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N^G-nitro-L-arginine Methyl Ester Reduces Stress-Related Feeding in the Rat Tail-Pinch Model

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CZECH, D. A., A. E. KLOSTERMAN AND K. T. LE SUEUR. *N^G-nitro-L-arginine methyl ester reduces stress-related feeding in the rat tail-pinch model.* PHARMACOL BIOCHEM BEHAV **60**(1) 91–96, 1998.—A possible role of nitric oxide (NO) in stress-related feeding was investigated in male rats using the tail-pinch (TP) model, in within-subjects experimental designs. An initial experiment demonstrated a dose-related reduction in TP-induced solid food intake over a 10-min test period with increasing dose (10, 25, and 50 mg/kg SC) of the NO-synthase (NOS) inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME), reaching statistical significance at 25 mg/kg L-NAME when compared to vehicle control ($p < 0.05$). Pattern analysis further revealed a decrease both in total duration of food-directed oral behavior and in percentage of longer duration (> 60 s) oral behavior bouts with increasing dose of L-NAME; both measures reached statistical significance at 50 mg/kg ($p < 0.01$). Pretreatment with 500 mg/kg of the NO precursor, L-arginine (L-arg), resulted in partial but not significant reversal of the attenuating effect of 25 mg/kg L-NAME on food intake. Latency to begin eating or gnawing was not significantly affected by L-NAME. In a subsequent experiment, L-arg alone (500 and 750 mg/kg) did not significantly alter TP-induced food intake. It is cautiously suggested that these results implicate involvement of NO in TP-induced feeding. © 1998 Elsevier Science Inc.

Food intake Feeding behavior L-Arginine L-NAME N^G-nitro-L-arginine methyl ester Nitric oxide Nitric oxide synthase inhibitor Rats Stress-related feeding Tail pinch

IT has recently been recognized that nitric oxide (NO), a naturally occurring vasodilating gas, might play an important role in mechanisms regulating feeding behaviors in animals under a number of conditions. There is evidence that NO functions as a neurotransmitter and intracellular messenger in both central and peripheral nervous systems (13,24). Pharmacologic manipulations purportedly interfering with production of endogenous NO have been reported to reduce food intake in food-deprived mice (25,26,28), rats (35), and chickens (8), and in genetically obese strains of mice (27) and rats (36). Similarly, morphine-stimulated food intake was thusly attenuated in mice (7). In these studies, NO production was restricted through inhibition of the catalytic enzyme, NO-synthase (NOS). Most recently, our laboratory has reported attenuation of chlordiazepoxide-induced feeding (10) and of feeding produced by glucoprivic challenge with insulin and 2-deoxy-D-glucose (11) in nondeprived mice following pretreatment with an NOS inhibitor. Feeding deficits could be restored to varying degree with L-arginine (L-arg), the natural substrate for NOS and NO precursor. Further, it has been reported that pretreatment with an NOS inhibitor can alter various parameters of feeding behavior, including time spent feeding and number and duration of meals in the rat (37).

In further probing the extent to and conditions under which inhibition of NO generation might influence feeding behaviors, we now report that pretreatment with the NOS inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME), systematically reduces feeding associated with exposure to a mild stressor—using the familiar rat tail-pinch (TP) model. Antelman and his colleagues demonstrated over 2 decades ago that application of an unavoidable peripheral stressor in the form of a tail pinch (mild pressure to the tail) produced a profile of

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behaviors in food-sated rats, which included eating, gnawing, and licking (3,4). This phenomenon is very reliable, and TP-induced eating is the most prevalent oral behavior exhibited. TP has been shown to facilitate recovery from the aphagia accompanying lateral hypothalamic lesions (2) and, if administered repeatedly over a prolonged period, can lead to overeating and marked weight gain (33). These latter findings, along with observations that tail-pinched rats tend to be finicky eaters (6,33)—exhibiting increased preference for highly palatable foods—have been viewed as paralleling some of the characteristics observed with overeating and obesity in humans under conditions of stress (1,20,30), and have contributed to the suggestion that TP-induced feeding might serve as a useful model for studying some aspects of such behavior. Multiple neurochemical and anatomical systems have been implicated in TP-induced feeding—most notably dopaminergic and opioid peptide systems [for reviews, see (1,30)]. There is also evidence to indicate that method of administering TP is differentially subserved by components of these systems, further reflecting the complex character of TP behavior (12,23).

METHOD

Animals

Adult male Sprague–Dawley albino rats from the Marquette University breeding colony, weighing 312–424 g at the start of testing, were individually housed and maintained on a 12 L:12 D cycle (lights on 0700 to 1900 h) in a temperature- and humidity-controlled colony room with ad lib access to pelleted food (Teklad rodent diet 8604) and tap water. Animals were screened and tested individually and all procedures were carried out during the light period between approximately 0930 and 1500 h.

Drugs

N^G-nitro-L-arginine methyl ester (L-NAME) and L-arginine (L-arg) were purchased from Sigma Chemical Co. (St. Louis, MO) and were freshly prepared in sterile 0.9% NaCl vehicle (Veh) on the morning of testing. Drugs (or vehicle) were injected SC in a volume of 0.1 ml/100 g (L-NAME) or 0.2 ml/100 g (L-arg) of body weight.

Apparatus

The tail-pinch (TP) screening/test unit was an open-top chamber measuring 28 × 28 × 40 cm high. Three walls, one with a hole for insertion of a water tube, were wood and covered with white contact paper; the fourth was clear Plexiglas. Tail pinch was administered with a padded spring-loaded clip suspended with string and a rubber band from a wooden beam assembly extending vertically 30 cm above the unit. The tail could thus be elevated about 2 cm above the level of the animal's head with the clip; this discouraged behavior directed at the tail and clip, while allowing freedom of movement. A camcorder was positioned 180 cm from the transparent wall of the TP chamber and connected to a VCR and video monitor located in a room adjoining the testing room. Videotaping was used in all but the acclimation and screening phases of the study.

Procedures

Acclimation and screening. Animals were individually placed in the test environment for a single 15-min acclimation trial. Food pellets were generously scattered on the floor and water was freely available. Tail pinch was not applied during this period. Over the next several days, rats were screened for TP-induced feeding behavior in single daily trials. They were first allowed to explore the unit containing food pellets and water for 2–3 min. The clip was then applied approximately 4 cm from the end of the tail and the 10-min screening trial begun. Behavior was monitored from the adjoining room. Continuous pinch over this trial length, and without investigator presence, was found to be quite effective in previous pilot work. A screening trial was judged to be successful if the animal engaged in chewing/feeding behavior for 1 (need not be continuous) of the 10 min. A criterion of two successful screens out of a possible four trials was required for inclusion in the experiment. The first 12 animals to meet the screening criterion were used. All 12 animals served under all drug and vehicle treatment conditions of the following protocols in a within-subjects experimental design.

Testing: L-NAME dose–response series. On a day of testing, the animal was weighed to the nearest 0.5 g, and injected SC with 10, 25, or 50 mg/kg of L-NAME or 0.9% NaCl vehicle; it was then returned to its home cage. Forty-five minutes later, the animal was brought to the testing room, placed into the test unit, and the tail clip applied. An additional treatment condition included NaCl vehicle injection without TP, serving as a baseline feeding control. The 10-min observation period was begun (time-marked on the videotape) following TP or appropriate delay (for baseline control condition). Preweighed pelleted food (same as provided for maintenance diet and during screening) was available on the floor and in a wall-mounted food pellet holder; water was freely available from a sipper tube. At test end, the rat was removed and all remaining food recovered. Recovered food, some having absorbed urine from the cage floor, was placed in a weigh boat and air-dried until the weight had stabilized. Latency to begin eating or gnawing pellets and all feeding pattern measures were determined upon later review of the videotapes by two or three reviewers who were blind to the treatment being scored. Pattern measures included total time engaged in eating, gnawing, or licking of food pellet or of crumbs from the floor—hereafter collectively referred to as food-directed oral behavior—and number of discriminable bouts of oral behavior. A bout was operationally defined as any continuous period of oral behavior lasting at least 2 s and followed by at least 5 s of nonoral activity. Bout length data were later organized into a series of time bins, which provided information on the number of bouts of various lengths; percentage of bouts of different lengths could then also be determined. Treatments were separated by at least 3 days and order was randomized.

Testing: L-arg interaction. To test for possible reversal of an NOS inhibitor effect, the same 12 animals were again weighed as above, and injected SC with 500 mg/kg of L-arginine, followed 15 min later by 25 mg/kg L-NAME at a different SC injection site. Forty-five minutes later, transfer to a test unit, application of TP, and testing were carried out as above. The L-arg interaction trial was the last treatment administered.

Subsequent to collection and analysis of interaction data, it was further decided to evaluate a possible effect of L-arg alone on food intake. A separate group of 10 acclimated and screened rats were injected SC with 0 (Veh), 500, and 750 mg/kg of L-arg 45 min before applying TP and also with Veh in the absence of TP (baseline control condition). Order of treatment was again randomized.

All research protocols were reviewed and approved by Marquette University's Institutional Animal Care and Use

Committee (IACUC), and are in compliance with the USDA Animal Welfare Act.

Statistical Analyses

Data for behavioral measures were evaluated separately with repeated-measures one-way ANOVAs. Pairwise comparisons were made with Dunnett's or Student's *t*-tests. Intake data were also adjusted for body weight and analyzed. Minimally acceptable alpha level was set at $p < 0.05$.

RESULTS

Food intake data are summarized in Fig. 1 (upper panel). Exposure to tail pinch, as expected, had a prominent stimulatory effect on food eaten. Mean (±SEM) intake under Veh/TP condition was 1.93 (±0.28) g, while no food was consumed during tests without TP applied. The ANOVA for the L-NAME dose–response series under TP condition (analysis not including the Veh/noTP condition) further revealed that L-NAME significantly attenuated TP-induced feeding in a dose-related manner, $F(3, 33) = 10.78$, $p < 0.001$. When compared to the Veh/TP condition, mean intakes were significantly lower at both 25 and 50 mg/kg of L-NAME ($p < 0.05$ or < 0.01), Dunnett's *t*-test. Food intake adjusted for body weight yielded similar results, $F(3, 33) = 11.55$, $p < 0.001$. Mean (±SEM) intakes were 0.57 (±0.07), 0.49 (±0.08), 0.36 (±0.07), and 0.15 (±0.05) g/100 g body weight, respectively, for the 0 (Veh), 10, 25, and 50 mg/kg L-NAME doses/conditions. A dose of 500 mg/kg of L-arg provoked a partial, but nonsignificant, reversal of the effect of 25 mg/kg L-NAME ($p > 0.05$).

Latency data are also shown in Fig. 1 (middle panel). The ANOVA for latency (s) to begin eating or gnawing in the L-NAME series under TP failed to show a significant overall drug effect ($p > 0.05$). Data for total time engaged in food-directed oral behavior are presented in Fig. 1 (lower panel). The ANOVA yielded $F(3, 33) = 3.08$, $p < 0.05$. When compared to Veh/TP condition, mean time was significantly lower only under the 50 mg/kg dose of L-NAME ($p < 0.01$), Dunnett's *t*-test. The distribution of food-directed oral behavior bouts under TP is summarized in Table 1. The ANOVA revealed that percentage of the longest duration (> 60 s) bouts decreased in a dose-related manner, $F(3, 33) = 3.49$, $p < 0.05$. When compared to the Veh/TP condition, these bouts were significantly less frequent at 50 mg/kg of L-NAME ($p < 0.01$), Dunnett's *t*-test. Percentage of bouts >60 s in the combined L-NAME/L-arg condition was also significantly lower than in the Veh/TP condition ($p < 0.05$), Student's *t*-test. No other distributions of bout lengths, or the distribution of total number of bouts, yielded a statistically significant difference.

Administration of L-arg alone in the later experiment did not significantly affect food intake ($p > 0.05$); means (±SEM) were 2.31 (±0.36), 1.90 (±0.26), and 1.74 (±0.24) g, respectively, for 0 (Veh), 500, and 750 mg/kg L-arg under TP. Again, no measurable amount of food was ingested under the Veh/noTP baseline feeding control condition.

DISCUSSION

The aim of the present study was to investigate a possible role of nitric oxide in stress-induced feeding behavior. Endogenous NO production was purportedly blocked with the neuronal NOS inhibitor, L-NAME, and food intake, latency to begin food-directed oral behavior, and oral behavior pattern were measured in the well-known rodent tail-pinch model.

A principal finding to emerge was that L-NAME significantly attenuated a robust TP-induced solid food consumption, and did so in a clearly dose-related manner. This observation is generally consistent with recent literature reports of feeding behaviors in animals treated both centrally and systemically with NOS inhibitors. Relative to vehicle condition, mean intakes were reduced by 9, 35, and 74%, respectively, at 10, 25, and 50 mg/kg of L-NAME. At the highest dose, four animals failed to eat any measurable amount of food, although they did exhibit food-directed oral behavior, and general activity appeared to be normal. TP-induced eating does appear to be somewhat less sensitive than certain other feeding stimulatory manipulations to the action of NOS inhibitors; e.g., doses of 5–10 mg/kg of L-NAME or N^G-nitro-L-arginine (L-NOARG) significantly reduced intake in food-deprived mice (26,28) or rats (35) and in morphine-treated mice (7). It should be pointed out that reduced NOS activity in the central nervous system following peripheral administration of competitive NOS inhibitors of the nitro-L-arginine analogue class has been clearly demonstrated—evidenced by decreases in the rate of conversion of radiolabeled L-arginine to L-citrulline (15,16,34,39).

Pretreatment with 500 mg/kg of L-arg, the substrate for NO synthesis, partially reversed a drop in TP-induced feeding produced by a moderate dose (25 mg/kg) of L-NAME. This reversal was quite modest, however, and did not reach statistical significance when compared to treatment with 25 mg/kg of L-NAME only ($p > 0.05$), Student's *t*-test. At the same time, a comparison between the combined L-arg/L-NAME and Veh/TP conditions also failed to yield a significant difference; this could be interpreted as supporting a reversal effect linked to L-arg pretreatment. Current data leave this issue unresolved. It will be important in future interaction experiments to extend the range of doses of both agents. We did not observe enhanced TP-induced feeding with even quite large doses of L-arg alone. Several articles have reported similar findings (7,10,25,35), perhaps due to already existing high levels of endogenous L-arg.

L-NAME had relatively little effect on latency to initiate feeding or other oral behavior. A seeming exception at the highest dose reflects an inflated mean. Three animals in the 50 mg/kg condition exhibited atypically long latencies to exhibit food-directed oral behavior of any kind; two of the three also did not eat. The lack of a differential latency effect could suggest that L-NAME's principal inhibitory action is on maintenance rather than on an activating effect of tail pinch—an action perhaps linked to stimulus properties of the food. This interpretation would not be inconsistent with currently unpublished data from our laboratory showing systemic administration of L-NAME to attenuate intake of a normally preferred saccharin solution in a two-bottle test in the rat, considered likely a consequence of its altering responsiveness to the taste of the ingestant. Perhaps the shift in the amount of food consumed in the current study might reflect an NOS-induced change in responsiveness to the taste and/or other salient property—perhaps olfactory or textural—of the ingestant.

Some support for an inhibitory action of L-NAME on maintenance of TP-induced behavior(s) might be suggested in the pattern analyses of food-directed oral behavior, evidenced by a clear dose-related inverse trend in total time engaged in food-directed oral behavior and percentage of bouts exceeding 60 s in duration with increasing dose of L-NAME.

Dopamine and opioid systems have been implicated in mediation of TP-induced feeding behaviors. Suppression of TP-induced feeding, for example, has been observed following

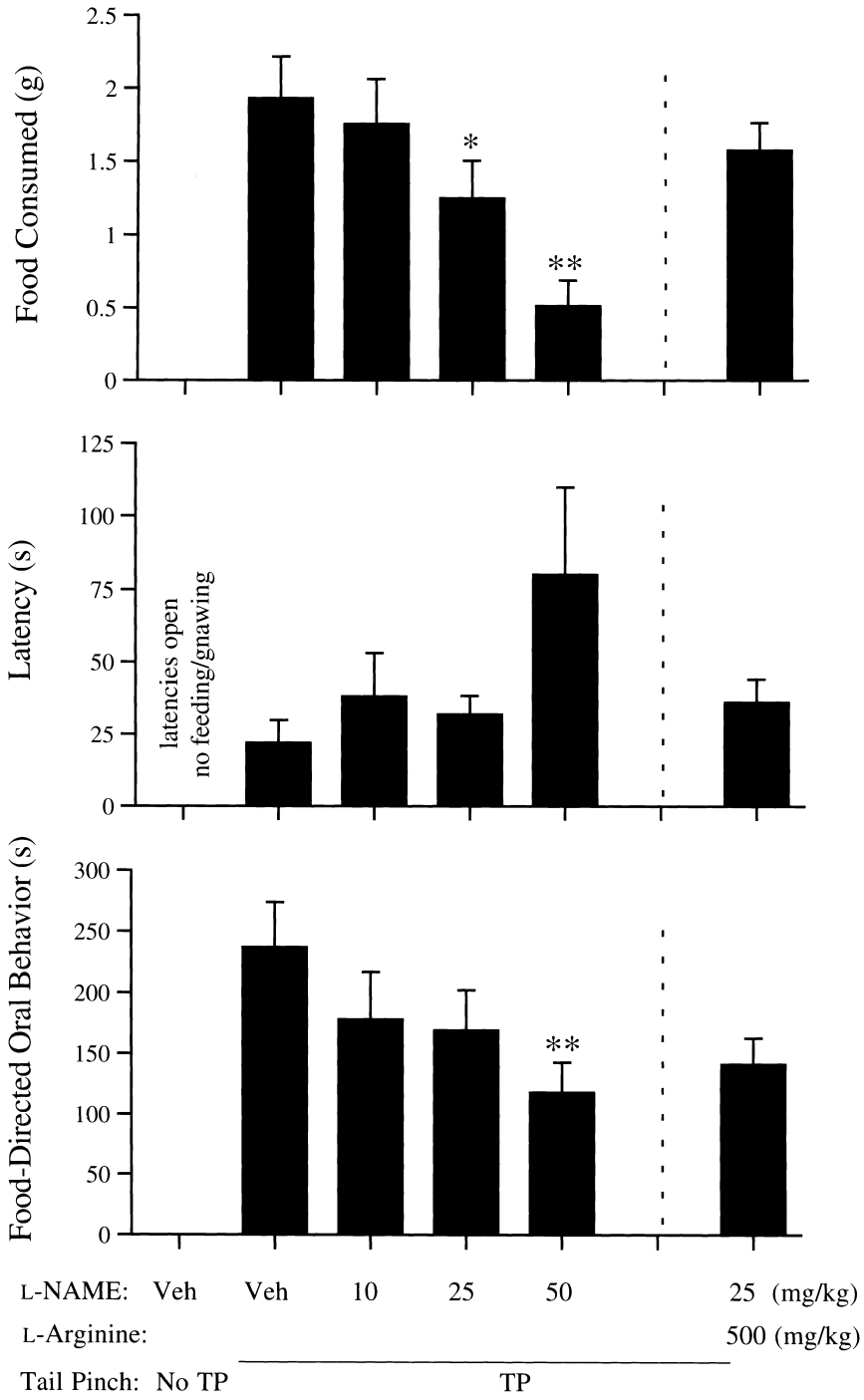

FIG. 1. Mean (±SEM) food consumed (upper panel), latency to begin eating or gnawing (middle panel) and total duration of food-directed oral behavior (lower panel) in tail-pinched (TP) or nonpinched (no TP) condition following treatment with L-NAME or 0.9% NaCl vehicle, or with combined L-NAME/L-arg treatment under tail pinch. $*p < 0.05$, $**p < 0.01$ compared to Veh/TP condition; Dunnett's *t*-test, one tail. No mean latency value is shown for the Veh/no-TP baseline control condition because no animals exhibited food-directed oral behavior in this condition.

TABLE 1
DISTRIBUTION OF FOOD-DIRECTED ORAL BEHAVIOR BOUT DURATIONS UNDER VARIOUS TREATMENTS WITH TP

Bout Duration Bin Size(s)	Dose (mg/kg)				
	Vehicle (0)	10	25	50	25 L-NAME 500 L-arg
≤10	16.7%	26.6%	38.0%	42.1%	33.1%
11–20	13.2	14.4	22.6	28.4	23.6
21–30	14.9	7.4	11.1	7.3	3.3
31–40	6.2	8.0	3.3	5.1	8.3
41–50	2.8	7.9	3.5	3.8	6.0
51–60	1.4	3.9	2.7	0.0	3.1
>60	38.3	22.2	18.7	5.7*	18.2†
Total bouts	[48]	[54]	[69]	[68]	[55]

Based on number of bouts displayed by each animal under a given treatment, the percentage of bouts of different lengths falling into each of the bins was calculated; this was necessary because number of bouts differed across both animals and conditions. Tabled values for bout duration represent the distribution of mean percents of different length bouts.

Total bouts = sum of bouts across all animals under a given treatment condition.

*$p < 0.01$ compared to vehicle condition; Dunnett's t-test (one tail).

†$p < 0.05$ compared to vehicle condition; Student's t-test (two tail).

administration of dopamine (3,4) and endogenous opioid (6,17,19,21,29) receptor antagonists. Hawkins et al., in extending earlier research, point to substantia nigra as a critical integrative site. Noting potentially supportive findings from several sources—pharmacological, anatomical, and electrophysiological—these investigators hypothesize that TP-induced stress might activate an opioid mechanism in the substantia nigra, which in turn initiates or modulates dopaminergic activity linked to ingestion of food (17). The complex character of TP-induced ingestive-linked behavior is further highlighted by evidence of differential activation of DA systems under different amounts (durations) of TP. Mantz et al. (23) found that brief (10 s) TP activated mesocortical DA system, with a minimal effect on mesolimbic DA system; in contrast, chronic (10 min) pinch selectively activated the mesolimbic DA system (12). Further, NOS activity has been demonstrated in substantia nigra as well as in other regions linked to feeding behavior (41). Recent work has provided evidence for interaction of NO and opioid mechanisms as well. NOS inhibitors have been shown to antagonize development of tolerance to morphine and to suppress some signs of withdrawal (5,22,43), and also to attenuate morphine-induced feeding (7); opposite effects were observed following treatment with L-arginine. It has recently been demonstrated that inhibition of corticotropin-releasing factor (CRF) dose-dependently modulates neuropeptide Y (NPY)- and TP-induced feeding; a low dose of the CRF antagonist, α-helical CRF(9–41), was shown to facilitate the intensity of the feeding response to NPY and TP, and also to decrease the latency to TP-induced feeding (18). We, however, did not find a latency effect. Costa's group (9) observed that the NOS inhibitor, N^G-monomethyl-L-arginine (L-NMMA) modulates the inhibitory effect of NO on stimulated release of CRF. Further, L-NAME has been shown to inhibit NPY-induced feeding in the mouse (26). These data, at least in part, point to NO interaction with CRF systems as influencing these two very different types of ingestive behavior systems.

Although mechanism(s) and site(s) of action remain unresolved, the literature points to altered NO activity peripherally as well as centrally that could contribute to changes in food intake behavior. NOS inhibitors have been shown to abolish reflexive relaxation of the stomach to accommodate intake of liquid or solid food in guinea pig (14), and to antagonize the lower esophageal sphincter muscle relaxation response to swallowing and to vagal stimulation in opussums (42). In dogs, NOS inhibition delayed gastric emptying of a solid food meal (31). Reduced ingestion is arguably consistent with inhibition of any of these gastrointestinal responses.

In summary, these initial data lead us to suggest possible involvement of NO in tail-pinch feeding. It will, however, be important to also evaluate NOS inhibition in other purported stress models reported to affect ingestive behaviors [as, e.g., sleep deprivation (32) and cold water swim (40)] in pursuing this research, and to include models that involve exposure to more natural stressors, such as defeat in aggressive encounters (38).

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