Pharmacology Biochemistry and Behavior, Vol. 46, pp. 787–791, 1993
Printed in the U.S.A.

0091-3057/93 $6.00 + .00

Centrally Administered Bacterial Lipopolysaccharide Depresses Feeding in Rats

CARLOS R. PLATA-SALAMÁN[1] AND JEFFREY P. BORKOSKI

School of Life and Health Sciences, University of Delaware, Newark, DE 19716

Received 12 January 1993

PLATA-SALAMÁN, C. R. AND J. P. BORKOSKI. *Centrally administered bacterial lipopolysaccharide depresses feeding in rats.* PHARMACOL BIOCHEM BEHAV 46(4) 787–791, 1993.—Bacterial lipopolysaccharide (LPS) suppresses feeding in rats when administered peripherally in the microgram range. In the present study, the effects of LPS (*Escherichia coli* serotype 0111 : B4) on the central regulation of feeding in rats maintained ad lib was investigated. Intracerebroventricular (ICV) microinfusion of LPS (0.1 to 1000 ng/rat) suppressed the short-term (2-h) and long-term (nighttime and total daily) food intakes, dose dependently. Computerized analysis of behavioral patterns demonstrated a significant reduction of meal size during the nighttime, whereas meal frequency and meal duration were also decreased, but not significantly. Water intake and locomotor activity also decreased. Intraperitoneal administration of LPS in doses equivalent to those administered centrally had no effect on food intake. The results suggest that centrally administered LPS acts directly in the central nervous system (CNS) to depress feeding.

Bacterial lipopolysaccharide Endotoxin Infection Neuroimmunology Immunomodulator Nervous system Immune system Behavior Feeding and drinking Food and water intake Anorexia Rat Intracerebroventricular administration Interleukin Meal pattern

BACTERIAL lipopolysaccharide (LPS, located in the outer layer of the outer membrane of most gram-negative bacteria) (22) is responsible for the pathophysiological changes associated with gram-negative infections (13). Previous studies in rats have shown that LPS depresses feeding following peripheral administration in the microgram range [25 μg/kg b.wt., IV (11); 100 μg/kg b.wt, IP (8); and 400 μg/kg, IP (6)]. One study, however, reported that intracerebroventricular (ICV) administration of 10 ng of *Escherichia coli* LPS did not affect food intake of fasted rats (12). In the present report, we reexamined the effects of *Escherichia coli* LPS on the central regulation of feeding in rats maintained ad lib. Our studies show that ICV administration of LPS in rats maintained ad lib induces a consistent and dose-dependent decrease of food intake.

METHOD

Subjects and Maintenance

Male Wistar rats weighing between 250 and 275 g at the beginning of the experiments were used. Rats were randomly assigned into groups and placed in individual cages. They were maintained ad lib on powdered rat food (No. 5012, Purina Mills) or on pellet rat chow (45-mg precision food pellets formula A; Noyes Co. Inc., NH) and tap water as previously described (21). Artificial light illumination was from 0600 to 1800 h and room temperature was kept at 21 ± 2°C. All rats were handled daily. After several days of adaptation of the rats to their home cages, brain cannulas were implanted. Test solutions were administered following a recovery period of 7 to 10 days after surgery.

Powdered Food Consumption

The measurement of intake of powdered food has been described elsewhere [see (21)], and in all cases food and water intakes were measured to within 0.1 g. Before and after the cannula implantation, the rats were fed ad lib daily, except between 1630 and 1800 h when food and water were removed to be measured and replaced. Premeasured food and water were presented at 1800 h. Food and water intakes were measured at 2000 (2-h consumption), at 0600 (nighttime consumption from 1800 to 0600 h), and at 1630 (daytime consumption from 0600 to 1630 h and total daily consumption from 1800 to 1630 h). During the 12-h nighttime measurements, a red incandescent bulb was used to provide dim illumination.

Feeding, Drinking, and Locomotor Activity Patterns

In separate experiments, the microstructure of eating, drinking, and locomotor activity patterns before and after the ICV microinfusions were recorded by a computer-aided, behavior-monitoring system. These rats were housed in special test chambers equipped with electromechanical pellet dispensers controlled by pellet-sensing photobeams, photoelectric

[1] To whom requests for reprints should be addressed.

lickometers, and photobeam sensors to measure locomotor activity. Pellets and water were available ad lib throughout the experiment. After adaptation to the chamber, test solutions were administered. Changes in food and water intakes, and locomotor activity before and after ICV microinfusions, were analyzed in terms of cumulative measures during the experiment. Data acquisition was through a central processing unit and a behavioral programming language that uses Turbopascal compiler to run four experimental stations simultaneously. The data from each input channel (pellets and drops of water delivered, and locomotor activity) was summed and recorded at 10-min intervals, 24 h/day. A meal was defined as the acquisition of at least five pellets preceded and followed by at least 20 min of no feeding (intermeal interval). Meal size was defined as the number of pellets eaten during a meal. Feeding rate was calculated from meal size divided by meal duration (pellets/min). Postprandial intermeal intervals were taken as the time from the last pellet in one meal to the first five pellets in the next.

Implantation of Brain Cannulas

Under intraperitoneal (IP) sodium pentobarbital (60–70 mg/kg) anesthesia, a guide cannula was implanted into the third ventricle at stereotaxic coordinates −2.1 anteroposterior and 0.0 lateral with respect to bregma, and 7.5–8.0 dorsoventral from the brain surface as previously described (21). A sterile 29-ga stainless steel obturator was used to ensure that the cannula remained patent.

Intracerebroventricular Microinfusion

Microinfusions were made into the third ventricle because of the importance of hypothalamic regions in the regulation of feeding. The ICV microinfusions (10 μl/rat, into unrestrained, undisturbed animals) were at the rate of 1 μl per 60 s using a Harvard 22 infusion pump (Harvard Apparatus, South Natick, MA). Each rat was infused between 1700 and 1800 h (i.e., before the nighttime or the period of eating in the rat). The method and verification of continuous ICV microinfusion have been described previously (21).

Randomly assigned groups received the ICV administration of either sterile physiological saline (0.15 M NaCl, 10 μl) or 0.01 to 1000 ng/rat bacterial lipopolysaccharide (*Escherichia coli* serotype 0111 : B4; Calbiochem, CA) dissolved in 10 μl 0.15 M NaCl. Each compound had a pH of about 7.0. After an experiment was completed, rats were deeply anesthetized with sodium pentobarbital, infused with 5 μl of pontamine sky blue (2%), and prepared for histology to localize the position of the cannula tip as previously described (21).

Intraperitoneal Administration

In other experiments, 10, 100, or 1000 ng/rat LPS was administered IP into cannulated rats.

Data Analysis

All results are expressed as means ± SD. Statistical analyses compared the preinfusion levels to those obtained after infusion of test solutions. Analyses were performed using the two-tailed, paired-sample Student's *t*-test. The two-sided Wilcoxon signed ranks test for two correlated samples was also applied when groups did not present homogeneity across the preinfusion and postinfusion levels. Data was also analyzed using analysis of variance (ANOVA) with treatment and percentage changes as sources of variation followed by post hoc tests for individual comparisons. Differences were considered to be significant only for $p < 0.05$.

RESULTS

The ICV microinfusion of physiological saline (control) or 0.01 ng/rat LPS did not affect short-term (2-h) or long-term (nighttime and total daily) food intake (Table 1). The ICV microinfusion of LPS (0.1 to 1000 ng/rat) decreased the 2-h and nighttime food intakes, dose dependently (Table 1) [$p < 0.05$, paired-sample Student's *t*-test for intragroup comparisons; $p < 0.001$, ANOVA, $F(8, 76) = 13.5$; $p < 0.001$, post hoc tests for individual comparisons, $F(1, 67) = 27.3$ to > 40]. The following daytime food intake increased for 0.1 (57%, from 2.1 to 3.3 g), 1.0 (55%, from 2.2 to 3.4 g), 5.0 (90%, from 2.0 to 3.8 g), 10.0 (112%, from 2.6 to 5.5 g), 100 (146%, from 1.3 to 3.2), 500 (133%, from 1.8 to 4.2), and 1000 (111%, from 1.9 to 4.0 g) ng/rat LPS-treated groups. This suggests compensation for the previous nighttime food intake decrease. Total daily food intakes were still suppressed because the decrease at nighttime was more prominent than the daytime compensation (Table 1). On the following postinfusion days (first day, 24–48 h after infusion; second day, 48–72 h after infusion; third day, 72–96 h after infusion; not shown), the 2-h, nighttime, and total daily food intakes recovered from the changes observed during the infusion day; this recovery of food intake was quicker in the rats treated with the low doses (0.1 to 10 ng LPS) relative to the rats treated with the high doses (100 to 1000 ng LPS). For example, in the 100 ng/rat LPS-treated group, the 2-h and nighttime food intakes were still significantly decreased to 4.2 ± 1.0 and 18.7 ± 1.6 g, respectively, on the first postinfusion day; in the same group, the 2-h and nighttime food intakes were 5.4 ± 1.0 g (not significant) and 21.4 ± 1.4 g (significantly different from the preinfusion level), respectively, on the second postinfusion day; on the third postinfusion day, however, the 2-h and nighttime food intakes were equivalent (5.6 ± 1.2 and 23.1 ± 1.9 g, respectively) to the preinfusion levels. Therefore, the groups treated with large doses of LPS required at least 3 days to recover food intake to the preinfusion levels.

In other experiments, peripheral (IP) administration of 10 to 1000 ng/rat LPS into cannulated rats did not affect short- or long-term food intake. After the IP administration of 10 ng/rat LPS ($n = 12$), the 2-h, nighttime, and total daily food intakes changed +13, +2, and +2%, respectively, not significantly different from the preadministration levels; for the 100 ng/rat LPS-treated group ($n = 10$), these changes were 0, −3, and +1%, respectively. The highest dose of LPS administered IP was 1000 ng/rat ($n = 18$); in this group, the nonsignificant changes (because of the intragroup variability) for the 2-h, nighttime, and total daily food intakes from the preadministration levels were −14, −12, and −9%, respectively. Therefore, the 1000 ng/rat LPS-treated group presented only a tendency to decrease food intake. This is consistent with previous studies that have required doses of ≥ 25 μg LPS/kg b.wt. to suppress food intake when administered peripherally (6,8,11).

To study the mode of action of LPS on food intake, an analysis of behavioral patterns before and after the ICV microinfusion of 10 ng/rat LPS was performed. The effects of this dose of LPS on 24-h behavioral parameters are summarized in Table 2. During the nighttime, the decrease of total intake was dependent primarily on a decrease of meal size;

TABLE 1

EFFECTS OF ICV MICROINFUSION OF LIPOPOLYSACCHARIDE (LPS) ON 2-h, NIGHTTIME, AND TOTAL DAILY FOOD INTAKES

Treatment Group		Preinfusion Averages	Infusion Averages	Percent Decrease
Control [8]	2-h	5.2 ± 1.4	5.5 ± 0.8	
(0.15 M NaCl)	Night	25.3 ± 1.9	25.8 ± 2.1	
	Total	27.4 ± 1.7	27.9 ± 1.8	
LPS [10]	2-h	5.3 ± 1.1	5.4 ± 0.9	
(0.01 ng)	Night	23.9 ± 1.7	23.4 ± 1.5	
	Total	25.7 ± 1.8	25.8 ± 1.5	
LPS [9]	2-h	7.5 ± 1.6	6.9 ± 1.8	-8%
(0.1 ng)	Night	25.9 ± 2.0	22.7 ± 2.6	-12%*
	Total	28.0 ± 1.8	26.0 ± 3.0	-7%
LPS [10]	2-h	5.9 ± 1.3	3.6 ± 1.0	-39%*
(1.0 ng)	Night	24.3 ± 2.8	20.5 ± 3.4	-16%*
	Total	26.5 ± 2.4	23.9 ± 3.0	-10%*
LPS [10]	2-h	5.8 ± 1.3	3.4 ± 1.5	-41%*
(5.0 ng)	Night	25.2 ± 3.1	17.7 ± 3.8	-30%*
	Total	27.2 ± 2.8	21.5 ± 2.7	-21%*
LPS [10]	2-h	6.0 ± 0.9	3.5 ± 1.5	-42%*
(10.0 ng)	Night	23.7 ± 2.0	14.3 ± 3.5	-40%*
	Total	26.3 ± 1.5	19.8 ± 4.8	-25%*
LPS [10]	2-h	5.6 ± 1.4	3.1 ± 1.2	-45%*
(100 ng)	Night	23.5 ± 1.8	11.1 ± 2.6	-53%*
	Total	24.8 ± 1.7	14.3 ± 2.6	-42%*
LPS [10]	2-h	6.4 ± 1.7	3.2 ± 0.8	-50%*
(500 ng)	Night	24.3 ± 2.7	9.6 ± 2.7	-60%*
	Total	26.1 ± 2.9	13.8 ± 2.9	-47%*
LPS [8]	2-h	6.3 ± 1.6	2.9 ± 1.5	-54%*
(1000 ng)	Night	24.7 ± 1.8	8.0 ± 1.6	-68%*
	Total	26.6 ± 2.0	12.0 ± 2.2	-55%*

Values are mean ± SD, g. Food intakes were measured from 1800 to 2000 h (2-h), 1800 to 0600 h (nighttime), and 1800 to 1630 h (total daily). Numbers in brackets are number of rats. Preinfusion and infusion averages are averages for 1 day.

*Significantly different, $p < 0.05$.

meal frequency and meal duration also decreased, but not significantly. The postprandial intermeal intervals were prolonged as a result of the decrease of meal frequency and meal duration. Water intake and locomotor activity also decreased. This suggests, at least in part, a reduction of prandial drinking and exploratory drive, which are part of feeding behavior. The decrease of food intake-to-water intake ratio also shows a greater effect on food intake than on water intake. During the daytime, total intake, meal frequency, water intake, and locomotor activity increased, and latency to eat the first meal from start the daytime decreased (Table 2). This suggests compensation for the previous nighttime changes. Total daily meal parameters were still consistent with the nighttime changes because of the limited daytime compensation except for meal frequency, which increased slightly. On the other hand, the ICV microinfusion of LPS vehicle (0.15 M NaCl, $n = 8$, not shown) did not result in significant changes during the nighttime (total intake and meal frequency decreased 5%, whereas meal size increased 3%, and water intake decreased 3%). All total daily behavioral parameters were also not significantly affected by the ICV microinfusion of LPS vehicle.

DISCUSSION

These results show that the ICV administration of *Escherichia coli* LPS decreases 2-h and nighttime food intakes in rats maintained ad lib through a reduction of meal size. This suppression of food intake by the ICV administration of LPS is accompanied by a decrease of water intake and locomotor activity. The peripheral administration of LPS in doses equivalent to those administered centrally [but still lower than the microgram doses of LPS that have been found to suppress feeding (6,8,11)] had no significant effect on food intake. This suggests that centrally administered LPS acts directly in the CNS to decrease short- and long-term food intakes.

In the present study, the ICV administration of LPS (*Escherichia coli* serotype 0111 : B4) induced a consistent, reliable, and dose-dependent decrease of short- and long-term food intakes in rats maintained ad lib. It has been previously reported that ICV administration of the same serotype of LPS did not affect food intake of fasted rats (12). The main differences between this report and the present study are the maintenance of the animals [fasted rats (12); ad lib, the present

TABLE 2

EFFECTS OF ICV MICROINFUSION OF LPS (10 ng/RAT, n = 12) ON NIGHTTIME, DAYTIME, AND TOTAL DAILY BEHAVIORAL PARAMETERS

Behavioral Parameter	Nighttime	Daytime	Total Daily
TI	448 ± 44 to 199 ± 77 (−56%)*	183 ± 47 to 230 ± 96 (+26%)*	631 ± 62 to 429 ± 139 (−32%)*
MF	6.0 ± 1.0 to 5.0 ± 1.4 (−17%)	3.5 ± 1.0 to 5.0 ± 1.2 (+43%)*	9.5 ± 1.8 to 10 ± 1.8 (+5%)
MS	75 ± 16 to 40 ± 10 (−47%)*	52 ± 13 to 46 ± 14 (−12%)	66 ± 12 to 43 ± 12 (−35%)*
MD	17.4 ± 4.0 to 15.6 ± 4.8 (−10%)	13.8 ± 3.2 to 13.3 ± 2.4 (−4%)	16.1 ± 2.7 to 14.4 ± 3.1 (−11%)
PIMIS	101 ± 14 to 129 ± 43 (+28%)	169 ± 61 to 132 ± 32 (−22%)	122 ± 22 to 127 ± 26 (+4%)
WI	7493 ± 2208 to 5570 ± 3007 (−26%)*	999 ± 851 to 1758 ± 822 (+76%)*	8492 ± 2256 to 7327 ± 3021 (−14%)
LA	2518 ± 939 to 797 ± 307 (−68%)*	335 ± 147 to 408 ± 266 (+22%)	2853 ± 1015 to 1205 ± 513 (−58%)*
Latency	61 ± 38 to 86 ± 127 (+41%)	144 ± 123 to 62 ± 60 (−57%)	
FR	4.31 ± 0.9 to 2.56 ± 0.7 (−41%)*	3.77 ± 1.5 to 3.46 ± 0.9 (−8%)	4.10 ± 0.8 to 2.99 ± 0.7 (−27%)*
FI/WI ratios	0.06 ± 0.02 to 0.04 ± 0.02 (−33%)*	0.18 ± 0.28 to 0.13 ± 0.06 (−28%)	0.07 ± 0.02 to 0.06 ± 0.02 (−14%)

Values are mean ± SD. +, represents mean percent increase from the preinfusion level or first value; −, represents mean percent decrease from the preinfusion level. Abbreviations: TI, total intake (number of pellets); MF, meal frequency (number of meals); MS, meal size (number of pellets); MD, meal duration (min); PIMIS, postprandial intermeal intervals (min); WI, water intake (number of water drops); LA, locomotor activity (number of breaks of photobeams on rat cage floor); latency, latency in first meal from start the nighttime or daytime; FR, feeding rate (meal size/meal duration); FI/WI ratios, food intake-to-water intake ratios (pellets/drops).

*Significantly different, $p < 0.05$.

study], the diet [liquid (12); powdered or pellet food, the present study], and the position of the cannula [right lateral ventricle (12); third ventricle or close to the hypothalamic feeding-associated sites, the present study]. In addition, the timing of administration of LPS is unclear in the report by McCarthy et al. (12). It is possible that the metabolic state of the animal (fasted vs. ad lib) may be an important determinant of LPS's action on food intake, as has been demonstrated with interleukin-1 (14). Other methodological factors such as the diet, cannula placement, and the preparation of LPS might also account for the different results between the report by McCarthy et al. (12) and the present study.

The LPS-induced feeding suppression may be mediated, at least in part, by other immunomodulators, because LPS has been shown to induce the neural and nonneural production of interleukin-1β (1,4,23–25), interleukin-6 (9,23), and tumor necrosis factor-α (5,9,10,23), immunomodulators that have been found to suppress food intake by direct action in the CNS in rats maintained ad lib (15,16,18–20). The presence of immunomodulators in the CNS (brain and cerebrospinal fluid) is the result of local synthesis—by cerebrovascular endothelial cells, microglia, astrocytes, monocytes, and activated T-lymphocytes that may infiltrate the CNS—and specific uptake from the peripheral circulation across the circumventricular organs and possibly the blood–brain barrier [for review see (17)]. It is possible that the disruption of the blood–brain barrier due to the cannula placement was still present, at least partially, when infusions of LPS were performed; therefore, immunomodulator induction by LPS may involve the activation of brain and infiltrating blood-borne immune cells.

Previous studies have also shown that interleukin-1β and tumor necrosis factor-α decrease food intake by direct action in the hypothalamus (7,17,20). Electrophysiological studies have demonstrated that one mechanism by which immunomodulators decrease food intake involves inhibition of glucose-sensitive neurons in the lateral hypothalamic area (20) and excitation of glucose-responsive neurons in the ventromedial hypothalamus (7). Furthermore, the intrahypothalamic administration of IL-1 also results in food intake suppression (3). The mode of action of LPS on feeding (that is, via a reduction of meal size) may involve the ventromedial hypothalamus, since excitation of this region terminates ongoing feeding, which may be expressed in the suppression of meal size. The potential participation of hypothalamic feeding-associated sites in the suppression of food intake by LPS may interact with other factors. LPS decreases locomotor activity, and a decrease of the overall activity related to the feeding drive will result in the suppression of feeding. It is important to note, however, that the specificity of LPS inhibiting feeding behavior remains to be tested with the appropriate behavioral paradigms. On the other hand, the reduction of water intake after the ICV administration of LPS may be a direct conse-

quence of food intake suppression (i.e., reduced prandial drinking); this is supported by the decrease of food intake-to-water intake ratio that indicates a greater effect on food intake than on water intake. However, we cannot exclude that centrally administered LPS acts directly in the CNS to regulate water intake.

The concentration of LPS in the cerebrospinal fluid of patients with bacterial meningitis ranges from picograms to 5.0 ng/10 μl (2). Considering the rat's normal cerebrospinal fluid volume (approximately 300 to 400 μl) [see (21)], we estimate that the concentration of LPS, if not metabolized, will be 250 to 333 pg/10 μl after a dose of 10 ng/rat. Furthermore, considering the rat's normal rate of cerebrospinal fluid turnover and secretion to be about 0.7% of the total volume/min [see (21)], the concentration of LPS after 120 and 240 min following administration would be approximately 43% and 18.5%, respectively, of the initial amount; that is, 107.5 and 46.5 pg/10 μl for a volume of 400 μl, and 143.5 and 62 pg/10 μl for a volume of 300 μl, at 120 and 240 min, respectively, according to $C_T = 10[S(1 - K)^T]/V$, where C_T is the concentration after time $_T$, 10 represents 10 μl, S the amount of test substance administered (here 10 ng/rat LPS, a very effective dose), K the volume of cerebrospinal fluid exchanged every min (here, a constant 0.7% of the volume of cerebrospinal fluid/min), V the volume of cerebrospinal fluid, and T the time elapsed after administration in min. Therefore, the amounts of LPS administered in the present studies are in the pathophysiological range observed in the cerebrospinal fluid. However, caution is necessary in comparing the concentrations of LPS used in the present studies in normal rats with the pathophysiological concentrations found during human disease.

The regulation of feeding by LPS could participate in the appetite suppression observed during gram-negative infections. This action could be direct and/or mediated by feeding-suppressive immunomodulators that are synthesized and released in response to LPS, including interleukin-1β, interleukin-6, and tumor necrosis factor-α.

ACKNOWLEDGEMENT

This work was partly supported by the University of Delaware Research Foundation.

REFERENCES

1. Anderson, J.; Bjork, L.; Dinarello, C. A.; Towbin, H.; Andersson, U. Lipopolysaccharide induces human interleukin-1 receptor antagonist and interleukin-1 production in the same cell. Eur. J. Immunol. 22:2617–2623; 1992.
2. Brandtzaeg, P.; Øvstebø, R.; Kierulf, P. Compartmentalization of lipopolysaccharide production correlates with clinical presentation in meningococcal disease. J. Infect. Dis. 166:650–652; 1992.
3. Chance, W. T.; Fischer, J. E. Aphagic and adipsic effects of interleukin-1. Brain Res. 568:261–264; 1991.
4. Clark, B. D.; Bedrosian, I.; Schindler, R.; Cominelli, F.; Cannon, J. G.; Shaw, A. R.; Dinarello, C. A. Detection of interleukin 1α and 1β in rabbit tissues during endotoxemia using sensitive radioimmunoassays. J. Appl. Physiol. 71:2412–2418; 1991.
5. Hallenbeck, J. M.; Dutka, A. J.; Vogel, S. N.; Heldman, E.; Doron, D. A.; Feuerstein, G. Lipopolysaccharide-induced production of tumor necrosis factor activity in rats with and without risk factors for stroke. Brain Res. 541:115–120; 1991.
6. Kent, S.; Kelley, K. W.; Dantzer, R. Effects of lipopolysaccharide on food-motivated behavior in the rat are not blocked by an interleukin-1 receptor antagonist. Neurosci. Lett. 145:83–86; 1992.
7. Kuriyama, K.; Hori, T.; Mori, T.; Nakashima, T. Actions of interferon-α and interleukin-1β on the glucose-responsive neurons in the ventromedial hypothalamus. Brain Res. Bull. 24:803–810; 1990.
8. Langhans, W.; Balkowski, G.; Savoldelli, D. Differential feeding responses to bacterial lipopolysaccharide and muramyl dipeptide. Am. J. Physiol. 261:R659–R664; 1991.
9. Lieberman, A. P.; Pitha, P. M.; Shin, H. S.; Shin, M. L. Production of tumor necrosis factor and other cytokines by astrocytes stimulated with lipopolysaccharide or a neurotropic virus. Proc. Natl. Acad. Sci. USA 86:6348–6352; 1989.
10. Martich, G. D.; Danner, R. L.; Ceska, M.; Suffredini, A. F. Detection of interleukin 8 and tumor necrosis factor in normal humans after intravenous endotoxin: The effect of antiinflammatory agents. J. Exp. Med. 173:1021–1024; 1991.
11. McCarthy, D. O.; Kluger, M. J.; Vander, A. J. The role of fever in appetite suppression after endotoxin administration. Am. J. Clin. Nutr. 40:310–316; 1984.
12. McCarthy, D. O.; Kluger, M. J.; Vander, A. J. Effect of centrally administered interleukin-1 and endotoxin on food intake of fasted rats. Physiol. Behav. 36:745–749; 1986.
13. Morrison, D. C.; Ryan, J. L. Endotoxins and disease mechanisms. Annu. Rev. Med. 38:417–432; 1987.
14. Mrosovski, N.; Molony, L. A.; Conn, C. A.; Kluger, M. J. Anorexic effects of interleukin 1 in the rat. Am. J. Physiol. 257: R1315–R1321; 1989.
15. Plata-Salamán, C. R. Food intake suppression by immunomodulators. Neurosci. Res. Commun. 3:159–165; 1988.
16. Plata-Salamán, C. R. Immunomodulators and feeding regulation: A humoral link between the immune and nervous systems. Brain Behav. Immun. 3:193–213; 1989.
17. Plata-Salamán, C. R. Immunoregulators in the nervous system. Neurosci. Biobehav. Rev. 15:185–215; 1991.
18. Plata-Salamán, C. R. Dexamethasone inhibits food intake suppression induced by low doses of interleukin-1β administered intracerebroventricularly. Brain Res. Bull. 27:737–738; 1991.
19. Plata-Salamán, C. R.; Ffrench-Mullen, J. M. H. Intracerebroventricular administration of a specific IL-1 receptor antagonist blocks food and water intake suppression induced by interleukin-1β. Physiol. Behav. 51:1277–1279; 1992.
20. Plata-Salamán, C. R.; Oomura, Y.; Kai, Y. Tumor necrosis factor and interleukin-1β: Suppression of food intake by direct action in the central nervous system. Brain Res. 448:106–114; 1988.
21. Plata-Salamán, C. R.; Oomura, Y.; Shimizu, N. Dependence of food intake on acute and chronic ventricular administration of insulin. Physiol. Behav. 37:717–734; 1986.
22. Raetz, C. R. H.; Ulevitch, R. J.; Wright, S. D.; Sibley, C. H.; Ding, A.; Nathan, C. F. Gram-negative endotoxin: An extraordinary lipid with profound effects on eukaryotic signal transduction. FASEB J. 5:2652–2660; 1991.
23. Righi, M.; Mori, L.; De Libero, G.; Sironi, M.; Biondi, A.; Mantovani, A.; Donini, S. D.; Ricciardi-Castagnoli, P. Monokine production by microglial cell clones. Eur. J. Immunol. 19: 1443–1448; 1989.
24. Ulich, T. R.; Guo, K.; Yin, S.; del Castillo, J.; Yi, E. S.; Thompson, R. C.; Eisenberg, S. P. Endotoxin-induced cytokine gene expression *in vivo*: IV. Expression of interleukin-1α/β and interleukin-1 receptor antagonist mRNA during endotoxemia and during endotoxin-initiated local acute inflammation. Am. J. Pathol. 141:61–68; 1992.
25. van Dam, A.-M.; Brouns, M.; Louisse, S.; Berkenbosch, F. Appearance of interleukin-1 in macrophages and in ramified microglia in the brain of endotoxin-treated rats: A pathway for the induction of non-specific symptoms of sickness? Brain Res. 588: 291–296; 1992.