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then determined to assess the influence of exogenous and endogenous melanocortins on LPS-induced fever, anorexia, and locomotion over a 24-h period. The results indicate that, despite the suppressive influence of exogenous and endogenous central melanocortins on LPS-induced fever, centrally administered melanocortins exacerbate LPS-induced anorexia and hypoactivity, and centrally acting endogenous melanocortins are involved in mediating LPS-induced anorexia.

### METHODS

#### Animals and Surgical Procedures

Adult male Sprague-Dawley rats (Taconic, Germanton, NY) initially weighing 270–300 g were used. The rats were initially housed in group cages (3 per cage) in a room with temperature controlled at 21 ± 1°C and a 12:12-h light-dark cycle (lights on at 0600). Standard rodent chow (PROLAB 3000, Agway, Syracuse, NY) and tap water were provided ad libitum throughout the experiments, except where indicated. All procedures were approved by the Animal Research Committee of Tufts University Medical School and New England Medical Center.

A week before the experiments, under pentobarbital sodium anesthesia (50 mg/kg ip), each rat was implanted intraperitoneally with a battery-operated radiotelemetry transmitter (Mini-Mitter, Sunriver, OR) for monitoring body temperature (Tb) and motor activity and an intracerebroventricular 22-gauge stainless steel guide cannula (Plastics One, VA) in the right lateral ventricle for intracerebroventricular injections as described previously (11). After surgery, the rats were placed in individual cages and housed in a separate room with temperature controlled at 25 ± 1°C, in or near the thermoneutral ambient temperature range for rats. Correct placement of intracerebroventricular cannulas was verified by injection of 10 µl of 0.1% cresyl violet through the guide cannula at the end of the experiment followed by postmortem brain dissection. Data obtained from rats with misplaced cannulas were excluded from analysis.

#### Animal Handling and Intracerebroventricular Injections

Each rat was used in only one experiment. To minimize the potential influence of nonspecific stress on results, each rat was conditioned daily to gentle handling for 5 consecutive days before experiments, including a simulated intracerebroventricular injection performed by removing the dummy cannula and connecting the injection device to the intracerebroventricular guide cannula. Intracerebroventricular injections were delivered at a speed of 2 µl/min using a 100 µl Hamilton syringe driven by a microinfusion pump (Bee, MF-9090, Bioanalytic Systems, West Lafayette, IN) as described earlier (11). Injection cannulas were left in place for 2 min after infusion to prevent any injectate reflux. Tb and Locomotion Measurement

Tb of rats was monitored continuously via a receiver placed under each cage. Emitted frequencies were transmitted into a peripheral processor (Mini-Mitter) connected to a personal computer, recorded at 10-min intervals, and converted into Tb values according to the frequency-temperature calibration curves, using the Vitalview software package (Mini-Mitter). Each transmitter was calibrated before experiments according to the manufacturer’s instructions. Gross locomotor activity was also measured using the Mini-Mitter system, as described previously (16). In this system, activity is detected as changes in the angular changes in transmitter position and recorded as motor activity counts.

#### Experimental Protocol

One day before experiments, rats were weighed and assigned arbitrarily to body weight-matched groups. Tb and motor activity of the rats were recorded at 10-min intervals starting at 0900. The rats were deprived of food at 1600, but free access to tap water was provided. Between 0900 and 1000 on the following day (designated day 1), rats were injected intraperitoneally with either saline (0.9% sterile NaCl) or LPS (100 µg/kg, in 200 µl saline), followed 30 min later by intracerebroventricular injection with either saline or one of two doses of α-MSH [30 or 300 ng (200 pmol)] in 6 µl of saline] or SHU-9119 [200 ng (168 pmol) in 4 µl of saline] as indicated below. Immediately after intraperitoneal LPS or saline treatment, preweighed rat chow pellets were placed in the chow bin for free access by the rats. Food consumption was measured at 2, 4, 6, 8, and 24 h after intraperitoneal saline or LPS by weighing the remaining food pellets along with any spillage into the cage. Recording of Tb, and motor activity was terminated at 1100 on day 2.

#### Drugs

SHU-9119 was prepared by Dr. Wei Yuan as described earlier (10). Stock solutions of LPS derived from Escherichia coli endotoxin (0111:B4, Sigma), α-MSH (Peninsula Laboratories, Belmont, CA), and SHU-9119 were prepared by dissolving in sterile saline containing 0.1% low endotoxin BSA at a concentration of 1 mg/ml and freezing in aliquots at −70°C. Immediately before experiments, fresh aliquots of the respective stock solutions were thawed and further diluted with saline to the respective injectate concentrations.

#### Data Analysis and Statistics

Average Tb values for 30-min periods were computed from Tb recorded at 10-min intervals. For each rat, Tb was expressed as change from a baseline value that was computed as the mean Tb during the 4-h period between 0600 and 1000 on day 1. To account for differences in feeding behavior, motor activity, and Tb associated with the photoperiod, the 24-h Tb data were accordingly divided into three periods for statistical analysis [0–8 h (lights on), 9–20 h (lights off), and 21–24 h (lights on)]. Integrated Tb responses [areas under the curves (AUC)] in each period of time were calculated using the trapezoidal method as described earlier (11). Motor activity for 30-min intervals was computed from the primary 10-min activity counts recorded by the telemetry system. The data were arbitrarily divided into three time blocks as described for Tb data. Hourly means of the motor activity counts during each time period were used for statistical analysis and computation of group means. For food intake, cumulative individual food intake at the indicated time intervals was used for statistical analysis and computation of group means. Treatment-associated group differences for Tb, AUC data, food intake, and locomotor activity were analyzed by one-way ANOVA followed by Scheffé’s test. Differences were considered statistically significant at values of P < 0.05.

### RESULTS

#### Effects of Intracerebroventricular Injection of α-MSH on Food Intake, Tb, and Motor Activity in LPS-Treated Rats

Food intake. Administration of LPS (100 µg/kg ip) significantly suppressed food intake in rats fasted...
overnight, beginning in the 0- to 4-h period and in all subsequent time intervals (Fig 1). The 24-h cumulative food intake in LPS-treated rats was reduced by 35% compared with vehicle-injected controls (Fig 1). Intracerebroventricular administration of α-MSH at doses of both 30 and 300 ng delivered 30 min after LPS injection potentiated LPS-induced reduction in food intake during the 0- to 2-, 0- to 4-, and 0- to 6-h time periods (Fig 1). Effects of the two α-MSH doses tested (30 and 300 ng) were similar. During the periods 0-8 and 0-24 h after LPS, the cumulative food intake in the α-MSH-treated rats remained decreased in comparison with that in rats not receiving α-MSH, but the effects failed to reach statistical significance (P = 0.25) (Fig 1).

Tb. As expected, intraperitoneal injection of LPS resulted in a marked rise in Tb which peaked 6-8 h after its injection and lasted >24 h. Intracerebroventricular injection of 30 ng α-MSH after LPS had no effect on LPS-induced fever (Fig 2). In contrast, intracerebroventricular administration of 300 ng α-MSH significantly suppressed LPS-induced fever 0-8 h after LPS injection, completely preventing the onset of fever for at least 3 h (Fig 2). During the period corresponding to the dark phase (9-20 h after LPS injection), the mean Tb in rats receiving LPS plus intracerebroventricular α-MSH (300 ng) remained lower than that in the rats treated with LPS plus intracerebroventricular saline (Fig 2A), but the effect was no longer statistically significant by comparison of Tb AUC data (Fig 3). Control rats receiving intraperitoneal and intracerebroventricular saline treatments exhibited only a negligible rise in Tb of <0.5°C throughout most of the 24-h measurement period (Fig 2A).

Locomotor activity. Baseline locomotor activities were similar in all treatment groups (Fig 3A). During the light phase (0-8 h after LPS treatment), the locomotor activity in LPS-treated rats was slightly, but not significantly, lower than that in intraperitoneal saline-treated controls (Fig 3B). Both intracerebroventricular doses of α-MSH produced somewhat greater decreases in motor activity that were statistically significant with those of controls (Fig 3). During the dark phase (9-20 h after LPS injection), all LPS-treated groups exhibited marked and significant reductions in locomotor activity compared with control rats receiving intraperitoneal and intracerebroventricular saline (Fig 3). Intracerebroventricular injection of 300 ng, but not 30 ng, of α-MSH significantly potentiated the LPS-induced suppression of locomotion during this period (Fig 3). During the period 21-24 h after intraperitoneal LPS, corresponding to the beginning of the
light phase of day 2, locomotor activity remained lower in rats treated with LPS plus intracerebroventricular \( \alpha \)-MSH than those in rats treated either with intraperitoneal LPS plus intracerebroventricular saline or with intraperitoneal/intracerebroventricular saline controls (effect was statistically significant for 300 ng but not for 30 ng \( \alpha \)-MSH) (Fig. 3).

Effects of Central MCR Blockade by Intracerebroventricular SHU-9119 on Food Intake, \( T_b \), and Locomotor Activity in Normal Rats

In rats fasted overnight but receiving no LPS treatment, intracerebroventricular administration of 300 ng \( \alpha \)-MSH significantly reduced cumulative food intake during the 0- to 4-, 0- to 6-, and 0- to 8-h postinjection intervals (\( P < 0.05 \) for each interval), but not during the 0- to 24-h interval. Comparable intracerebroventricular injection of 30 ng \( \alpha \)-MSH had no effect on food intake. LPS treatment suppressed locomotor activity only slightly during the period 0–8 h post-LPS but dramatically reduced motor activity during the dark phase (9–20 h post-LPS) (\( P < 0.01 \)) (Fig. 6). Intracerebroventricular SHU-9119 had no effect on the LPS-induced suppression of locomotor activity (Fig. 6).

Effects of Intracerebroventricular Injection of \( \alpha \)-MSH on Food Intake, \( T_b \), and Locomotor Activity in LPS-Treated Rats

Food intake. To assess whether endogenous central melanocortins are involved in mediating LPS-induced anorexia, we tested the effect of intracerebroventricular injection of the MC3-R/MC4-R antagonist SHU-9119 on food intake in fasted, LPS-treated rats. Intracerebroventricular SHU-9119 significantly inhibited the LPS-induced suppression of cumulative food intake during the 0- to 24-h post-LPS interval (\( P < 0.05 \)); food intake during this period in rats treated with LPS plus intracerebroventricular SHU-9119 was not significantly different from that in control rats not treated with LPS (Fig. 4). The anti-anorexic effect of intracerebroventricular SHU-9119 appeared as a progressive trend beginning in the 0- to 6- and 0- to 8-h post-LPS intervals, but reached statistical significance only during the 0- to 24-h interval. In control rats receiving intraperitoneal saline rather than LPS, intracerebroventricular SHU-9119 had no effect on food intake (Fig. 4).

\( T_b \). Consistent with our previous results (11), intracerebroventricular injection of SHU-9119 (200 ng) exacerbated LPS-induced fever during the period 0–8 h after LPS, but not during subsequent intervals (Fig. 5). Intracerebroventricular administration of SHU-9119 alone had no significant effect on \( T_b \) in control rats receiving intraperitoneal saline rather than LPS (Fig. 5).

Locomotor activity. LPS treatment suppressed locomotor activity only slightly during the period 0–8 h post-LPS but dramatically reduced motor activity during the dark phase (9–20 h post-LPS) (\( P < 0.01 \)) (Fig. 6). Intracerebroventricular SHU-9119 had no effect on the LPS-induced suppression of locomotor activity (Fig. 6). Furthermore, in the absence of LPS treatment, intracerebroventricular SHU-9119 had no effect on locomotor activity compared with that in controls receiving intraperitoneal/intracerebroventricular saline (Fig. 6).
intake (Fig. 7). Neither intracerebroventricular dose of α-MSH affected Tb or locomotor activity significantly in these rats (data not shown).

DISCUSSION

The principal finding of this study concerns the divergent roles of melanocortins in regulating different components of the LPS-induced acute phase response. The anorexic effect of LPS was potentiated by exogenous intracerebroventricular α-MSH and was reversed by central MCR blockade, indicating that centrally acting endogenous melanocortins may be involved in mediating LPS-induced anorexia. Exogenous intracerebroventricular α-MSH also exacerbated LPS-induced hypoactivity. In contrast, exogenous and endogenous melanocortins were shown to alleviate LPS-induced fever in the same experiments, consistent with previous findings (2, 11, 12).

The observations that exogenous α-MSH potentiated and that central MCR blockade reversed LPS-induced anorexia are consistent with the compelling array of evidence supporting a suppressive role of central melanocortins in the normal regulation of food intake (6, 13, 36). Nevertheless, in the present studies, the effects of intracerebroventricular α-MSH (agonist) and SHU-9119 (antagonist) on LPS-induced anorexia were qualitatively distinct from those seen in control fasted rats. First, the potentiating effect of exogenous α-MSH on anorexia in fasted, LPS-treated rats was exhibited in Fig. 7. Neither intracerebroventricular dose of α-MSH affected Tb or locomotor activity significantly in these rats (data not shown).

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Fig. 6. Effect of intracerebroventricular injection of SHU-9119 (200 ng) on locomotor activity in fasted rats treated intraperitoneally with LPS (100 µg/kg) or saline (same experiment as shown in Fig. 5). A: time course of locomotor activity over 24 h after LPS administration in presence and absence of intracerebroventricular SHU-9119. Activity is displayed as counts/30-min interval. Error bars were omitted for clarity. Horizontal black bar indicates dark period. B: mean hourly locomotor activity for the indicated intervals after intraperitoneal injection. Statistical significance of between-group comparisons computed and indicated as in Fig. 3. **P < 0.01.

Fig. 7. Effect of intracerebroventricular injection of α-MSH (30 and 300 ng) after 18-h fast on cumulative food intake in normal rats. α-MSH was injected 30 min after intraperitoneal saline. Numbers of animals in respective groups are Sal/Sal (n = 6); Sal/MSH (300 ng, n = 7); Sal/MSH (30 ng, n = 6). Symbols immediately above bars indicate significant difference by comparison with Sal/Sal control group (1-way ANOVA followed by Scheffe’s test). *P < 0.05.
more rapidly and at a lower dose than α-MSH-induced inhibition of food intake in the control fasted rats (0- to 2- vs. 0- to 4-h interval; 30 ng vs. 300 ng, respectively) (Figs. 1 and 7). Second, the dose of SHU-9119 used in this study reversed the LPS-induced suppression of food intake in fasted rats during the 0- to 24-h post-LPS interval, but had no effect by itself in similarly fasted control rats. These differences between LPS-treated and untreated rats are indicative of increased responsiveness to the anorectic action of α-MSH and an apparent enhancement of the anorectic role of endogenous melanocortins during the LPS-induced inflammatory state. Similarly, the suppressive effects of α-MSH on T₃ and locomotion also appeared to be state dependent, because they were not observed in control fasted rats. The mechanisms involved in these state-dependent changes in α-MSH responsiveness are unknown, but the phenomenon of LPS-induced responsiveness to the T₃-lowering action of α-MSH is highly consistent with previous results (2, 11, 12).

The factors involved in mediating LPS-induced anorexia are poorly understood. Although LPS-induced cytokines, including TNF-α, IL-1β, and IL-6, are known to induce anorexia (4, 22, 26, 30), none of these cytokines has been proven to be essential for LPS-induced anorexia. For instance, anorexic responses to LPS persist in IL-1β-deficient, IL-6-deficient, and TNF-α double receptor-knockout mice (7, 8, 18). Other studies suggested a role of leptin in mediating LPS-induced anorexia. Leptin is a cytokine produced by white adipocytes that is thought to participate in the normal feeding- and fasting-induced regulation of appetite and energy disposition. Fasting suppresses leptin secretion, whereas treatment of fasted rodents with LPS or proinflammatory cytokines increased leptin gene expression and plasma leptin levels (9, 26). However, as was found in the case of proinflammatory cytokines, leptin signaling is not an absolute requirement for LPS-induced anorexia, because leptin-deficient ob/ob mice and leptin receptor-deficient db/db mice do exhibit LPS-induced anorexia, although the db/db mice exhibit partial resistance to the effect (5). Available evidence thus suggests that multiple cytokines are probably involved in mediating LPS-induced anorexia, and the long-term absence of a given cytokine or cytokine receptor can elicit effective compensatory responses that preserve the illness-associated anorexic response.

The roles of endogenous melanocortins in modulating LPS-induced febrile and anorexic responses appear to be temporally distinguishable. Intracerebroventricular SHU-9119 treatment reversed the LPS-induced anorexia that occurred during the full 24-h post-LPS period, but it had no apparent effect on LPS-induced anorexia during the first several hours after LPS. In contrast, this treatment exacerbated LPS-induced fever during the first several hours post-LPS (Fig. 5), and in our previous study the same treatment produced a blockade of the anti-pyretic effect of exogenous intracerebroventricular α-MSH that was virtually immediate (11). Therefore, endogenous melanocortins appear to be involved in mediating the later phase of LPS-induced anorexia, but not the earlier phase of anorexia occurring during the first few hours after LPS treatment. In this connection, intracerebroventricular treatment with SHU-9119 blocked leptin-induced anorexia in rats during the first 4 h after leptin administration (27, 28), implicating a role of central melanocortin receptors in mediating the acute anorexic effects of leptin. Leptin secretion gradually increases after cytokine administration in fasted mice, peaking at 7 and 10 h, respectively, after TNF-α and IL-1 injection (26). Therefore, one potential sequence of events that theoretically could account for the contribution of endogenous melanocortins to the later phase of LPS-induced anorexia is the following: LPS-induced release of proinflammatory cytokines, which then stimulate release of leptin (9, 26), which may then activate proopiomelanocortin neurons to release central melanocortins that suppress feeding by acting via the MC4-R and/or MC3-R (27, 28). Further studies would be needed to test this hypothesis.

The effects of melanocortins on LPS-induced suppression of feeding behavior have not previously been reported. However, in one relevant study, it was reported that the anorexia resulting from central injection of IL-1β in rats was inhibited by intracerebroventricular administration of α-MSH (35). The present results do not necessarily conflict with those findings, because the mechanisms of LPS-induced and IL-1β-induced anorexia are clearly distinct, as indicated by several lines of evidence from previous studies. First, IL-1 appeared not to be involved in LPS-induced anorexia, because intracerebroventricular injection of IL-1 receptor antagonist failed to inhibit LPS-induced anorexia, whereas it did prevent the anorexia induced by intracerebroventricular or intraperitoneal IL-1β (14). Second, IL-1β-deficient mice exhibited LPS-induced anorexia (16). Third, the anorexic effects of IL-1β and LPS are qualitatively different, because the anorexic effect of LPS was attributable to reduction of meal frequency, whereas the anorexic response to IL-1β resulted primarily from reduced meal size (17). Therefore, the differential effects of intracerebroventricular α-MSH on the anorexic states induced by intraperitoneal LPS (present study) and intracerebroventricular IL-1 (35) are not surprising.

Another question addressed by the present study is whether LPS-induced anorexia is dependent on the febrile state. Because intracerebroventricular α-MSH potentiated LPS-induced anorexia while simultaneously suppressing fever, the results indicate that LPS-induced anorexia is not secondary to the LPS-induced fever. These results are thus consistent with those in the earlier study of McCarthy et al. (20), which showed that LPS-induced anorexia persisted in rats despite suppression of the accompanying fever by salicylate.

The present studies also revealed that intracerebroventricular α-MSH potentiates the hypoactivity resulting from LPS treatment. Both of the tested intracerebroventricular doses of α-MSH suppressed locomotor activity in the fasted LPS-treated rats. This appeared
to be a behavioral action rather than a result of any impairment of motor system function per se, because the animals exhibited normal posture and no neurological signs of motor dysfunction or difficulty (e.g., tremor, rotation, freezing, etc.) and the effects were not observed in the absence of LPS treatment. To our knowledge, the effects of centrally administered melanocortins on general motor activity in LPS-treated animals have not previously been studied. Most previous studies of melanocortin effects on motor-related behaviors have concerned their stimulatory effects on grooming behavior, which are generally manifested within a higher dose range than that used in the present study (1, 3). In the present studies, no evidence of altered grooming behaviors, including face washing, scratching, paw and tail licking, or shakes, was noted, probably due to the low intracerebroventricular doses of α-MSH used.

The mechanisms involved in α-MSH-induced suppression of locomotor activity are unknown, but one factor that may have contributed to this effect is the observed reduction in feeding behavior by α-MSH. After the overnight fast, hunger was presumably the primary motivation for, and feeding-related movement a major source of, bodily movement during the light (normally inactive) phase in LPS-treated rats. Consistent with this possibility, the suppression of locomotion by α-MSH was first exhibited during the light phase (0–8 h after LPS), concomitant with its potentiation of LPS-induced anorexia, whereas LPS treatment alone did not significantly inhibit locomotion during this period. However, the α-MSH-induced hypoactivity cannot be wholly attributed to its suppression of feeding behavior, because intracerebroventricular SHU-9119 treatment reversed LPS-induced suppression of food intake without affecting LPS-induced suppression of locomotion. Moreover, the latter finding clearly establishes that the contribution of endogenous melanocortins to LPS-induced anorexia represents a behavioral influence rather than a result of any impairment of normal motor system functions.

The persistence of the suppressive effect of α-MSH on locomotion contrasted with that of its antipyretic effect. The higher α-MSH dose significantly reduced locomotion during the 21- to 24-h post-LPS period, whereas both the antipyretic effect of α-MSH and the suppressive effect of LPS alone on locomotion had subsided by that time. These findings further underscore the divergent effects of melanocortins on different aspects of the acute phase response.

The specific brain MCR subtype(s) involved in mediating the anorexic effects of melanocortins in LPS-treated rats cannot be determined from this study, but a potential role of the MC4-R and/or MC3-R is suggested by several lines of evidence. First, MC3-R and MC4-R are the predominant MCR mRNA subtypes for which mRNA transcripts are known to be expressed in rat brain. In contrast, mRNA encoding the other principal MCR subtype reportedly expressed in the rat brain, MC5-R, is of very low abundance, as it is not detectable by sensitive RNAse protection assay or in situ hybridization but only by the ultrasensitive polymerase chain reaction (32). Second, SHU-9119, which reversed LPS-induced anorexia after intracerebroventricular injection, is an antagonist having similar potencies on the rat MC3-R and rat MC4-R in vitro, but is a full agonist of the MC5-R subtype (10, 11). The effect of SHU-9119 on LPS-induced anorexia probably reflects MCR antagonism rather than agonism, because α-MSH, which is a nonselective MCR agonist, potentiated, rather than inhibited, LPS-induced suppression of feeding behavior. Third, a physiological role of MC4-R in mediating anorexic central actions of melanocortins in normal animals is strongly supported by studies involving antagonist and agonist administration (6, 28), genetic ablation of MC4-R (13), and overexpression of the native MC4-R and MC3-R antagonist proteins agouti and agouti-related peptide (21, 36).

In summary, the present results demonstrate that melanocortins modulate different aspects of the acute phase response in a highly selective and qualitatively different manner. Centrally administered α-MSH exacerbates LPS-induced anorexia and hypothermia, and endogenous melanocortins appear to contribute to LPS-induced anorexia, despite their ameliorating influence on LPS-induced fever. α-MSH and MCR antagonist treatments were ineffective in the absence of LPS treatment, suggesting that responsiveness to their effects is cytokine dependent. These findings indicate that the influence of centrally acting melanocortins on the coordinated host response to inflammation and infection extends to behavioral and metabolic activities involved in the regulation of energy balance.

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