European Journal of Pharmacology, 41 (1977) 343—345

Rapid communication

ACTH-INDUCED EXCESSIVE GROOMING INVOLVES BRAIN DOPAMINE

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Received 8 December 1976, accepted 9 December 1976

Peptides derived from ACTH are known to induce excessive grooming in the rat when administered intraventricularly (Gispen and Wiegant, 1976). Recent studies indicate that naloxone and naltrexone, specific opiate antagonists, block this peptide-induced behavior and that morphine and endogenous opiate-like peptides, injected in low doses into the ventricles, can mimic this ACTH-induced response (Gispen and Wiegant, 1976; Wiegant et al., 1976). The grooming elicited by small doses of morphine administered systemically to rats appears to be dependent on intact noradrenergic and dopaminergic systems (Ayhan and Randrup, 1973). Furthermore, it has been shown that the dopamine-containing nucleus caudatus is indispensable for the initiation of certain morphine-induced behaviors (Cools et al., 1974). For these reasons the possible involvement of brain dopamine (DA) in ACTH-induced excessive grooming was studied.

Male rats, weight 200—220 g, of an inbred Wistar strain were used. 10 days prior to the observation session, a plastic cannula was implanted into the brain ventricular system (foramen interventriculare, König and Klippel, A6360). In addition, a number of rats received bilateral stainless steel cannulas into either the neostriatum (König and Klippel coordinates: A = 9.4; H = 1.0; L = 2.0) or the substantia nigra (König and Klippel coordinates: A = 2.4; H = 2.6; L = 1.4). Grooming behavior was analysed as described earlier, using a 15th sec sampling technique, making possible a maximum score of 200 per 50 min observation session (Gispen and Wiegant, 1976).

The first experiment was designed to investigate the effect of various doses of systemically injected haloperidol (0.1—0.5 mg/kg i.p., 60 min prior to observation) on the excessive grooming induced by $ACTH_{1-24}$ (1 μg/μl/rat, intraventricularly, 15 min prior to observation). The data show that 1 μg of $ACTH_{1-24}$ induced excessive grooming, and that this response was suppressed by haloperidol (table 1A). Haloperidol treatment itself seemed not to affect ongoing behavior of rats which received saline intraventricularly. An additional DA antagonist, flufenazine, was tested as well. 60 h prior to the intraventricular injection of $ACTH_{1-24}$ (1 μg/μl), rats received a long acting flufenazine preparation (Anatensol, Squibb, 0.5 mg/kg s.c.) or its solvent. Ongoing behavior of control rats during the observation session was not affected by this DA antagonist either, but the excessive grooming induced by intraventricular injection of $ACTH_{1-24}$ was suppressed (table 1A). Previous studies have shown that this effect of the peptide is elicited through an interaction with central nervous structures and not through a classical endocrine mechanism (see Wiegant et al., 1976). The data of table 1A are therefore

TABLE 1

DA antagonists and $ACTH_{1-24}$ -induced excessive grooming.

A				B			
Treatment		n	Grooming score**	Treatment		n	Grooming score
Systemic	I. ventr.			Neostriatum	I. ventr.		
Saline	$ACTH_{1-24}$	8	157 ±14**	Saline	$ACTH_{1-24}$	6	108 ± 23**
Haloperidol+ 0.1	$ACTH_{1-24}$	6	97 ±24**	Haloperidol 1 μg	$ACTH_{1-24}$	6	24 ± 4
Haloperidol 0.2	$ACTH_{1-24}$	5	48 ±20	$ACTH_{1-24}$ 3 μg	Saline	6	28 ± 4
Haloperidol 0.5	$ACTH_{1-24}$	3	25 ± 6	Saline	Saline	6	35 ± 5
Haloperidol 0.1	Saline	4	11 ± 5				
Saline	Saline	4	20 ± 5	S. nigra	I. ventr.		
Oil	$ACTH_{1-24}$	6	162 ±16**	Saline	$ACTH_{1-24}$	5	153 ± 13**
Flufe++ 0.5	$ACTH_{1-24}$	6	77 ±18	Haloperidol 1 μg	$ACTH_{1-24}$	5	133 ± 12**
Oil	Saline	4	53 ±20	$ACTH_{1-24}$ 0.2 μg	Saline	6	126 ± 17**
Flufe 0.5	Saline	4	41 ± 2	Saline	Saline	6	46 ± 6

*Data for grooming scores are mean ±S.E.M. The intraventricular dose of $ACTH_{1-24}$ was 1 μg in 1 μl.
**Significantly higher than control group ($p < 0.05$ Dunnett's test).
+Haloperidol in mg/kg.
++Flufe = flufenazine in mg/kg.

interpreted as evidence for a central dopaminergic component. To further substantiate this conclusion, a first attempt was made to characterize the dopaminergic component in terms of the possible involvement of the substantia nigra and neostriatum.

Rats with cannulas in the neostriatum bilaterally and in the ventricular system were injected 15 min prior to the observation session with haloperidol (1 μg/μl) bilaterally in the neostriatum and $ACTH_{1-24}$ (0.5 μg/μl) in the ventricles or with saline (neostriatum) and $ACTH_{1-24}$ (ventricles). In the subsequent observation session, it was found that the neostriatal injection of haloperidol markedly suppressed ACTH-induced grooming (table 1B). Haloperidol treatment per se did not affect grooming activity of saline-treated rats. Interestingly, bilateral injection of up to 3 μg of $ACTH_{1-24}$ in the neostriatum failed to induce excessive grooming. If, however, $ACTH_{1-24}$ was injected into the substantia nigra (bilateral, 15 min prior to observation session), as little as 0.2 μg/0.5 μl per injection was sufficient to elicit the behavioral response, with the magnitude of the response being similar to that seen after 1 μg administered intraventricularly (table 1B). Bilateral injection of haloperidol (1 μg/0.5 μl) into the substantia nigra did not suppress the grooming induced by $ACTH_{1-24}$ (1 μg intraventricularly).

Thus, both peripheral injection of DA antagonists (table 1A) and DA-receptor blockade in the neostriatum (table 1B) suppressed ACTH-induced excessive grooming. Since $ACTH_{1-24}$ injection was ineffective in the neostriatum but effective in the substantia nigra, it is tempting to speculate that a nigrostriatal DA pathway is involved. Morphine can induce excessive grooming (Ayhan and Randrup, 1973; Gispen and Wiegant, 1976) and in cats, bilateral injection of haloperidol into the n. caudatus blocks the onset of the behavioral response to morphine treatment (Cools et al., 1974). Recently, it was shown that the activity of mesencephalic and diencephalic DA systems in the rat is affected by α-MSH, which is identical to $[Ac\text{-}Ser^1]ACTH_{1-13}\text{-}NH_2$ and

equipotent to $ACTH_{1-24}$ in inducing grooming (Wiegant et al., 1976) and by morphine (Lichtensteiger and Lienhart, 1975). Furthermore, ACTH-like peptides have considerable affinity for rat brain opiate receptors (see Wiegant et al., 1976). We therefore propose that a common dopaminergic component is involved in ACTH- and morphine-induced behavior. Experiments are in progress to elucidate the nature of the DA-system involved.

Acknowledgements

The authors wish to thank J.H. Brakkee and P. Van Wel for their excelent technical assistance. This study was supported in part by grant no. 13-31-03B from FUNGO/ZWO, Den Haag

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