Effect of nitric oxide synthase inhibitors on short-term appetite and food intake in humans

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Vozzo, Rosalie, Gary A. Wittert, Michael Horowitz, John E. Morley, and Ian M. Chapman. Effect of nitric oxide synthase inhibitors on short-term appetite and food intake in humans. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R1562–R1568, 1999.—Animal studies suggest that nitric oxide (NO) may be a physiological regulator of appetite; NO synthase (NOS) inhibition suppresses food intake in rats, mice, and chickens. It is not known whether NO has any effect on appetite in humans. We have used guanidino-N-monomethyl L-arginine (L-NMMA) and guanidino-N-nitro-L-arginine methyl ester (L-NAME), both competitive, nonselective inhibitors of NOS, in two separate studies to evaluate the role of NO in the short-term regulation of appetite in humans. In study I, 13 men (18–25 yr) underwent paired studies, in randomized, double-blind fashion, after an overnight fast. L-NMMA (4 mg·kg⁻¹·h⁻¹) or saline (0.9%) was infused intravenously at a rate of 40 ml/h for 1.5 h. In study II, eight men (18–26 yr) underwent three randomized, double-blind studies after an overnight fast. L-NAME (75 or 180 µg·kg⁻¹·h⁻¹) or saline (0.9%) was infused intravenously at a rate of 20 ml/h for 120 min. Hunger and fullness were measured using visual analog scales; blood pressure and heart rate were monitored, and 30 min before the end of the infusion, subjects were offered a cold buffet meal. Total caloric intake and the macronutrient composition of the meal were determined. Both L-NMMA (P = 0.052) and L-NAME (P < 0.05; both doses) decreased heart rate, L-NMMA increased diastolic blood pressure (P < 0.01), and L-NAME increased systolic blood pressure (P = 0.052). Neither drug had any effect on caloric intake or sensations of hunger or fullness. Despite having significant effects on cardiovascular function in the doses used, neither L-NMMA nor L-NAME had any effect on feeding, suggesting that NO does not affect short-term appetite or food intake in humans.

NO functions as a vasodilator (17) and a neurotransmitter at nonadrenergic, noncholinergic neurons (16) and plays a role in nociception (8) and memory formation (21).

The results of animal studies suggest that NO may also be involved in the regulation of appetite. Morley and Flood (9) demonstrated that a single administration of the NOS inhibitor L-NNA to food-deprived mice reduced short-term food intake. Subsequent studies in rats (23), chickens (1), and in the marsupial Smilhopsis crassicaudata (26) yielded similar observations, providing evidence that NO may have a role in the control of feeding behavior. It has been speculated that both central and peripheral mechanisms contribute to the L-Arg analog-induced anorexia (14, 22). Furthermore, chronic exposure to L-Arg analogs elicits an anorectic (decreased food intake and body weight) response (10) to which lean, but not genetically obese (11, 23), rodents (23) rapidly become tolerant. These observations have lead to the hypothesis that obesity may be associated with an increased NO tone, because obese individuals may be more sensitive than their lean counterparts to the appetite-suppressant effects of NOS inhibition and that manipulation of NOS activity may have a potential role in the treatment of obesity. However, no studies have examined the effects of NO on appetite and food intake in humans.

There are substantial differences in both the potencies and the selectivity for different NOS isoforms by all L-Arg analogs (3). For this reason we have examined the effect of two analogs. In the present study the NOS inhibitors L-NMMA and L-NAME were administered to healthy young men to determine whether NO has a role in the short-term regulation of human appetite. We hypothesized that acute NOS inhibition would suppress appetite and food intake.

NITRIC OXIDE (NO) is a short-lived gas produced endogenously by the action of NO synthase (NOS) on the amino acid L-arginine (L-Arg) (19). L-Arg analogues, such as N⁶-monomethyl-L-arginine (L-NMMA), N⁶-nitro-L-arginine (L-NAME), and N⁶-monomethyl-L-arginine (L-NMMA), are considered competitive, nonselective inhibitors of NOS (7) and have been used to study the physiological effects of NO. Endogenous NO production is widespread and has been shown to exert multiple, diverse physiological effects. For example, NO functions as a vasodilator (17) and a neurotransmitter at nonadrenergic, noncholinergic neurons (16) and plays a role in nociception (8) and memory formation (21).

METHODS

Subjects

Two separate studies were performed. In study I L-NMMA was infused, and in study II L-NAME was infused. Thirteen (study I) or eight (study II) healthy male volunteers (18–26 yr) with body mass indexes between 20.3 and 26.1 kg/m² were studied; no subject participated in both studies. All subjects were nonsmokers and unrestrained eaters as determined by a score of <10 on the eating restraint questionnaire of Stunkard and Messick (24). Other exclusion criteria included gastrointestinal, respiratory, or cardiovascular disease (including hypertension), diabetes mellitus, hypersensitivity to glyceryl trinitrate, anemia, current use of medications known or thought to alter gastrointestinal function, and previous gas-
trointestinal surgery. The study was approved by the Royal Adelaide Hospital Ethics Committee, and written, informed consent was obtained from each subject.

**Protocol**

Both studies. Studies were separated by at least 7 days. Subjects were instructed not to undertake vigorous exercise or consume alcohol for at least 24 h before each study day. Subjects arrived at the test center at 0830, having fasted (except for water) from 2100 the previous night. At this time intravenous cannulas were inserted into a vein in each forearm: one to receive infusions, the other from which blood samples were taken. Subjects then rested for 30 min until t = 0 min. All studies were performed in a quiet room. Subjects were allowed to read or listen to the radio, but not to read about food- or eating-related subjects. In both studies, if systolic blood pressure increased by >30 mmHg from baseline or diastolic blood pressure increased >20 mmHg from baseline, the infusion was terminated. On their final study day all subjects were informally asked, by the investigator blinded to the treatment infusions (RV), whether they thought they had received active treatment on the first, second, or third day.

**Study I: Effect of L-NMMA**

Subjects were studied on 2 separate days. An intravenous infusion of 0.9% saline (60 ml/h) was commenced at t = 0 min and continued until t = 150 min. Starting at t = 60 min, subjects received a 90-min intravenous treatment infusion (40 ml/h) of either saline (0.9%) or L-NMMA (Cilinital, Lautelfingen, Switzerland; 4 mg·kg⁻¹·h⁻¹) in saline (0.9%) in randomized order. This study was double blind: neither the subject nor the investigator performing the studies was aware of the treatment solution. At t = 120 min (30 min before the end of the treatment infusion) subjects were offered a cold buffet meal, prepared in excess of what they would normally be expected to eat, and encouraged to eat as much as they wanted in the following 30 min and/or until they were comfortably full. Subjects received the same meal on both days. The infusion ended at the conclusion of the 30-min meal period (t = 150 min). Subjects then rested for a further 30 min, after which time the study was complete. Except during meal time, when they were seated, subjects remained in a supine position with the upper body elevated 30° above the horizontal.

**Study II: Effect of L-NAME**

Subjects were studied on 3 separate days. An intravenous infusion of 0.9% saline (60 ml/h) was commenced at t = 0 min and continued until t = 150 min. Starting at t = 30 min, subjects received a 120 min intravenous treatment infusion (20 ml/h) of either saline (0.9%) or L-NAME (Cilinital; 75 or 180 μg·kg⁻¹·h⁻¹) in saline (0.9%), in randomized, double-blind fashion. At t = 120 min (30 min before the end of the treatment infusion) subjects were offered a cold buffet meal, prepared in excess of what they would normally be expected to eat, and encouraged to eat as much as they wanted in the following 40 min and/or until they were comfortably full. Subjects received the same meal on all 3 study days. The meal ended at t = 150 min, and the infusion ended at t = 160 min. Subjects then rested for a further 20 min, after which time the study was complete. Except during meal time, when they were seated, subjects remained in a supine position with the upper body elevated 30° above the horizontal.

**Measurements of sensations of appetite and food intake**

Visual analog scales (VAS) assessing hunger, fullness, and nausea ratings were administered at t = 0 min every 15 min until t = 120 min and then at t = 150 and 180 min (study I) or at t = 160, 165, 180, and 195 min (study II). The VAS were in the form of a questionnaire, with the opposites of a particular sensation written at either end of a 10-cm horizontal line, for example hungry vs. not hungry, full vs. empty, and nauseated vs. not nauseated (20). Other parameters assessed were drowsiness, anxiety, tiredness, clear headedness, sociability, happiness, predicted (not actual) strength, efficiency, friendliness, satiety, thirst, desire to eat, and prospective food consumption. To describe how strong their feeling of the particular sensation was at a given time point, subjects were instructed to place a vertical mark at the appropriate place on each of the lines. Sensations associated with appetite were then quantified (in cm). The same investigator (RV) administered all questionnaires. In study I, subjects were made aware that the primary aim of the study was to assess the effects of L-NMMA on sensations of appetite and on food intake. However, in study II, subjects were not informed of the major aim of the study but told that the study would assess the effects of L-NAME on cardiovascular function in the pre- and postprandial states.

In both studies, the meal consisted of sliced bread (white and whole meal), nondairy spread, mayonnaise, sliced ham, chicken, cheese, tomato, cucumber and lettuce, and milk (study I) or iced coffee (study II), orange juice, low-fat strawberry yogurt, chocolate custard, vanilla ice cream, and an apple, pear, and banana (6). Vegetarian subjects were offered a boiled egg (n = 2; study I) or additional vegetables, beetroot, carrot, and three-bean mix (n = 1; study II) in place of the meats. The total energy content of the food offered to the subjects was ~2,400 kcal. All food items were weighed (to 0.1 g) before and after the meal, and the duration of eating was recorded. Energy consumption and macronutrient intake were calculated from the amount of food consumed during the buffet meal, using the DIET/4 food composition computer program (Xyris Software, Highgate Hill, Queensland, Australia).

Measurements of blood pressure and pulse rate. In study I, at t = 0 min, t = 30 min, and then every 15 min until the end of the study, heart rate was measured by cardiac auscultation using a stethoscope and blood pressure (BP) was measured between the first (systolic pressure) and fourth (diastolic pressure) Korotkoff sounds, in the right arm, using a mercury sphygmomanometer (Accoson, London, UK). The same investigator (RV) performed all blood pressure and heart rate readings. Mean arterial BP (mmHg) was calculated as diastolic BP + 1/3 (systolic BP – diastolic BP). In study II, BP and heart rate were measured every 15 min, except at t = 150 min and at 160 min, using a Dinamap vital signs monitor 8100 (Critikon, Sydney, Australia).

**Statistical Analyses**

All data are expressed as means ± SE. Mean arterial BP and heart rate and hunger, fullness, and nausea ratings were analyzed using two-way ANOVA with repeated measures, with time and treatment as the two parameters, using the Sigma Stat software package (Jandel Scientific). Post hoc analyses were performed using the Student-Newman-Keuls procedure. Appetite ratings are expressed as changes from baseline, where baseline is the mean of the 0–60 min (study I) or 0–30 min (study II) values. A two-tailed Student’s paired t-test was used to compare the means for caloric intake and macronutrient composition in study I. A two-way ANOVA with repeated measures was used to compare the means for caloric intake and macronutrient composition in study II. A P value of <0.05 was considered statistically significant.
RESULTS

All treatments were well tolerated by all subjects, and there were no adverse events. Subjects stated that they experienced no symptoms that made them think they were receiving the NOS inhibitor on a particular day and did not apparently identify the treatment days any more often than by chance alone.

Effects of L-NMMA and L-NAME on BP and Heart Rate

Both L-NMMA and L-NAME increased BP and decreased heart rate (Figs. 1 and 2). There was a significant effect of time on blood pressure in both studies, such that mean arterial BP during and after the meal was 3–5 mmHg higher than at the beginning of the treatment infusion. BP did not increase to an extent where these infusions needed to be terminated in any subject. There was an effect of L-NMMA and L-NAME such that heart rate was lower than on saline infusion days.

Study I: L-NMMA

During the baseline saline infusions there were no significant differences in systolic (control vs. L-NMMA, 120.5 ± 1.7 vs. 122 ± 1.8 mmHg; F_1,103 = 0.6, P > 0.05), diastolic (control vs. L-NMMA, 82.2 ± 2 vs. 79.8 ± 2 mmHg; F_1,103 = 1.3, P > 0.05), or mean arterial (control vs. L-NMMA, 94.8 ± 1.8 vs. 93.9 ± 1.8 mmHg; F_1,103 = 0.3, P > 0.05) BP between control and L-NMMA infusion days. Although L-NMMA had no effect on the change in systolic BP from baseline (F_1,207 = 0.2, P > 0.05; Fig. 1A, top), L-NMMA increased diastolic BP by 4.5% during treatment infusions (control vs. L-NMMA, 81.7 ± 1.3 vs. 85.4 ± 1.0 mmHg; F_1,207 = 15.1, P < 0.01), an effect that was evident 30 min after commencement of the treatment infusion (Fig. 1A, bottom). There was also a significant effect of L-NMMA on mean arterial BP (F_1,207 = 7.9, P < 0.05); L-NMMA increased mean arterial BP by 3.0 ± 0.7 mmHg during treatment infusions compared with the saline control.

During the baseline saline infusions, there were no significant differences in heart rate between control and treatment days (control vs. L-NMMA, 56.9 ± 2.0 vs. 56.4 ± 2.1 beats/min; F_1,105 = 0.3, P = 0.6). Although there was no effect of L-NMMA on heart rate (F_1,207 = 0.4, P > 0.05; Fig. 2A), there was a time x treatment interaction that just failed to reach statistical significance, such that the increase in heart rate that occurred at the end of both treatment infusions was not as great when L-NMMA was infused compared with when saline was infused (saline vs. L-NMMA, 7.2 ± 1.8 vs. 4.4 ± 1.9 change in heart rate from baseline, beats/min; F_7,207 = 2.1, P = 0.052).

Study II: L-NAME

During baseline saline infusions there were no significant differences in systolic (control vs. low vs. high, 120.3 ± 3.1 vs. 122.8 ± 3.2 vs. 121.9 ± 3.1 mmHg; F_2,71 = 0.4, P > 0.05), diastolic (control vs. low vs. high, 56.7 ± 3 vs. 59.7 ± 3.1 vs. 61.3 ± 3.1 mmHg; F_2,71 = 1.1, P > 0.05), or mean arterial (control vs. low vs. high,
During the baseline saline infusions, there were no significant differences in heart rate between control and treatment days (control vs. low dose vs. high dose, 61.7 ± 2.4 vs. 59.0 ± 2.5 vs. 58.4 ± 2.4 beats/min; \( F_{2,71} = 1.2, P = 0.3 \)). Both doses of L-NAME decreased heart rate throughout the treatment infusion compared with the saline control (control vs. low dose vs. high dose, 6.9 ± 1.4 vs. 6.4 ± 1.4 vs. 0.2 ± 1.9 change in heart rate from baseline, beats/min; \( F_{2,259} = 11.2, P < 0.05; \) Fig. 2B).

Effect of L-NMMA and L-NAME on Sensations of Appetite and on Food Intake

Pretreatment ratings of hunger (\( F_{1,129} = 2.4, P = 0.1 \)), fullness (\( F_{1,129} = 2.1, P = 0.2 \)), and nausea (\( F_{1,129} = 0.1, P = 0.7 \)) did not differ significantly between the 2 treatment days in study I nor between the 3 treatment days in study II (hunger, \( F_{2,71} = 2.0, P = 0.1 \); fullness, \( F_{2,71} = 2.6, P = 0.1 \); nausea, \( F_{2,71} = 0.1, P = 0.8 \)). As expected, consumption of the meal increased fullness (L-NMMA, \( F_{4,29} = 65.6, P < 0.0001 \); L-NAME, \( F_{4,237} = 33.9, P < 0.0001 \)) and decreased hunger (L-NMMA, \( F_{4,29} = 72.1, P < 0.0001 \); L-NAME, \( F_{9,237} = 32.4, P < 0.0001 \); Fig. 3, top and middle, respectively). Nausea ratings were not significantly affected by the meal (L-NMMA, \( F_{4,29} = 1.69, P = 0.2 \); L-NAME, \( F_{9,237} = 1.4, P = 0.2 \); Fig. 3, bottom panels). Neither L-NMMA nor L-NAME in either dose studied had any effect on ratings of hunger (L-NMMA, \( F_{1,129} = 2.1, P = 0.2 \); L-NAME, \( F_{2,237} = 0.9, P = 0.4 \)), fullness (L-NMMA, \( F_{1,129} = 1.6, P = 0.2 \); L-NAME, \( F_{2,237} = 0.9, P = 0.5 \)), or nausea (L-NMMA, \( F_{1,129} = 0.2, P = 0.9 \); L-NAME, \( F_{2,237} = 1.1, P = 0.4 \) (Fig. 3).

No subject consumed all the food offered, and only one subject ate for the entire 40 min (study II). Energy intake was unaffected by both L-NMMA (\( P = 0.8 \)) and L-NAME (\( F_{2,23} = 0.02, P = 0.9 \); Tables 1 and 2). Neither the L-NMMA infusion nor the L-NAME infusions were associated with any significant changes in macronutrient composition of the food consumed or duration of eating (Tables 1 and 2).

There was no effect of either L-NMMA or L-NAME on other parameters assessed by VAS, including drowsiness, anxiety, tiredness, clear headedness, sociability, happiness, predicted strength, efficiency, friendliness, satiety, thirst, desire to eat, and prospective food consumption (data not shown).

**DISCUSSION**

Animal studies, in mice (9), rats (23), chickens (1) and in the marsupial Sminthopsis crassicaudata (26), have suggested that NO may have a role in the regulation of feeding behavior. Administration of L-Arg analogs, which act as competitive, apparently nonselective NOS inhibitors, to food-deprived animals results in suppression of food intake. Our study is the first to examine the role of NO in the regulation of human feeding. We demonstrated that 1.5- and 2-h intravenous infusions of the L-Arg analogs L-NMMA and L-NAME had no effect on appetite ratings or on food...
intake during the later part of the infusions. This is despite the doses of L-NMMA and L-NAME being sufficient to produce cardiovascular effects consistent with peripheral NOS inhibition, namely suppression of heart rate and elevation of BP. Our study therefore provides evidence that NO is unlikely to be involved in the regulation of short-term appetite in humans.

Potencies and selectivity of L-Arg analogs differ markedly (3); thus, to examine these potential differences, we studied the effects of two analogs. There is some evidence that in relation to vasoconstriction L-NAME is at least ten times more potent than L-NMMA (17); we have shown a similar difference with respect to inhibition of food intake (26) in S. crassicaudata. In view of

Table 1. Weight, caloric content, and macronutrient content of buffet meal consumed by healthy subjects during intravenous infusion of saline and L-NMMA

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>L-NMMA (4 mg·kg(^{-1})·h(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, g</td>
<td>1,159.2 ± 61.5</td>
<td>1,156.8 ± 88.8</td>
</tr>
<tr>
<td>Energy intake, kcal</td>
<td>1,280.6 ± 84.1</td>
<td>1,267.5 ± 99.5</td>
</tr>
<tr>
<td>Carbohydrate, %total</td>
<td>48.2</td>
<td>48.0</td>
</tr>
<tr>
<td>Protein, %total</td>
<td>19.7</td>
<td>19.4</td>
</tr>
<tr>
<td>Fat, %total</td>
<td>32.1</td>
<td>32.6</td>
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</table>

Values are means ± SE (n = 13). L-NMMA, N\(^\circ\)-monomethyl-L-arginine. Analysis by Student's paired t-test showed that there were no significant differences.
this, it is not surprising that comparable effects on BP and heart rate were observed after both drugs despite the fact that the dose of L-NAME administered was 17–40 times lower than that of L-NMMA. It has also been demonstrated that N^G^\text{-methyl-L-arginine exhibits competitive inhibition of endothelial NOS and irreversible inhibition of macrophage NOS (12). Furthermore, L-NNA is selective for brain compared with inducible NOS (4). Both of the drugs we studied had similar effects: neither drug had any effect on appetite, and both drugs produced comparable hemodynamic effects. The increase in BP and heart rate was unexpected, but possibly resulted from the change in posture (from supine to sitting) and slight increase in activity while eating. Therefore, our study provides no evidence for a selective action of either L-NMMA or L-NAME on any NOS isoform.

The apparent discrepancy between suppression of food intake in animals by L-Arg analog administration and the absence of such effect in humans may be due to species differences. Alternatively, it is possible that in the doses required to reduce food intake in animals, these drugs produce a nonspecific noxious effect leading to aversion, rather than a true suppressive effect on appetite. The dose of L-NAME required to produce anorexia in animals (10 mg/kg in mice, 50 mg/kg in rats, 100 mg/kg in S. crassicaudata) (5, 10, 26) is higher than the dose we have found to be without effect on appetite in humans. Similarly we have shown that a higher dose of L-NMMA (1,000 mg/kg) was required to suppress food intake in S. crassicaudata than we administered to humans in this study. The issue of whether drugs produce appetite-suppressive effects secondary to the production of malaise is optimally addressed in animals using conditioned taste-aversion tests. Ideally, animals receive test drugs after, rather than before, exposure to a novel taste, thus they are conditioned to associate the novel taste with malaise. Subsequent exposure to the same novel taste results in diminished intake in those animals that have previously received a drug producing aversion. Nevertheless, the results of these tests are difficult to interpret, as no single method has been agreed on and well known rodenticides cannot be shown to produce a conditioned taste aversion in some studies. To our knowledge, only two conditioned taste-aversion tests have been performed using L-NAME (5, 15) and none using L-NMMA. The report by Prendergast et al. (15) that L-NAME apparently does produce conditioned taste aversion (i.e., malaise) is probably more accurate than that of Hui and Chan (5), who administered test drugs before novel food exposure and did not demonstrate conditioned taste aversion. We are currently performing a conditioned taste-aversion test with L-NAME to address this issue in S. crassicaudata.

Alternate explanations for the observed lack of effect of L-Arg analogs on appetite and food intake in the study include inadequate duration of NOS blockade and/or inadequate dose of the L-Arg analogs. The first explanation seems unlikely, given that the infusions were administered for 90 and 120 min and had significant cardiovascular effects during this time due to endothelial NOS inhibition (2); L-NMMA produces endothelium-dependent vasoconstriction (7, 13). Furthermore, L-Arg analogs have been shown to suppress food intake in animals within 30 min of a single intraperitoneal injection (9).

The doses of L-NMMA and L-NAME used were chosen on the basis of those shown to have effects on factors associated with appetite regulation, namely hormone secretion and gut motility, in previous human studies. Comparable doses of L-NAME have been shown to affect insulin and ACTH secretion in healthy young men. A dose of 90 µg/kg iv over 60 min reduces the stimulatory effect of L-Arg on insulin secretion (2), as well as producing a marginal increase in mean arterial BP. A 40 µg/kg bolus plus a further 50 µg/kg for 1 h enhanced the ACTH response to hypoglycemia (25). The higher of the two L-NAME doses in our study is greater, both in total dose administered (360 µg/kg) and hourly rate (180 µg·kg\(^{-1}\)·h\(^{-1}\)) than in those studies, whereas the lower dose delivered a slightly lower hourly rate (75 compared with 90 µg·kg\(^{-1}\)·h\(^{-1}\)) but somewhat greater total dose (150 µg/kg compared with 90 µg/kg). The dose of L-NMMA used in this study, 4 mg·kg\(^{-1}\)·h\(^{-1}\), has been shown to stimulate small intestinal fasting motility in normal subjects (18). This dose of L-NMMA, when infused for 1 h, increased the number of small intestinal migrating motor complexes. Furthermore, the doses of L-NMMA and L-NAME administered in the present studies were sufficient to exert cardiovascular effects, consistent with suppression of peripheral NOS activity. Therefore, although not definitely the case, it seems likely that the doses used were sufficient to influence appetite if NO has such an effect. Where higher doses of these L-Arg analogs might theoretically have effects on appetite, peripheral administration of such doses would probably be accompanied by even greater effects on cardiovascular parameters such as BP and heart rate than observed in this study, which would very likely render these analogs unacceptable for clinical use.

Several studies in animals have provided evidence that the appetite-suppressive effects of L-Arg analogs may be due to central as well as peripheral NO
blockade. For example, food intake is suppressed when rats are treated with intracerebroventricular L-NNA (23). In fact, doses that do not suppress food intake on peripheral administration produce hypophagia after central administration (23). Choi et al. (1) used L-NNA to demonstrate a similar effect in chickens. In addition, we have recently shown in the marsupial S. crassicaudata that acute peripheral administration of L-NAME suppresses both food intake and central (hypothalamic and cortical) NOS activity (26). This suggests that, at least in marsupials, L-NAME crosses the blood-brain barrier. We have no comparable information for L-NMMA and it is unclear as to whether L-NMMA and L-NAME actually cross the blood-brain barrier in humans. In the present study we were limited by the route of administration of L-Arg analogs and did not have the capacity to assess central NOS activity. Therefore, despite the apparent peripheral suppression of NOS activity, a lack of central suppression could explain the absence of effect of these L-Arg analogs on human feeding.

In summary, despite exerting peripheral effects on the cardiovascular system consistent with inhibition of endothelial NOS, neither L-NMMA nor L-NAME had any effect on short-term appetite or feeding in humans. This suggests that peripheral NO is not involved in the short-term control of feeding. Although central NO activity may play a role in appetite regulation, the present study provides no evidence for a role of endogenous NO in the regulation of human appetite.

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