit feeding in the NaCl treated rats. We then tested whether the dynorphin depleting regimen might act similar to naloxone and depress spontaneous nocturnal feeding and the hyperphagia induced by 2-deoxy-D-glucose (2-DG) or 24 hr food deprivation and not depress insulin induced feeding [12]. Finally, the effects of naloxone (3.0 mg/kg) on feeding induced by several challenges in animals treated with the 2% NaCl regimen were also tested in order to ascertain any possible additive effects.

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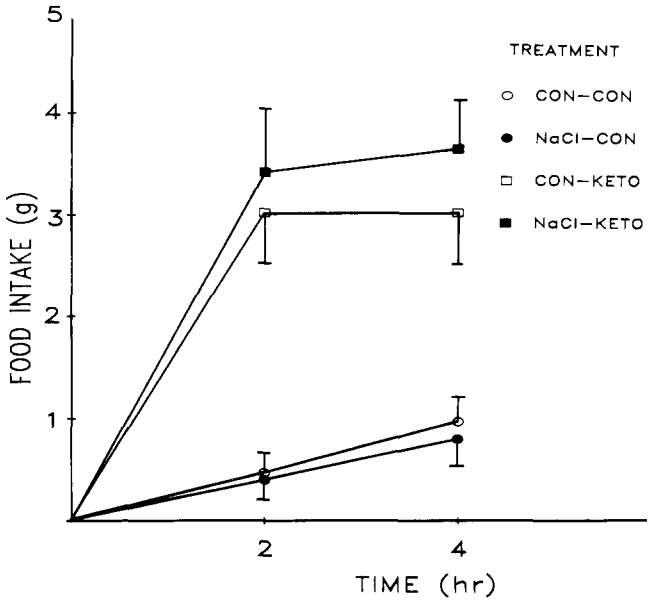

FIG. 1. Daytime feeding response to injection of ketocyclazocine (KETO, 3.0 mg/kg) or the appropriate vehicle (CON) in rats drinking tap water and in rats forced to drink 2% NaCl for 5 days. Each bar represents the mean (±S.E.) food intake (g) for 6 rats.

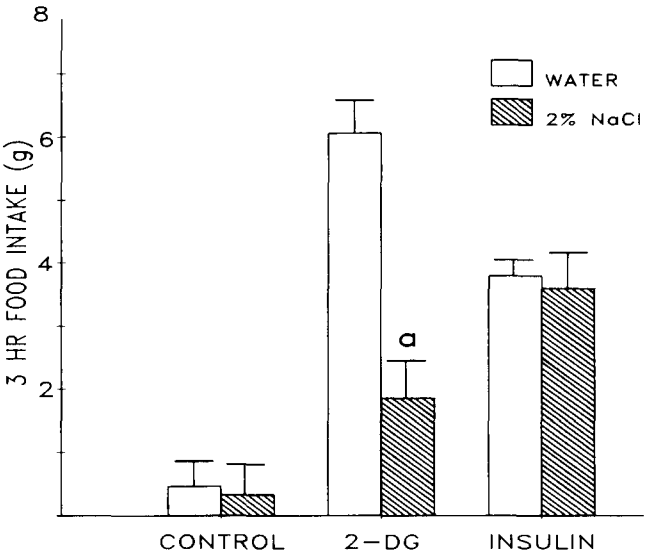

FIG. 2. Daytime feeding response to injection of saline (control), 2-deoxy-D-glucose (2-DG, 400 mg/kg) and insulin (10 U/kg) in control rats drinking tap water and rats forced to drink only a 2% NaCl solution for 5 days (NaCl). Each bar represents the mean (±S.E.) food intake (g) for 6 rats. a=$p<0.01$ vs. the rats given 2-DG and water.

EXPERIMENT 1

Ketocyclazocine is a kappa opiate receptor agonist which produces a rapid and reliable dose-related increase in feeding [13,19], presumably via activation of the kappa opiate receptors involved with ingestive behavior. If the anorexia observed in 2% NaCl treated animals were due to depletion of the kappa agonist dynorphin, then feeding induced by direct kappa receptor stimulation by ketocyclazocine should remain intact. To test this possibility we examined the effect of 5 days forced 2% NaCl imbibition on ketocyclazocine-induced feeding.

Method

Twenty-four male, Sprague-Dawley rats (250–400 g), purchased from Harlan Sprague-Dawley Inc. (Indianapolis, IN), were housed individually in metal cages (25×21×20 cm) for at least 10 days prior to testing. Animals were handled and given saline injections in four preliminary sessions to habituate them to the experimental procedures. During the acclimation period, the animals had free access to Wayne Lab Blox placed on the cage floor and water was available as needed through a stoppered drinking bottle attached to the cage. Illumination was on a 12/12 hr schedule with light onset at 0800 hr. Room temperature was maintained at 24–26°C. Half of the animals were maintained on tap water, while the other half received only a 2% NaCl solution. On the fifth day of NaCl drinking, daytime feeding was initiated 3 hr into the lighting cycle by SC injection of ketocyclazocine (3.0 mg/kg) or the appropriate vehicle for each control group. Two and 4 hr intakes were measured to the nearest 0.1 g by subtracting spillage on paper towels and uneaten food from a premeasured supply. The appropriate drinking fluid was available throughout the feeding period.

Ketocyclazocine was obtained from the Sterling Winthrop Research Institute. The solution for injection was made fresh just prior to injection by dissolving ketocyclazocine base in distilled water with an equimolar amount of HCl. The solution was injected in a volume of 1.0 ml/kg.

The four experimental groups consisted of six randomly assigned animals, and statistical significance was tested by analysis of variance and post-hoc Newman-Keuls analysis.

Results and Discussion

Ketocyclazocine increased daytime 2 and 4 hr food intake approximately sixfold with the majority of food consumed in the first 2 hr (Fig. 1). Five days of 2% NaCl drinking did not decrease ketocyclazocine hyperphagia when compared to the tap water control group.

Since sodium decreases the *in vitro* binding of opiate agonists to the opiate receptor [21], high NaCl intake could conceivably inhibit opioid mediated feeding by decreasing the affinity of opioid receptors. Since the hyperphagic response to ketocyclazocine was unchanged in the NaCl treated rats, the sensitivity of the kappa opiate receptor was not altered. Thus, the resistance of ketocyclazocine-induced eating to the NaCl regimen argues against an effect of sodium at the receptor level. This finding is also consistent with the possibility that the suppression of opioid related food intake by NaCl could be due to depletion of dynorphin, the endogenous ligand for the kappa opioid receptor.

EXPERIMENT 2

Based on their sensitivity to inhibition by naloxone, feeding induced by 2-DG, food deprivation and nocturnal feeding appear to involve EO [12]. Spontaneous daytime feeding and

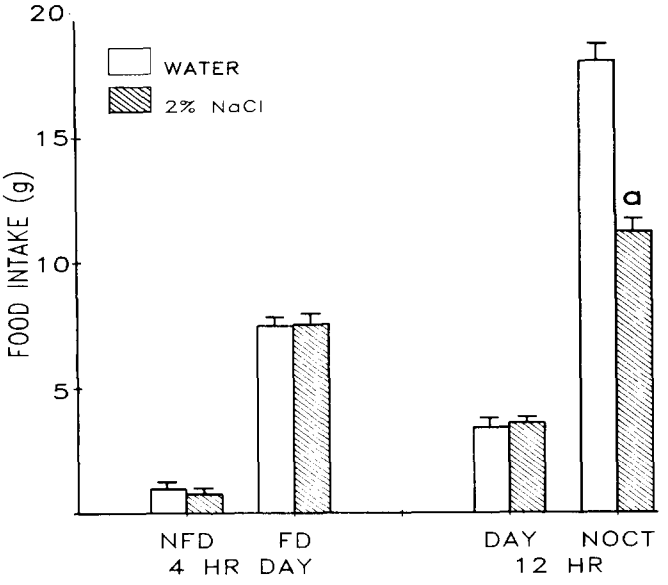

FIG. 3. Food intake (g) in rats maintained for 5 days on 2% NaCl or tap water. Following a 24 hr period of food deprivation (FD), food was returned and 4 hr daytime intake was measured. Four hr intake was also measured in non-food deprived (NFD) controls. In a separate group of rats, 12 hr spontaneous food intakes were measured during daytime (DAY) and during the nocturnal (NOCT) period. Each bar represents the mean (±S.E.) food intake for 6 rats. a=$p<0.01$ vs. the 12 hr nocturnal intake of rats receiving tap water.

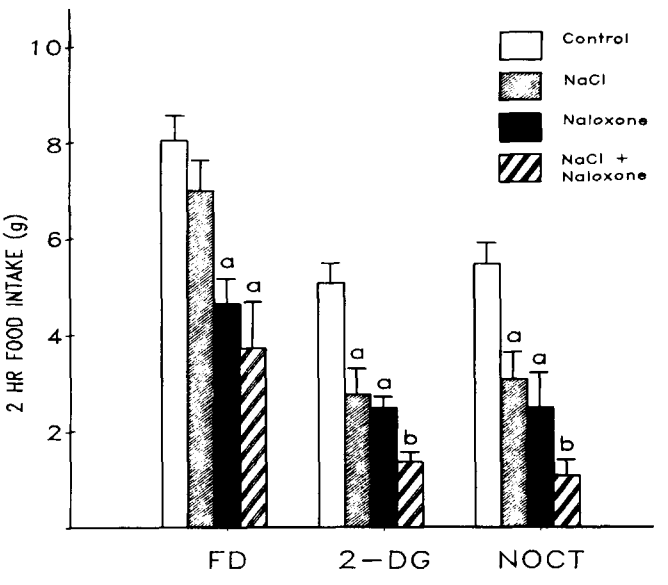

FIG. 4. Food intake (g/2 hr) following 24 hr food deprivation (FD), 2-deoxy-D-glucose (2-DG, 400 mg/kg), and during spontaneous nocturnal (NOCT) feeding. Groups denoted control and naloxone only were maintained on tap water. Groups denoted NaCl only and NaCl +naloxone were forced to drink 2% NaCl for 5 days. The dose of naloxone was 3 mg/kg. Each bar represents the mean (±S.E.) for 6–7 rats. a=$p>0.05$ vs. the mean for the control group for that feeding stimulus. b=$p<0.05$ vs. the mean for the NaCl only group for that feeding stimulus.

food intake induced by insulin are not as sensitive to naloxone-induced suppression [12]. If dynorphin is the critical EO in naloxone-sensitive feeding conditions, and if 2% NaCl imbibition depletes dynorphin in the relevant area(s) of the brain then only naloxone-sensitive hyperphagias should be affected by the NaCl regimen. Therefore, we examined whether the effects of 5 days forced imbibition of 2% NaCl resembled those of naloxone on several feeding conditions.

Method

Male Sprague-Dawley rats (Harlan) were housed individually and acclimated as in the previous experiment.

Daytime feeding studies were initiated 3 hr after light onset, when food intake is low. Food intake was stimulated by subcutaneous (SC) injection of 2-DG (400 mg/kg), insulin (10 U/kg), or by 24 hr food deprivation. Control rats received 0.9% saline injections. Spontaneous nocturnal and daytime feeding was also monitored. All feeding studies were performed in the home cage. Food intake was measured as previously described. Either tap water or a 2% NaCl solution was available ad lib during all feeding experiments.

In order to examine the effects of 2% NaCl drinking on food intake, two groups of animals were used for each hyperphagic stimulus. The first group was maintained on tap water, while the second group received only 2% NaCl for 5 days. Feeding studies took place on day 5 (or night 4) of NaCl imbibition.

Sources of drugs were: 2-DG from U.S. Biochemical (Cleveland, OH) and insulin (Iletin U-100) from Eli-Lilly and Co. The 2-DG and insulin solutions were made fresh by dissolving them in 0.9% saline immediately prior to injection. All injections were given SC in a volume of 1.0 ml/kg.

Experimental groups consisted of 6 randomly assigned animals. Statistical significance for each feeding condition was assessed by analysis of variance and significantly different groups were identified by subsequent Newman-Keuls analysis when indicated.

Results and Discussion

The 2% NaCl regimen selectively attenuated certain naloxone-sensitive hyperphagias. The effects of 2-DG and insulin administration on feeding of rats maintained on 2% NaCl for 5 days are presented in Fig. 2. Both 2-DG and insulin administration increased 3 hr daytime feeding of non-deprived rats ($p<0.01$). The 2-DG induced feeding response in rats maintained on the 2% NaCl drinking solution was attenuated by 65% compared to control 2-DG treated rats ($p<0.01$). In contrast, 3 hr insulin induced feeding was not affected by the forced 5 day consumption of the 2% NaCl drinking solution. Twenty-four hr food deprivation produced an approximate sevenfold increase in 4 hr daytime food intake, which was unaffected by 2% NaCl imbibition (Fig. 3). Mean 12 hr spontaneous nocturnal food intake was reduced by 38% ($p<0.01$) in rats maintained on the NaCl regimen compared to tap water drinking controls (Fig. 3). Twelve hr spontaneous daytime food intake was not affected by NaCl imbibition (Fig. 3).

The suppression of 2-DG induced feeding and nocturnal feeding by the 5 day imbibition of a 2% NaCl solution was in agreement with our original hypothesis. Since the same regimen did not suppress insulin-induced or spontaneous daytime feeding, the anorexic effect was probably not due to non-specific effects of the NaCl regimen (e.g., sickness or malaise). If this regimen depletes dynorphin in the pertinent

regions of the brain, dynorphin could be an EO responsible for the naloxone-sensitive component of 2-DG and nocturnal, but not insulin hyperphagia.

The inability of the NaCl regimen to reduce 24 hr food deprivation induced feeding was unexpected, since food deprivation hyperphagia is readily reduced by naloxone [12]. It would appear that the NaCl regimen did not deplete the EO mediating the food deprivation induced feeding, although non-opioid compensatory mechanisms cannot be discounted.

EXPERIMENT 3

The failure of the 2% NaCl regimen to suppress food deprivation feeding indicates that not all naloxone-sensitive hyperphagias are sensitive to this pituitary dynorphin-depleting regimen. One possible explanation could be that a non-opioid compensatory mechanism may interact with the food deprivation stimulus, when dynorphin levels are depleted. Another possibility is that all of the opioid-related hyperphagic stimuli contain the same naloxone-sensitive component, but differ in whether they contain a NaCl-sensitive component. Therefore, we tested the effect of naloxone on 2-DG, nocturnal and food deprivation hyperphagia in rats maintained on 2% NaCl or tap water.

Method

Male, Sprague-Dawley rats (Harlan) were individually housed and acclimated as in the previous experiments. Naloxone HCl (3.0 mg/kg) was administered 10 to 15 min prior to testing of animals drinking either tap water or 2% NaCl for 5 days. Injections of 0.9% saline were given to individual tap water and NaCl groups in a similar fashion. Two hr daytime feeding induced by 2-DG (400 mg/kg), 24 hr food deprivation, and 2 hr spontaneous nocturnal feeding were measured in this paradigm. Food intake was measured as described in the first experiment.

Naloxone HCl was obtained from Endo Laboratories. Drug solutions were made fresh by dissolving them in 0.9% saline just prior to injection. All injections were given SC in a volume of 1.0 ml/kg.

Each experimental group contained at least six rats. Each experiment consisted of the following groups: a non-feeding-stimulated control group (data not shown), a feeding-stimulated group (i.e., food deprivation, nocturnal), a feeding-stimulated/NaCl-treated group, a feeding-stimulated/naloxone-treated group, and a feeding-stimulated group which received both naloxone and NaCl. Statistical significance was assessed by one-way analysis of variance. When the analysis of variance indicated a significant effect, post hoc comparisons were made using the Newman-Keuls procedure.

Results and Discussion

Figure 4 summarizes the 2 hr food intakes for each of the three feeding responses (food deprivation, 2-DG, and nocturnal). Food intake was increased in response to each of the feeding stimuli ($p<0.05$ vs. non-stimulated controls; not shown). As expected, naloxone alone inhibited ($p<0.05$) food intake for every stimulus (42 to 54% decrease). Forced imbibition of NaCl failed to decrease intake following 24 hr food deprivation in agreement with Fig. 2. Feeding induced by 2-DG was depressed by 45% in the NaCl group ($p<0.05$) and naloxone reduced 2-DG induced feeding in NaCl treated rats by an additional 50% ($p<0.05$). Two hr nocturnal feeding was attenuated by 44% ($p<0.05$) by NaCl imbibition and was further reduced by 64% ($p<0.05$) after naloxone injection.

The inhibitory effects of NaCl imbibition on the hyperphagia following 2-DG treatment or during nocturnal feeding were consistent with those observed in Figs. 2 and 3. The ability of naloxone to reduce food deprivation-induced eating in the 2% NaCl treated animals (Fig. 4) suggests that non-opioid compensatory mechanisms do not account for the lack of effect of the NaCl regimen in these animals. Therefore, the NaCl regimen does not appear to deplete the EO mediating food deprivation-induced feeding.

All three hyperphagic conditions tested contained a naloxone-sensitive component, while only nocturnal and 2-DG hyperphagia were further suppressed by the NaCl regimen. Interestingly, naloxone and NaCl appeared to exert additive suppressant effects on 2-DG induced and nocturnal feeding. This may indicate separate NaCl-sensitive and naloxone-sensitive components mediating these hyperphagias. Alternatively, incomplete depletion of dynorphin at the pertinent area by the NaCl regimen or opiate receptor changes could also account for the additional suppressive effect of naloxone in these animals.

GENERAL DISCUSSION

We have demonstrated that certain naloxone-sensitive feeding conditions are also sensitive to a pituitary dynorphin depleting regimen, the forced imbibition of 2% NaCl. However, the anorexic profile of NaCl treated rats did not parallel exactly that of naloxone-treated animals, since food deprivation induced feeding was reduced by naloxone injection, but not by NaCl consumption. The failure of the 2% NaCl regimen to decrease deprivation-induced feeding is of interest. Since the ED_{50}'s of naloxone in blocking nocturnal, 2-DG and food deprivation induced feeding were in the same dosage range [12], our initial and most simple assumption was that only one EO was involved in all naloxone-sensitive hyperphagias. If one common EO is involved in these hyperphagias, it is unlikely that the NaCl regimen is depleting this opioid, since food deprivation induced feeding was not attenuated. Alternatively, the EO involved in food deprivation hyperphagia may differ from that involved in 2-DG and nocturnal feeding. This is a distinct possibility since NaCl imbibition is somewhat specific for dynorphin as pituitary beta-endorphin is not affected [6]. There is other evidence that food deprivation hyperphagia is not completely equivalent to 2-DG or nocturnal feeding. Feeding induced by 2-DG is sensitive to beta-adrenergic blockade, while food deprivation induced eating is not [2]. Also, nocturnal feeding is associated with increased hypothalamic dynorphin, whereas hypothalamic dynorphin levels are not altered in food deprived animals [22,23].

It is important to recognize that NaCl imbibition produces many effects in addition to the depletion of pituitary dynorphin and these effects could contribute to the anorexic effect. For example, dopaminergic involvement is suggested by the observation that dopamine synthesis is increased in 2% NaCl drinking animals [1]. An increase in dopamine synthesis could decrease feeding in a manner similar to mazindol, which exerts its anorexic effect via activation of dopaminergic mechanisms [10]. However, it has also been reported that dopamine is associated with increased food intake due to an increase in chewing behavior [18]. Thus it would appear that an increase in dopamine synthesis induced by 2% NaCl might have dual effects on feeding depending on the particular dopaminergic site affected by 2% NaCl imbibition.

NaCl induced release of anorexigenic neuropeptides is

another possible explanation. Corticotropin releasing factor (CRF) is one such peptide [17]. Dynorphin and CRF do coexist in some hypothalamic neurons [24], but there are no reports of increased release of CRF with NaCl drinking, and Hollt *et al.* reported that 2% NaCl has no effect on adenohypophysial beta-endorphin [6]. Also, CRF is known to attenuate food deprivation induced feeding [17], which was not affected by the NaCl regimen in our study. Vasopressin is an important neuropeptide which is released by NaCl imbibition [9], but vasopressin itself does not appear to affect feeding [8, 15, 25]. Thus, the NaCl induced anorexia is probably not secondary to effects on CRF, beta-endorphin or vasopressin.

In summary, certain opioid related hyperphagias were inhibited by the forced imbibition of 2% NaCl, a regimen which depletes neurointermediate pituitary dynorphin levels. The effect was specific, as non-opioid related feeding was unaffected. These findings, along with the ability of direct kappa receptor activation by ketocyclazocine to stimulate feeding in NaCl treated animals, would appear to agree with the hypothesis that the anorexic effects of NaCl imbibition may be due in part to dynorphin depletion. However, the lack of an effect on all naloxone-sensitive hyperphagias was indicated by the intact food deprivation hyperphagic response in NaCl drinking rats. This finding and the observation that 2-DG and nocturnal feeding may possess separate naloxone-sensitive and NaCl-sensitive components do not support our original hypothesis. However, since Przewlocki *et al.* have correlated dynorphin levels in the pituitary and hypothalamus with food intake [22], similar experiments which examine the effect of NaCl on dynorphin levels in these areas would be beneficial in determining the possible role of dynorphin in the 2% NaCl induced anorexia.

ACKNOWLEDGEMENTS

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