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Monosodium Glutamate Does Not Alter ACTH- or Apomorphine-Induced Penile Erection and Yawning

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ARGIOLAS, A , M. R MELIS, W FRATTA, A MAURI AND G L GESSA *Monosodium glutamate does not alter ACTH- or apomorphine-induced penile erection and yawning* PHARMACOL BIOCHEM BEHAV 26(3)503–507, 1987 —The effect of the intracerebroventricular (ICV) injection of ACTH 1–24 (1, 5 and 10 μg) or the subcutaneous administration of apomorphine (20 and 80 μg/kg SC) on spontaneous penile erection and yawning was studied in rats treated with monosodium glutamate (MSG), a treatment that depletes hypothalamic ACTH, α-MSH and endorphin-like peptides. Neonatal MSG treatment failed to antagonize either apomorphine- or ACTH-induced yawning in male and female rats, or to alter the number of penile erection episodes induced by the two substances in male rats In contrast, hypophysectomy, that does not alter the concentration of hypothalamic ACTH and α-MSH, caused a marked prevention of apomorphine- and ACTH-induced responses, in agreement with previous studies The results suggest that the integrity of opiomelanotropinergic neurons in the hypothalamus is not necessary for the induction of yawning and penile erection by ACTH-derived peptides, and that apomorphine and other dopamine agonists apparently do not induce penile erection and yawning by releasing an ACTH-derived peptide in brain

Apomorphine ACTH Monosodium glutamate Hypophysectomy Penile erection Yawning

THE intracerebroventricular (ICV) injection of adrenocorticotropin (ACTH), α-melanocyte stimulating hormone (α-MSH) and derived peptides, induces excessive grooming, yawning, stretching and penile erection in rats. While grooming occurs already at doses of 0.1 nmol of ACTH or α-MSH, doses higher than 1–2 nmol are needed for inducing the latter effects (for a review see [4] and [12]). While the importance of penile erection in reproduction does not need to be further stressed, the other behaviours are important as indicators of arousal In particular, grooming is believed to have a deactivating role in restoring behavioural homeostasis [13], while yawning and stretching are believed to have the role of increasing attention when sleep is pressing in front of a danger or social circumstances (for a review on the physiological significance of yawning and stretching see [4]). The above behavioural responses are thought to be mediated by a direct action of ACTH-MSH peptides in the hypothalamus, since this brain area has been found the most sensitive for the induction of the above effects by ACTH 1–24 [4]. Accordingly, recent studies have demonstrated the existence of neurons in the central nervous system containing pro-opiomelanocortin, the 31 kD protein precursor of ACTH, α-MSH and β-endorphin These neurons originate in the arcuate nucleus of the hypothalamus and send their projections to this and other brain regions (for a review see [17])

Yawning and penile erection can be induced in rats also by the systemic adminstration of low doses of dopamine (DA) agonists other than by ACTH-MSH peptides. It has been suggested that DA agonists may induce such responses by releasing an ACTH-derived peptide from the pituitary gland [20]. Recently, it has been discovered that the neonatal administration of monosodium glutamate (MSG) induces the almost complete depletion of ACTH, α-MSH and β-endorphin in the rat hypothalamus [9,15], providing a useful model to study the function of these peptides in brain. It has been also shown that hypophysectomy, that eliminates circulating ACTH, α-MSH and β-endorphin without altering their concentration in the hypothalamus [2,14], reduces penile erection and yawning induced not only by apomorphine [20], but also by ACTH 1–24 [22]. Two main conclusions derive from the above findings (1) an intact pituitary function is needed for the expression of the above responses of both ACTH and apomorphine, and (2) apomorphine apparently does not induce penile erection and yawning by releasing an ACTH-derived peptide from the pituitary gland. However, the possibility remains that apomorphine induces yawning and penile erection by releasing an ACTH-derived peptide from central opiomelanotropinergic neurons. In an attempt to clarify the role of hypothalamic ACTH-MSH peptides in the expression of penile erection and yawning, we have studied the effect of ACTH 1–24 and apomorphine on the above responses in neonatally MSG-treated rats.

METHOD

Intact male and female rats, and male sham-hypophysectomized and hypophysectomized rats (Sprague Dawley) were purchased from Charles River (Como, Italy). Animals were caged in groups of 4–6 with water and standard laboratory food ad lib, on a 12 hr-light-dark cycle (lights on at

07:00). For MSG treatment, 3 groups of 40 newborn Sprague Dawley rats received either no treatment, or a subcutaneous injection of 4 g/kg of monosodium-L-glutamate (Sigma) in aqueous 40% solution, or 10% sodium chloride (isoosmotic control) in the 1st, 3rd, 5th, 7th and 9th day of life The pups were left with their mother for 1 month and finally housed in groups of 4–6, males and females in separate cages. At approximately 4 months of age, the animals were stereotaxically (David Kopf Instruments, USA) implanted with a stainless-steel chronic guide cannula (22 gauge) aimed at one lateral ventricle under chloral hydrate anaesthesia, 5 days before the experiments (coordinates 1 mm anterior to bregma, 1 5 mm lateral to midline, 2 mm ventral to dura) [18] A similar guide cannula was implanted in 4 month old rats, sham-hypophysectomized and hypophysectomized 1 month before the experiments. Ten μl of saline with or without ACTH 1–24 (Peninsula Lab , San Carlos, CA) was injected into a lateral ventricle (ICV) by means of an internal cannula (28 gauge) connected by a polyethylene tubing to a 10 μl Hamilton syringe driven by a micrometric screw Each experimental group received saline alone, or with 1 or 5 or 10 μg of ACTH 1–24 ICV with a 2 day period between successive injections For apomorphine treatment, apomorphine-HCl (Sigma) was dissolved in saline containing 0 1% ascorbic acid and injected subcutaneously (SC) in a volume of 200 μl on the back of the neck Each experimental group received saline or 20 or 80 μg/kg SC of apomorphine with a 60 min period between successive injections. After ICV or SC injections, rats were placed individually into Plexiglas cages (30×30×30 cm) and observed continuously for 1 or 2 hr, as indicates in the legend of the tables, during which penile erection and yawning episodes were scored by an observer informed of the experimental groups that were treated, but not of the treatments that were performed, in order to eliminate subjective evaluations. Statistical analysis of the data was performed by Student's t-test when experimental and a control group were compared. Group means were analyzed by analysis of the variance followed by Duncan's multiple range test. Rats were weighed and killed by decapitation 2 weeks after the experiments. Brains were rapidly removed, the hypothalami and pituitary glands were dissected, weighed and immediately homogenized in 1 N HCl containing 5% formic acid (V/V), 1% trifluoroacetic acid (V/V) and 1% sodium chloride (W/V) After a preliminary purification on a Sep pak C18 cartridge (Waters Associates), ACTH and α-MSH were measured by radioimmunoassay as previously described [2,11]

TABLE 1

BODY AND PITUITARY WEIGHT OF NORMAL, MSG-TREATED AND HYPOPHYSECTOMIZED RATS

Treatment	Sex	N	Body Weight (g)	Pituitary Weight (mg)
None	M	10	350 ± 15	10 8 ± 0 5
None	F	10	260 ± 14	10 5 ± 0 3
Neonatal Saline	M	8	345 ± 16	10 6 ± 0 4
Neonatal MSG	M	8	235 ± 22*	6 8 ± 0 6*
Neonatal Saline	F	8	255 ± 15	10 3 ± 0 4
Neonatal MSG	F	7	190 ± 15*	7 0 ± 0 5*
Sham Hypophysectomy	M	6	315 ± 20	10 6 ± 0 8
Hypophysectomy	M	10	212 ± 10*	—

Each value is the mean ± S E M

*$p<0$ 001 with respect to control (no treatment) and to neonatal saline (Student's t-test or Duncan's multiple range test)

RESULTS

Table 1 shows the body weight of control, MSG-treated, sham-hypophysectomized and hypophysectomized rats The weight of the pituitary glands also is included A decrease of 30% and 25% in the body weight of male and female MSG-treated rats, respectively, was found A 30% decrease was also found in the weight of pituitary glands Hypophysectomy produced the expected blockade of growth, as indicated by the marked difference (~40%) in the body weight of sham-hypophysectomized and hypophysectomized rats

Neonatal MSG treatment caused the almost complete disappearance of ACTH and α-MSH immunoreactivity in the rat hypothalamus (90% decrease), in agreement with

TABLE 2

HYPOTHALAMIC AND PITUITARY ACTH AND α-MSH CONTENT IN NORMAL, MSG-TREATED AND HYPOPHYSECTOMIZED RATS

			Hypothalamus		Pituitary	
Treatment	Sex	N	ACTH ng/mg prot	MSH ng/mg prot	ACTH ng/mg prot	MSH ng/mg prot
None	M	10	0 89 ± 0 10	4 19 ± 0 5	45 0 ± 1 0	380 ± 20
None	F	10	0 91 ± 0 08	4 05 ± 0 3	42 5 ± 1 6	396 ± 15
Neonatal Saline	M	8	0 90 ± 0 09	4 08 ± 0 2	44 3 ± 2 0	396 ± 16
Neonatal MSG	M	8	0 15 ± 0 09*	0 50 ± 0 1*	47 2 ± 3 0	385 ± 17
Neonatal Saline	F	8	0 91 ± 0 08	4 12 ± 0 2	48 1 ± 2 0	390 ± 21
Neonatal MSG	F	7	0 16 ± 0 08*	0 60 ± 0 1*	45 7 ± 1 8	380 ± 15
Sham Hypophysectomy	M	6	0 85 ± 0 10	4 00 ± 0 2	40 9 ± 3 0	368 ± 34
Hypophysectomy	M	10	0 75 ± 0 10	3 89 ± 0 2	—	—

Hypophysectomy was performed one month before the experiments ACTH and α-MSH were measured by radioimmunoassay as previously described [2,11]

Each value is the mean ± S E M *$p<0$ 001 (Duncan's multiple range test)

TABLE 3

INDUCTION OF YAWNING BY ACTH 1-24 IN NORMAL, MSG-TREATED AND HYPOPHYSECTOMIZED RATS

			μg ICV ACTH 1-24			
			0	1	5	10
Treatment	Sex	N	No Yawns/Rat			
None	M	10	2 0 ± 0 1	3.0 ± 0 3	9 0 ± 1 6*	18 2 ± 2 0*
None	F	10	1 8 ± 0 2	2 5 ± 0 5	10.5 ± 1 8*	17 2 ± 3 0*
Neonatal Saline	M	8	3 0 ± 0 3	3 0 ± 0 6	10 6 ± 1 0*	21 0 ± 4.0*
Neonatal MSG	M	8	2 0 ± 0 2	3 1 ± 0 6	11.0 ± 2 0*	20 1 ± 4.0*
Neonatal Saline	F	8	1 9 ± 0 5	3 0 ± 0 8	10 0 ± 1 6*	18.5 ± 2.5*
Neonatal MSG	F	7	2 8 ± 0 4	1 9 ± 0 5	9 2 ± 1.2*	19.3 ± 1.8*
Sham Hypophysectomy	M	6	2 5 ± 0 5	2.6 ± 1 0	11.0 ± 2 0*	18.5 ± 4.0*
Hypophysectomy‡	M	10	1 0 ± 0 5	2 0 ± 1 0	3 2 ± 1 0†	6 5 ± 0 6*†

Experimental groups received each ICV dose of ACTH 1–24 in increasing order, with a 2 day period between successive injections After treatment, rats were placed individually into Plexiglas cages and observed for 2 hr during which yawning episodes were counted Yawning was usually coordinated with stretching Each value is the mean ± S E M of the yawns per rat scored during the observation period *$p<0$ 001 with respect to controls (ACTH 1–24=0) (Student's t-test or Duncan's multiple range test). †$p<0$ 001 with respect to the corresponding sham-hypophysectomized group (Duncan's multiple range test) ‡=only 3 out of 10 rats showed yawning

TABLE 4

INDUCTION OF PENILE ERECTION BY ACTH 1-24 IN NORMAL, MSG-TREATED AND HYPOPHYSECTOMIZED RATS

		μg ICV ACTH 1-24			
		0	1	5	10
Treatment	N	No Penile Erections/Rat			
None	10	0 5 ± 0 1	1 0 ± 0 4	2 0 ± 0 3*	3 4 ± 0 6*
Neonatal Saline	8	0 3 ± 0 1	0 5 ± 0 1	2 4 ± 0 5*	3.8 ± 0 4*
Neonatal MSG	8	0 6 ± 0 2	0 9 ± 0 2	2.2 ± 0.3*	3 0 ± 0 3*
Sham Hypophysectomy	6	0 4 ± 0 2	0 5 ± 0 3	2 0 ± 0 4*	3 8 ± 0 5*
Hypophysectomy‡	10	0 3 ± 0 1	0 8 ± 0 2	0 9 ± 0 2†	1 0 ± 0 3†

Experimental groups received each ICV dose of ACTH in increasing order, with a 2 day period between successive injections After treatment, rats were placed individually into Plexiglas cages and observed for 2 hr during which penile erection episodes were counted (see the Method section for details) Each value is the mean ± S E.M of the episodes scored during the observation period *$p<0$ 001 with respect to controls (ACTH=0) (Student's t-test or Duncan's multiple range test) †$p<0$ 001 with respect to the corresponding sham-hypophysectomized group (Duncan's multiple range test) ‡=only 3 out of 10 rats showed penile erection

previous studies [9,15]. In contrast, pituitary ACTH and α-MSH referred to the protein content were found to be unmodified. Unlike MSG treatment, hypophysectomy failed to alter significantly hypothalamic ACTH and α-MSH, as previously reported [2,14] (Table 2).

As shown in Table 3, the ICV injection of 5 or 10 μg, but not of 1 μg of ACTH 1–24, induced yawning in control, neonatally saline- and MSG-treated rats. The intensity of the behaviour was similar in all groups of either sexes. In addition to yawning, usually coordinated with stretching, almost 100% of male rats also showed repeated episodes of penile erection (Table 4) The symptomatology began 25–30 min after treatment and lasted 2–3 hr. Penile erections and yawning episodes usually occurred separately. Each penile erection lasted 0.5–2 min and was associated with genital grooming. Yawning episodes lasted 1–2 seconds. In contrast, hypophysectomy reduced ACTH-induced yawning and penile erection (Tables 3 and 4) in agreement with previous studies [22].

Like ACTH 1–24, apomorphine (20 and 80 μg/kg SC) induced a similar number of yawning and penile erection episodes in control, neonatally saline- and MSG-treated male rats. The symptomatology induced by apomorphine was similar to that induced by ACTH 1–24, except that it started 5–10

TABLE 5

INDUCTION OF PENILE ERECTION AND YAWNING BY APOMORPHINE IN NORMAL, MSG-TREATED AND HYPOPHYSECTOMIZED MALE RATS

		μg/kg SC of Apomorphine					
		0	20	80	0	20	80
Treatment	N	No Penile Erections/Rat			No Yawns/Rat		
None	10	0 3 ± 0 2	1 8 ± 0 3*	3 8 ± 0 5*	3 0 ± 0 5	8 7 ± 1 0*	18 0 ± 0 9*
Neonatal Saline	10	0 2 ± 0 2	2 0 ± 0 5*	3 7 ± 0 3*	2 0 ± 0 6	8 0 ± 0 6*	17 4 ± 1 0*
Neonatal MSG	8	0 4 ± 0 3	2 2 ± 0 7*	3 6 ± 0 6*	1 9 ± 0 4	7 5 ± 0 8*	15 8 ± 0 6*
Sham-Hypophysectomy	6	0 5 ± 0 3	2 5 ± 0 8*	4 0 ± 0 8*	2 1 ± 0 8	9 0 ± 1 2*	16 8 ± 1 0*
Hypophysectomy	10	0 4 ± 0 2	1 0 ± 0 2†	1 4 ± 0 3*†	1 3 ± 0 6	4 0 ± 0 5*†	6 5 ± 1 4*†

Experimental groups received each dose of apomorphine SC in increasing order, with a 1 hr period between successive injections After treatment, rats were placed individually into Plexiglas cages and observed for 60 min during which penile erection and yawning episodes were counted Each value is the mean ± S E M of the number of penile erections and yawns per rat scored during the observation period *$p<0$ 001 with respect to controls (apomorphine=0), †$p<0$ 001 with respect to the corresponding sham-hypophysectomized group (Duncan's multiple range test)

min after treatment and lasted for 40–50 min and yawning was usually not coordinated with stretching In contrast, a marked decrease in the number of penile erection and yawning episodes induced by apomorphine was observed in hypophysectomized rats (Table 5), in agreement with previous studies [20]

DISCUSSION

The present results show that the depletion of hypothalamic ACTH and α-MSH by neonatal MSG treatment does not modify yawning and penile erection induced by ICV ACTH 1–24 or by low doses of systemic apomorphine. The reduced growth of MSG-treated rats, that is secondary to the destruction of hypothalamic growth hormone releasing hormone [5], seems not to be important for the expression of ACTH- and apomorphine-induced responses In contrast, penile erection and yawning induced either by ACTH 1–24 or by apomorphine, were prevented by hypophysectomy, in agreement with previous studies [20,22] Taken together, the prevention of ACTH-induced yawning and penile erection by hypophysectomy and the ineffectiveness of hypothalamic ACTH-MSH depletion by MSG to alter ACTH-induced effect, indicate that an intact pituitary function rather than the integrity of hypothalamic ACTH-MSH-containing neurons, is important for the induction of yawning and penile erection by ACTH-MSH peptides As previously discussed [22], this suggests that the pituitary gland exerts a permissive role in the expression of ACTH- and apomorphine-induced penile erection and yawning In agreement with this hypothesis, hypophysectomy has been found to cause a marked decrease in central behavioural effects induced by other neuropeptides, and this decrease was completely prevented by the combined administration of testosterone, corticosterone and growth hormone [8]

On the other hand, previous studies have shown that hypophysectomy does not modify excessive grooming induced by ACTH [12], indicating that such responses might be mediated by a different mechanism. However, the above studies were performed in 5 days hypophysectomized rats, while one month hypophysectomized rats were used in the present study. Therefore, it is possible that the failure of hypophysectomy to modify ACTH-induced grooming was due to the short post-operative period used in the previous study

The failure of hypothalamic ACTH-MSH depletion to modify ACTH-induced yawning and penile erection is surprising Indeed, if yawning, stretching and penile erection after ICV ACTH are really due to the stimulation of brain ACTH-MSH receptors, one would expect a compensatory increase in the sensitivity of these receptors, but this was not observed In agreement with the present study, neonatal MSG treatment was found to be unable to modify excessive grooming induced by ACTH [7] and to induce significant changes in opiate receptors [23] Moreover, an attenuated analgesic response to morphine [6] and a significant reduction in the stress-induced prolactin release [16] have been shown in MSG-treated rats However, these changes suggest a decreased rather than an increased sensitivity to opiates and ACTH-MSH peptides

The inability of neonatal MSG treatment to modify apomorphine-induced penile erection and yawning suggests that apomorphine and other DA agonists do not induce such responses by releasing an ACTH-derived peptide from central ACTH-MSH containing neurons Thus, although both apomorphine and ACTH-derived peptides induce penile erection and yawning, it is possible that they act by a different mechanism or at different steps in the neuronal circuitry involved in the expression of these responses If really apomorphine and ACTH act one after the other to induce yawning and penile erection, it is likely that the site of action of ACTH-derived peptides is situated after that of apomorphine, since ACTH-induced response is not antagonized by doses of neuroleptic drugs that completely prevent apomorphine-induced response [21]

Recently, we have found that the ICV injection of nanogram amounts of oxytocin induces penile erection and yawning in male rats [1] The powerful effect of oxytocin in eliciting the above responses, together with the presence of this neuropeptide in brain neurons in addition to the posterior pituitary, raises the possibility that apomorphine and/or ACTH-derived peptides induce penile erection and yawning by releasing oxytocin in some brain area or vice versa The failure of neonatal MSG treatment to modify significantly the hypothalamic concentration of oxytocin [19] leads us to speculate that apomorphine induces penile erection and

yawning by releasing oxytocin in brain Accordingly, both penile erection and yawning induced by oxytocin or apomorphine, but not by ACTH 1–24, have been found to be prevented by the ICV injection of the oxytocin antagonist $d(CH_2)_5$ Tyr-(Me)-Orn^8 vasotocin [3].

In conclusion, although the possibility that ACTH-MSH peptides induce the above responses by acting in some extrahypothalamic brain area where they are not depleted by neonatal MSG treatment [10] cannot by completely ruled out, the depletion of hypothalamic ACTH and α-MSH does not alter penile erection and yawning induced by ACTH 1–24 and apomorphine

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