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Glycyl-L-Glutamine Antagonizes α-MSH-Elicited Thermogenesis

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RESCH, G. E. AND W. R. MILLINGTON. *Glycyl-L-glutamine antagonizes α-MSH-elicited thermogenesis.* PEPTIDES **14**(5) 971–975, 1993.—The objective of this study was to determine whether glycyl-L-glutamine [β-endorphin(30–31)] modulates the thermoregulatory actions of α-MSH. Microinjection of α-MSH (0.06 nmol) into PGE_2-responsive thermogenic sites in the medial preoptic area of rats generated a hyperthermic response, inducing a 0.85 ± 0.19°C rise in colonic temperature (T_c) within 45 min. Coadministration of glycyl-L-glutamine (3.0 nmol) completely blocked the response, maintaining T_c at baseline levels. This was not attributable to glycyl-L-glutamine hydrolysis because coadministration of glycine and glutamine had no effect on α-MSH-induced thermogenesis. Glycyl-L-glutamine, injected alone, was similarly without effect. These data indicate that glycyl-L-glutamine inhibits α-MSH-induced thermogenesis but is devoid of thermoregulatory activity itself.

α-MSH Glycyl-L-glutamine β-Endorphin Dipeptide Proopiomelanocortin Preoptic area Thermoregulation

α-MELANOCYTE-STIMULATING hormone (α-MSH) is thought to play an important role in the homeostatic regulation of body temperature. Previous studies have shown that, in the rat, α-MSH generates hyperthermia when injected directly into the preoptic area and adjacent sites in the anterior hypothalamus (POA/AH) (27,29), a prominent thermoregulatory region. Dispersed throughout the POA/AH are neurons that respond to changes in ambient temperature, transynaptically generating compensatory autonomic and behavioral responses that maintain body temperature within normal limits (4,28). Thermogenic sites in the rat POA/AH, identified according to their responsiveness to prostaglandin E_2 (PGE_2) injection, are highly sensitive to α-MSH, and doses as low as 1 pmol induce a significant rise in colonic temperature (T_c) (29). Injection of α-MSH into PGE_2-responsive POA/AH sites in rats placed in a cold environment also facilitates behavioral performance in a cued discrimination task reinforced by a thermal reward, suggesting that α-MSH activates integrative autonomic and behavioral thermoregulatory mechanisms (29).

In contrast, α-MSH lowers body temperature in rabbits when injected either intraventricularly (ICV) (15,18) or directly into the POA/AH (10). α-Melanocyte-stimulating hormone also acts as a highly potent antipyretic agent in rabbits, effectively reducing fever produced by endotoxin, cytokines, and other pyrogenic agents at doses considerably lower than required to elicit hypothermia when given alone (12,16,18,23). It inhibits fever induction in rats (6,35), as well, although its antipyretic effect in rats has not been as extensively investigated. As a result, comparably less is known about the thermoregulatory effects of α-MSH in rats, the species in which most research on α-MSH and related peptides has been conducted.

The POA/AH contains relatively high levels of endogenous α-MSH and is densely innervated by neurons in the medial basal hypothalamus that synthesize proopiomelanocortin (POMC), the precursor to α-MSH as well as β-endorphin and related neuropeptides (24). The thermoregulatory actions of POMC-derived peptides other than α-MSH have been little studied, however. β-Endorphin(1–31) generates hyperthermia when injected into the POA/AH, albeit at higher doses than α-MSH (20,34). But like POMC, β-endorphin(1–31) also serves as a precursor to other structurally related peptides. β-Endorphin(1–31) can undergo both *C*-terminal proteolysis and *N*-terminal acetylation posttranslationally, generating β-endorphin(1–27), β-endorphin(1–26), and the *N*-acetylated derivatives of all three peptides (36). β-Endorphin(1–31) is the predominant form synthesized in the POA/AH and hypothalamus, although substantial amounts of β-endorphin(1–27) and β-endorphin(1–26) are also present, together comprising approximately 40% of total β-endorphin immunoreactivity; *N*-acetylated β-endorphin derivatives are relatively minor end products of hypothalamic β-endorphin processing, however (3,9,22,36).

The endoproteolytic conversion of β-endorphin(1–31) to β-endorphin(1–27) also generates a dipeptide, glycyl-L-glutamine [β-endorphin(30–31)] (25). Glycyl-L-glutamine has been isolated from brain and the pituitary gland where, as one might predict, it is present in amounts corresponding to the aggregate concen-

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tration of β-endorphin(1–27) and β-endorphin(1–26) (25). Unlike other POMC-derived peptides, however, the physiological actions of glycyl-L-glutamine have not been extensively investigated, and its role in thermoregulation is entirely unknown.

Nevertheless, previous studies have demonstrated that glycyl-L-glutamine is a biologically active peptide. Parish et al. reported, for example, that glycyl-L-glutamine reduces the firing frequencies of brain stem neurons when applied iontophoretically (25), and additional investigations have shown that glycyl-L-glutamine produces neurochemical, immunological, and trophic effects in both brain and peripheral tissues (1,13,17,19,21). In several of these reports, the response produced by glycyl-L-glutamine either opposed or directly modulated that of other coreleased POMC peptides. Hirsch and O'Donohue found, for example, that glycyl-L-glutamine inhibits the characteristic behavioral effects of central α-MSH administration, grooming and the stretching and yawning syndrome, without inducing any behavioral response when injected alone (14). In light of these findings, we evaluated whether glycyl-L-glutamine also modulates the hyperthermic response produced by α-MSH injection into the medial preoptic area (mPOA). We found that indeed it does; glycyl-L-glutamine completely abolished α-MSH-induced thermogenesis when the two peptides were coadministered into previously identified PGE_2-responsive thermogenic sites in the mPOA, but exhibited no independent thermoregulatory activity when injected alone.

METHOD

Male Sprague–Dawley rats (200–250 g; Sasco, Inc., Omaha, NE) were housed under a 12:12-h light:dark cycle with free access to food and water. Each animal was anesthetized with ketamine (90 mg/kg) and acepromazine maleate (10 mg/kg), and a 24-ga guide cannula was stereotaxically implanted in the mPOA with the tip positioned 0.5 mm lateral to the midsuture line at bregma and 7 mm below the skull surface (26), as described previously (28,29). The PGE_2-responsive thermogenic sites were identified by injecting PGE_2 (3 nmol/1 μl; Sigma Chemical Co., St. Louis, MO) through a 29-ga injection cannula lowered through the guide cannula in 0.2 mm step-wise increments until a ≥ 0.5°C increase in T_c was detected. The PGE_2-sensitive injection sites

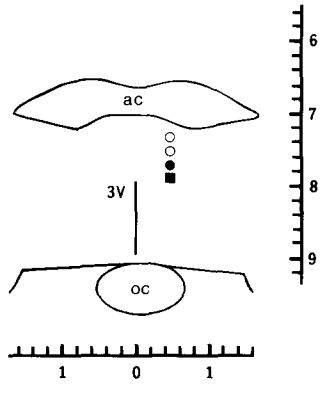

FIG. 1. Localization of sites in the mPOA differentially responsive to PGE_2- and α-MSH-elicited thermogenesis. The illustration shows a representative experiment in which four injections were placed at 0.2 mm intervals in a dorsoventral track 0.5 mm lateral to the midline. These sites generated either no response to PGE_2 (3 nmol) injection (open circles); a ≥ 0.5°C increase in T_c following PGE_2, but no response to α-MSH (0.06 nmol) injection (filled circle); or a ≥ 0.5°C T_c increase following PGE_2 and α-MSH, injected separately (filled square). AC, anterior commissure; 3V, third ventricle; CO, optic chiasm.

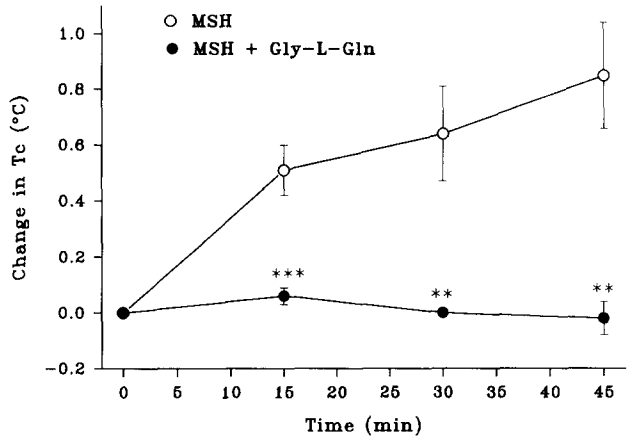

FIG. 2. Glycyl-L-glutamine antagonizes the hyperthermic response to mPOA α-MSH injection. α-MSH (0.06 nmol) was injected either alone (open circles) or together with glycyl-L-glutamine (3 nmol; filled circles) into previously identified PGE_2-sensitive thermogenic sites in the mPOA and T_c was measured at 15-min intervals thereafter. Data are presented as mean ± SEM; $n = 6$ animals in each group. $^{**}p < 0.01$ and $^{***}p < 0.001$ differs from α-MSH treatment alone at the same time interval.

were then screened for a similar response to α-MSH; stereotaxic coordinates for sites responsive to both PGE_2 and α-MSH were used in subsequent experiments. As shown in Fig. 1, only a subset of PGE_2-sensitive sites generated a hyperthermic response to subsequent α-MSH injection. Histological examination following Evans blue dye injection revealed that injection sites responsive to both PGE_2 and α-MSH were most often localized in the dorsomedial mPOA but were also found more ventrally, although at a lower frequency (unpublished data).

α-Melanocyte-stimulating hormone (0.06 nmol; Peninsula Laboratories, Belmont, CA), glycyl-L-glutamine (3.0 nmol; Bachem California, Torrance, CA), or glycine plus glutamine (3.0 nmol each amino acid; Sigma Chemical Co.) were dissolved in 1 μl sterile, nonpyrogenic 0.85% NaCl and injected into the mPOA over a 30-s time interval. The experiments were conducted in awake, unrestrained animals previously conditioned to handling. Colonic temperature was recorded at 15-min intervals for 30 min before and 45 min after peptide administration using a thermistor probe attached to a telethermometer (Yellow Springs Instrument Co., Yellow Springs, OH). Statistical differences among treatment groups were analyzed by analysis of variance (ANOVA) followed by Duncan's multiple range test or Student's t-test.

RESULTS

Glycyl-L-glutamine inhibited the thermogenic effect of α-MSH when the two peptides were coinjected into previously identified PGE_2- and α-MSH-responsive thermoregulatory injection sites in the rat mPOA (Fig. 2). Consistent with previous dose–response studies (27,29), α-MSH (0.06 nmol) microinjection into the mPOA elicited a hyperthermic response, elevating T_c 0.85 ± 0.19°C (mean ± SEM; $n = 6$) within 45 min. Coinjection of glycyl-L-glutamine (3.0 nmol) completely abolished the response to α-MSH, maintaining T_c at baseline levels throughout the 45-min duration of the experiment. Glycyl-L-glutamine, injected alone, produced no significant change in T_c (Table 1). These data suggest that glycyl-L-glutamine inhibits α-MSH-induced thermogenesis but is devoid of thermoregulatory activity itself.

TABLE 1

GLYCYL-L-GLUTAMINE BLOCKS THE HYPERTHERMIC RESPONSE TO α-MSH BUT DOES NOT AFFECT COLONIC TEMPERATURE WHEN INJECTED ALONE

Treatment	Change in T_c (°C)
Saline (6)	+0.15 ± 0.06
Gly-L-Gln (4)	−0.10 ± 0.09
α-MSH (6)	+0.64 ± 0.17*
α-MSH + Gly-L-Gln (6)	0.00 ± 0.02
α-MSH + Gly + Gln (2)	+0.55 ± 0.05†

T_c was recorded 30 min after rats received either saline, glycyl-L-glutamine (3 nmol), α-MSH (0.06 nmol), or α-MSH combined with either glycyl-L-glutamine (Gly-L-Gln) or equimolar amounts of glycine (Gly) plus glutamine (Gln). The peptides or amino acids were injected in a volume of 1 μl into previously identified PGE_2- and α-MSH-sensitive thermogenic sites in the mPOA. (Values represent the mean ± SEM change in T_c.)

* Differs from saline $p < 0.01$.

† Differs from α-MSH + Gly-L-Gln $p < 0.05$.

The experimental design used in these experiments required α-MSH to be injected twice into the same mPOA site; an initial injection of α-MSH alone followed by a second injection containing α-MSH combined with glycyl-L-glutamine. This raises the possibility that the observed inhibitory response may have resulted from tolerance to repeated α-MSH administration, rather than from glycyl-L-glutamine. To test this, we repeated the initial experiment but this time omitted glycyl-L-glutamine, delivering two α-MSH (0.06 nmol) injections into the same mPOA sites 4 h apart. Serial α-MSH injections elicited comparable thermogenic responses; 15 min after the first and second α-MSH injections, T_c was elevated by 0.50 ± 0.10°C and 0.55 ± 0.15°C, respectively, and after 30 min, by 0.70 ± 0.30°C and 0.95 ± 0.45°C. Hence, the response to a second α-MSH injection was clearly not attenuated, compared to experimentally naive animals.

A second alternative explanation is the possibility that glycyl-L-glutamine's inhibitory activity is attributable to one of its constituent amino acids, glycine or glutamine, rather than the dipeptide itself. To test this, we coadministered equimolar amounts of glycine and glutamine (3 nmol) with α-MSH into PGE_2- and α-MSH-responsive mPOA injection sites. Amino acid injection produced no effect whatsoever on the response to α-MSH; α-MSH-induced hyperthermia followed the same time course and amplitude as observed following α-MSH alone (Table 1). Thus, glycyl-L-glutamine metabolism does not explain its inhibitory activity.

We next examined the duration of glycyl-L-glutamine's inhibitory activity by injecting α-MSH into the same mPOA site 3 h, 24 h, or 48 h following glycyl-L-glutamine administration. Unexpectedly, we found that the inhibitory effect of glycyl-L-glutamine was quite long in duration. The mPOA α-MSH injection 3 h following glycyl-L-glutamine failed to induce a significant rise in T_c (Table 2). The α-MSH-induced thermogenesis showed a tendency to recover after 24 h, due primarily to an enhanced response in a single animal, but only after 48 h was the characteristic hyperthermic response observed. Similarly, α-MSH did not alter T_c 3 h following combined α-MSH and glycyl-L-glutamine injection, although the response fully recovered 48 h thereafter (data not shown). These data indicate that glycyl-L-glutamine produces a long-lasting inhibition of α-MSH-elicited thermogenesis, although the mechanism responsible for the temporal delay in response recovery is not readily apparent.

DISCUSSION

α-Melanocyte-stimulating hormone induces a significant hyperthermic response when injected at doses of 1 pmol or more into thermogenic sites in the rat mPOA (27,29). Here we report that α-MSH-elicited thermogenesis is inhibited by coadministration of glycyl-L-glutamine, the C-terminal dipeptide of β-endorphin(1–31), which is cosynthesized with α-MSH in the hypothalamus and other brain regions (25). This finding was not attributable to the repeated administration of α-MSH, consistent with prior evidence that multiple ICV α-MSH injections do not induce tolerance to the peptide's antipyretic effects (7). Coadministration of glycine and glutamine was also ineffective, indicating that glycyl-L-glutamine's inhibitory activity did not result from metabolism to its constituent amino acids. Together, these findings support the conclusion that glycyl-L-glutamine specifically inhibits α-MSH-induced thermogenesis.

Prostaglandin E_2 is thought to be an essential mediator of pyrogen-induced fever as well as other thermogenic compensations to environmental and pathologic challenges (16,30). Prostaglandin E_2 may also be involved in the homeostatic regulation of normal body temperature based on electrophysiological data showing that a subset of POA/AH heat- and cold-sensitive neurons responds to PGE_2 application (5). Prostaglandin E_2-elicited hyperthermia is thus a useful criterion for identifying thermogenic injection sites in the POA/AH. The present finding that PGE_2-sensitive sites do not invariably respond to α-MSH suggests that these POA/AH subregions are not uniformly innervated by POMC neurons. These data extend prior evidence that PGE_2-sensitive sites respond differentially to acetylcholine and other neurotransmitters, and further substantiate the conclusion that PGE_2-responsive neurons are heterogeneous with respect to their synaptic innervation (28,31–33).

The thermoregulatory actions of α-MSH have recently been the focus of considerable interest based on evidence that the

TABLE 2

THE RECOVERY OF α-MSH-ELICITED THERMOGENESIS FOLLOWING GLYCYL-L-GLUTAMINE INJECTION

Treatment	Change in T_c (°C)
Gly-L-Gln	−0.10 ± 0.09
α-MSH 3 h	−0.02 ± 0.15
α-MSH 24 h	+0.15 ± 0.09
α-MSH 48 h	+1.20 ± 0.28*

Glycyl-L-glutamine (Gly-L-Gln; 3.0 nmol) was injected into PGE_2-sensitive mPOA thermogenic sites of four animals, and 3 h, 24 h, and 48 h thereafter, α-MSH (0.06 nmol) was injected according to the same stereotaxic coordinates. T_c was recorded 30 min after peptide administration. (Data are presented as mean ± SEM change in T_c.)

* Differs from glycyl-L-glutamine treatment: $p < 0.01$.

peptide produces antipyresis in rabbits (12,16,18). α-Melanocyte-stimulating hormone effectively reduces fever induced in rabbits by a variety of agents, including endotoxin, interleukin-1 (IL-1), IL-6, and tumor necrosis factor, when administered either ICV or intravenously at doses that are inactive when given alone; indeed, α-MSH is reported to be 25,000 times more potent than acetaminophen when centrally injected (23). These intriguing findings raise the possibility that α-MSH generates its antipyretic effects by acting upon thermoregulatory neurons within the POA/AH. Feng et al. tested this hypothesis but found that α-MSH is relatively ineffective at reducing fever when injected directly into the rabbit POA/AH; the minimally effective POA/AH dose was substantially higher than the requisite ICV antipyretic dose (10). Quite low α-MSH doses effectively antagonize fever in rabbits when injected into the septal area, however, suggesting that the septum, rather than the POA/AH, may be its site of antipyretic action (11). Evidence that fever enhances septal α-MSH release further supports this conclusion (2). Whether a comparable site specificity occurs in rats remains to be determined. α-Melanocyte-stimulating hormone reportedly reduces fever in rats (6,35), although the specific brain region that mediates its antipyretic action has not been investigated (6,35).

Glycyl-L-glutamine is synthesized when β-endorphin(1–31) undergoes posttranslational endoproteolytic conversion to β-endorphin(1–27). A detailed analysis of glycyl-L-glutamine's distribution in brain has not been reported, although relative amounts of the dipeptide can be inferred from regional analysis of β-endorphin(1–27) and β-endorphin(1–26) concentrations (25). In the hypothalamus (9,22,36) and POA/AH (3), these *C*-terminally shortened β-endorphin peptides constitute approximately 40% of total β-endorphin immunoreactivity, suggesting that glycyl-L-glutamine is also produced in substantial amounts. Glycyl-L-glutamine appears to be a more abundant product of β-endorphin(1–31) processing in the intermediate pituitary lobe (36) and certain brain regions (8,36), however, where β-endorphin(1–31) is more extensively processed. But despite its apparent quantitative importance, relatively little is known about glycyl-L-glutamine's physiological role in brain.

Behavioral and physiological studies support the concept that glycyl-L-glutamine is a biologically active peptide that acts as both a neuromodulator in brain and a circulating hormone in the periphery. Behavioral studies have shown that glycyl-L-glutamine inhibits the grooming and stretching and yawning syndromes induced by α-MSH without generating any response when administered alone (14). Glycyl-L-glutamine also inhibits β-endorphin(1–31)-induced grooming, but not catatonia, implying that the dipeptide does not act simply as an α-MSH receptor antagonist (14). Together with the present data, these results suggest that glycyl-L-glutamine modulates the effects of other coreleased POMC-derived peptides but exhibits no independent activity when given alone.

Other investigations have disclosed exceptions to this generalization, however, showing that glycyl-L-glutamine can also act independently, producing a variety of central and peripheral actions. Electrophysiologic studies revealed, for example, that glycyl-L-glutamine inhibits the firing frequencies of brain stem neurons when applied iontophoretically; this inhibitory activity was not mediated by glycine or mu opioid receptors because pretreatment with either strychnine or naloxone failed to block the response (25). Glycyl-L-glutamine produces effects in peripheral tissues, as well, potentiating mitogen-induced lymphocyte proliferation (21) and modulating the expression of acetylcholinesterase molecular forms in superior cervical ganglia (17), cultured skeletal muscle cells (19), and cardiac myocytes (1). Hence, the present finding that glycyl-L-glutamine inhibits α-MSH-elicited thermogenesis is consistent with accumulating evidence that glycyl-L-glutamine produces both independent and modulatory actions in brain and peripheral tissues.

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