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Short communication

DISTINCT DOPAMINERGIC SYSTEMS IN ACTH-INDUCED GROOMING

ALEXANDER R. COOLS *, VICTOR M. WIEGANT ** and WILLEM HENDRIK GISPEN **

** Department of Pharmacology, University of Nijmegen, The Netherlands*
*** Division of Molecular Neurobiology, Rudolf Magnus Institute for Pharmacology, and Laboratory of Physiological Chemistry, Medical faculty, Institute of Molecular Biology, Padualaan 8, Utrecht, The Netherlands*

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Excessive grooming behavior induced in rats by intraventricular injection of $ACTH_{1-24}$ was inhibited by selective pharmacological manipulation of two functionally distinct types of dopaminergic terminals (DA_e and DA_i) in the neostriatum or the nucleus accumbens. It is concluded that when $ACTH_{1-24}$ produces the behavioral response it modulates the activity of both the DA_e and the DA_i systems.

Excessive grooming Brain dopamine Distinct dopamine receptors ACTH Neuropeptides

1. Introduction

Morphine and fragments of pituitary and brain peptides (endorphins and ACTH) share a number of properties with respect to their effects on the central nervous system (see review Gispen et al., 1977). For instance, they all have an affinity for brain opiate receptors and elicit excessive grooming behavior in rodents (Wiegant et al., 1977a), while specific opiate antagonists inhibit this induction of excessive grooming (Wiegant et al., 1977a). Furthermore, certain behavioral effects of either morphine or $ACTH_{1-24}$ treatment can be suppressed by intrastriatally applied dopamine antagonists such as haloperidol (Cools et al., 1974; Wiegant et al., 1977b).

Recently it was proposed that there are at least two functionally opposing and pharmacologically distinct dopaminergic systems: an excitation-mediating dopaminergic system (DA_e system) and an inhibition-mediating dopaminergic system (DA_i system) (Cools, 1977). In the rat DA_e terminal areas are mainly within the neostriatum, although some are also present within the nucleus accumbens. The reverse appears to hold for DA_i terminal areas which are mainly within the nucleus accumbens (Cools, 1977). In the present paper we report experiments on the dopaminergic component in ACTH-induced excessive grooming with special reference to these distinct DA systems.

2. Materials and methods

2.1. Animals and surgery

Male rats, weight 200—220 g, of an inbred Wistar strain were anaesthesized with sodium pentobarbital (50 mg/kg, i.p.) and stereotaxically implanted with one polyethylene cannula directed to the foramen interventriculare and paired stainless steel cannulas into either the left and right neostriatum (König and Klippel coordinates: A = 9.4, L = 2.0, D = 1.0) or into the left and right nucleus accumbens (coordinates: A = 9.4, L = 1.2, D = 0.6) (for technical details: Gispen et al., 1975; Pijnenburg et al., 1976).

2.2. Injections and drugs

All intracranial injections were performed free hand in non-restrained, conscious rats. Injection volumes were: foramen interventriculare, 3 μl; neostriatum, 1 μl per side; nucleus accumbens, 0.5 μl per side. Synthetic $ACTH_{1-24}$ was a gift from Organon Int. BV. The following drugs were used: dopamine hydrochloride (Koch-Light), haloperidol (Serenase®, Janssen Pharmaceutical), ergometrine maleate (Halewood Chemicals), (3,4-dihydroxyphenylamino)-2-imidazoline hydrochloride (DPI, Boehringer Sohn, Ingelheim), apomorphine hydrochloride (Brocades).

2.3. Behavioral analysis and treatment

The behavioral experiments were started after a post-operation interval of at least 10 days. Grooming behavior, which was elicited by intraventricularly applied $ACTH_{1-24}$, was analysed as described earlier (Gispen et al., 1975). Every 15th sec the observer determined whether an animal displayed an element of the maintenance behavior. Thus, 200 grooming scores could be obtained in a 50 min period.

The activity of the DA_e system in either neostriatum or nucleus accumbens was manipulated by local injections of DA, the DA_e agonist apomorphine or the DA_e antagonist haloperidol (Cools, 1977). The activity of the DA_i system in the neostriatum or nucleus accumbens was manipulated by local injections of the DA_i agonist DPI and the DA_i antagonist ergometrine (Cools, 1977). Ergometrine was given 60 min prior to $ACTH_{1-24}$ (cf Cools et al., 1978), all other drugs were administered immediately after $ACTH_{1-24}$. Saline was used in control experiments. The observation session started 15 min after ACTH administration and lasted for 50 min. After completion of the experiments, the rats were killed and brains sectioned to determine the position of the cannulas (for details: Pijnenburg et al., 1976). The data presented below are derived from experiments in which the injection sites were correctly placed into the target areas.

3. Results

Injection of $ACTH_{1-24}$ into the foramen interventriculare induced excessive grooming (0.5 μg: 130—150 positive scores). If $ACTH_{1-24}$ was bilaterally injected into either the nucleus accumbens or the neostriatum (1.0 μg) no excessive grooming was observed (data not shown). However, bilateral administration of DA agonists or antagonists in either nucleus accumbens or neostriatum interfered with ACTH-induced excessive grooming (fig. 1). Bilateral local application of apomorphine (5 μg/μl) or haloperidol (1 μg/μl) in the neostriatum inhibited the ACTH-induced behavior, but local application of DA (5 μg/μl) was without effect. In addition, bilateral local application of ergometrine (0.5 μg/0.5 μl) or DPI (5 μg/0.5 μl) in the nucleus accumbens suppressed the display of the grooming response. If, however, haloperidol was injected into the nucleus accumbens or ergometrine

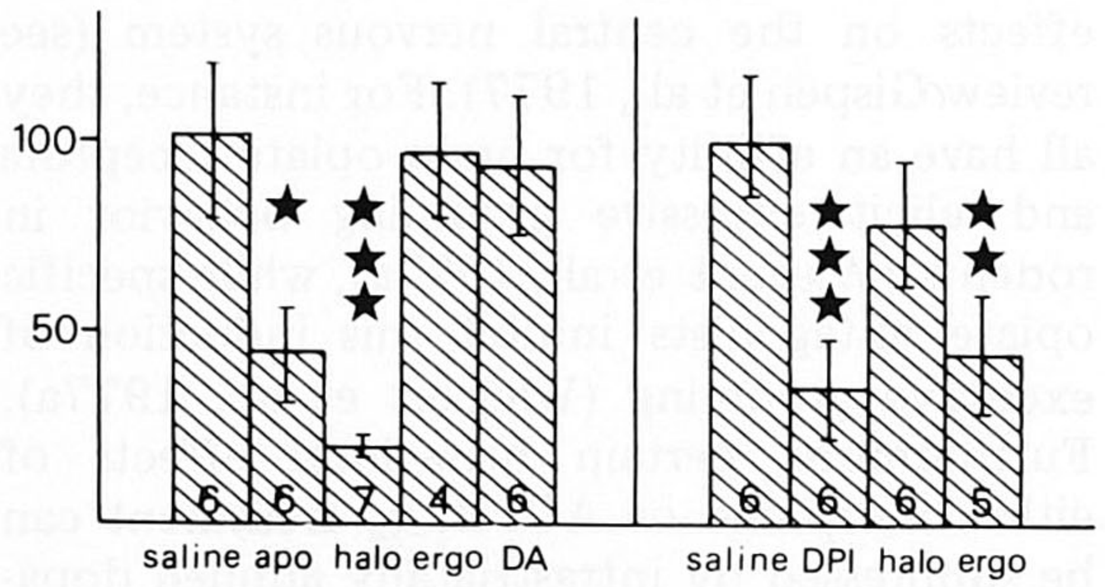

Fig. 1. The effect of selective manipulation of the DA_e and the DA_i system in the neostriatum (left) and the nucleus accumbens (right) on the excessive grooming response induced by intraventricular injection of 0.5 μg $ACTH_{1-24}$. Drugs were injected in the following doses: apomorphine (apo): 5 μg; haloperidol (halo): 1 μg; ergometrine (ergo): 0.5 μg; dopamine (DA): 5 μg and DPI: 5 μg. The excessive grooming response was expressed as percentage of the control value (= saline). Bars represent the mean ± S.E.M. The number of animals per group is indicated in the bars. * $2P \leq 0.05$, ** $2P \leq 0.025$, *** $2P \leq 0.01$ (Student's *t*-test).

TABLE 1

Effect of combined treatment with haloperidol and ergometrine on the grooming activity induced by $ACTH_{1-24}$.

Treatment			Grooming activity [1]	n
Foramen interventriculare	Nucleus accumbens			
$ACTH_{1-24}$	Saline [2]	Saline [3]	122 ± 8	20
$ACTH_{1-24}$	Saline	Haloperidol (2.5 μg)	92 ± 9	10 [4]
$ACTH_{1-24}$	Ergometrine (0.5 μg)	Saline	28 ± 10	10 [5]
$ACTH_{1-24}$	Ergometrine (0.5 μg)	Haloperidol (2.5 μg)	64 ± 14 [4]	10 [5]

[1] Data for grooming scores are mean ± S.E.M. The intraventricular dose of $ACTH_{1-24}$ was 0.3 μg.
[2] Administered 60 min prior to ACTH injection.
[3] Administered directly after ACTH injection.
[4] $2P < 0.05$, [5] $2P < 0.01$ (Student's *t*-test).

into the neostriatum, the ACTH-induced behavior was hardly interfered with.

In an attempt to manipulate both the DA_e and the DA_i system in the nucleus accumbens during $ACTH_{1-24}$-induced excessive grooming the effect of a local injection of both haloperidol and ergometrine in the nucleus accumbens on the grooming response was studied. As can be seen in table 1, a high dose of haloperidol inhibited ACTH-induced excessive grooming to a moderate extent, whereas ergometrine treatment led to a total blockade of this response. Interestingly, combination of the two drugs resulted in a partial restoration of the ACTH-induced grooming.

4. Discussion

The present data confirm the previously suggested involvement of a dopaminergic component in ACTH-CNS interactions (Wiegant et al., 1977b; Iuvone et al., 1977). With respect to grooming the effect of ACTH seems to be localized at the cell bodies rather than at the dopaminergic terminals, since direct application of ACTH into the substantia nigra but not in the neostriatum or the nucleus accumbens induced excessive grooming (Wiegant et al., 1977b, this paper).

As mentioned in the Introduction, there are two functionally opposed and pharmacologically distinct DA systems. Although they are differentially influenced by apomorphine, haloperidol, DPI and ergometrine, they are equally affected by DA (Cools, 1977). Using a DA_e antagonist (haloperidol) in the region with few DA_e receptors (nucleus accumbens) or a DA_i antagonist (ergometrine) in a region with few DA_i receptors (neostriatum) led to little if any interference with the behavioral response. However, stimulation or inhibition of the DA_e system in the neostriatum or the DA_i system in the nucleus accumbens markedly inhibited ACTH-induced excessive grooming. Therefore, it is likely that ACTH modulates the activity of both dopaminergic systems.

Thus, a specific balance between the activity of DA_e and DA_i systems underlies ACTH-induced grooming. Such reasoning is supported by the finding that haloperidol treatment did not potentiate but rather counteracted the ergometrine-induced inhibition of grooming: the counteraction of the locally disturbed balance between DA_e and DA_i activity was parallelled by a partial restoration of the suppressed grooming. Likewise, DA, being unable to affect this balance (Cools, 1977) did not alter the grooming activity.

Morphine produces a characteristic, time-dependent shift in the balance between DA_e

and DA_i activity within the feline brain: from predominant DA_e activity during the "early" morphine effects towards predominant DA_i activity during the "late" morphine effects (Cools et al., 1978). The exact nature of the interaction of the two different DA systems in ACTH-induced grooming is not yet understood. A more specific study is necessary, especially to define the timing of the differential onset of the two systems (Cools et al., 1978). However, considering the present results in view of the data availabe about morphine it is likely that morphine and $ACTH_{1-24}$ affect similarly the distinct DA systems within the brain, presumably by modulating the activity of neurones located in the substantia nigra.

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