ACTIONS OF ANTIDEPRESSANT AND NEUROLEPTIC DRUGS ON ACTH- AND NOVELTY-INDUCED BEHAVIOR IN THE RAT

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The present study deals with the effects of psychoactive drugs (neuroleptics and antidepressants) on ACTH-induced excessive grooming in the rat. The neuroleptics haloperidol and clozapine and the antidepressants amitriptyline, nomifensine and mianserin all suppressed the grooming response in a dose-dependent manner. The neuroleptic sulpiride was ineffective even at high doses. Experimental evidence is presented suggesting that the suppression of peptide-induced grooming was not the result of competing behavioral activity elicited by the drug itself. Instead it is assumed that the psychoactive drugs tested affected directly the activity of the neural substrate underlying the peptide-induced behavior. In view of the complexity of the mechanisms of action of the drugs tested it is argued that this substrate may be a more complex one than the dopamine systems as suggested before.

Neuroleptics Antidepressants ACTH Grooming Novelty Behavior

1. Introduction

Recently, several authors have shown that the study of grooming behavior of rodents in solitary test situations may provide useful information on central neurotransmitter systems and behavior (see Gispen and Isaacson, 1981). Such studies include neuropharmacological manipulation of excessive grooming evoked in the rat by i.c.v. ACTH (Wiegant et al., 1977; Cools et al., 1978; Gispen et al., 1980), of grooming seen after swimming or of grooming as displayed by rodents in novel observation chambers (Jolles et al., 1979; Green et al., 1979). The use of relatively specific antagonists suggested that the grooming response depends on the integrity of neural pathways with dopaminergic and/or opiate receptors (Gispen and Isaacson, 1981).

The effects of psychoactive drugs, presumably affecting brain function by dopaminergic/noradrenergic mechanisms, on ACTH-induced excessive grooming are reported here. In addition, it

is considered whether the influence of these drugs on excessive grooming may have resulted from a direct effect on the neural substrate underlying the peptide-induced behavior or from competing behavioral activity of the psychoactive drug itself.

2. Materials and methods

2.1. Animals and surgery

Male Wistar rats (TNO W74, Winkelmann, Borcheln, FRG) weighing approximately 150 g were used. Cannulation of the brain ventricular system at the level of the foramen intraventriculare was performed at least 5 days prior to the behavioral test day, essentially as described before (Brakkee et al., 1979). The animals were kept single-caged with a day-night cycle with light on between 6:00 a.m. and 7:00 p.m. and received food (Altromin[®], Altrogge, Lage, FRG) and water ad libitum.

2.2. The grooming test

The display of excessive grooming was recorded using a time sampling method as described before (Gispen et al., 1975). In short, conscious rats received an intraventricular (i.c.v.) injection of 3 μ l of either saline or ACTH₁₋₂₄ (0.3 μ g/3 μ l) dissolved in saline. The rats were then placed individually in glass observation boxes in a soundproof room under dim light. Using a 15 s time sampling procedure, the display of excessive grooming (vibration, face washing, body grooming, scratching, paw licking, head shake, body shake and genital grooming; see Gispen and Isaacson, 1981) was recorded for a period of 50 min, beginning 15 min after the injection. The data are expressed as % of the maximal possible grooming score ($50 \times 4 = 200 = 100\%$).

The effect of the psychoactive drugs was tested after systemic administration of the drugs prior to the behavioral test as indicated in the legends. To make sure that incorrect cannula placement would not obscure the test results, all rats received a second i.c.v.-injection of ACTH₁₋₂₄ (0.3 μ g/3 μ l saline) 48 h after the experiment and their grooming behavior was again recorded. Only the results of the first test on those rats which displayed excessive grooming behavior at the second test (scores of 70% or more) were analyzed (effective cannula placements over 90%; see also Brakkee et al., 1979). Unless specified otherwise, all tests were carried out between 10:00 and 12:00 a.m. The data are presented as mean percentage inhibition, whereas the statistical analysis was performed on the absolute amount of grooming displayed at the first test. The grooming displayed per rat per treatment group was analysed using a one-way analysis of variance followed by a supplementary t-test. The ED₅₀ were estimated graphically.

2.3. Novel box response

In order to characterize the behavior of rats placed into the novel box as used in the grooming test, naive rats were placed in these observation cages and 6 behavioral elements were recorded during a period of 15–65 min using a 15 s time sampling procedure. Thus, every 15th s it was de-

termined whether the rat displayed grooming, rearing, licking/sniffing, motor activity, sitting and sleeping. In one experiment, the behavioral response was determined as a function of the time of the day when the test was done (from 8:00 a.m. to 4:00 p.m.). The effect of psychoactive drugs on this behavior in the novel box was recorded in the second experiment. These drugs were tested in doses previously estimated to be in the range of the ED₅₀ for their reduction of ACTH-induced grooming behavior.

2.4. Drugs

The drugs used were as follows: Haloperidol (Janssen), clozapine (Sandoz), sulpiride (Schörrholz), amitriptyline (Tropon), nomifensine (Hoechst), mianserin (Organon). The psychoactive drugs were administered in an injection volume of 0.5 ml/100 g body weight. ACTH₁₋₂₄ was a gift of Dr. H.M. Greven (Organon Int. Ltd., Oss, The Netherlands).

3. Results

3.1. ACTH₁₋₂₄-induced grooming: dose-response curve

In this experiment, the rats received i.c.v. either saline or different doses of ACTH₁₋₂₄ (0.03, 0.3 or 3.0 μ g in 3 μ l saline). Saline-treated rats, placed in a novel glass box usually displayed exploratory and grooming behavior which could last for 25–35 min after the i.c.v. injection, but then they invariably fell asleep and thus showed little grooming activity during the total observation period (15–65 min, $\bar{x} = 34 \pm 4$, $n = 5$). Notably, the amount of grooming behavior thus obtained was similar throughout the day, whereas other behaviors seen in the novel box after i.c.v. saline seemed to vary as a function of the time of day (see below). As can be seen in fig. 1, ACTH₁₋₂₄ dose-dependently induced excessive grooming, and activity was nearly maximal with 0.3 μ g (one-way analysis of variance: between groups $F = 41.05$; df 16; 3; $P < 0.001$; within the peptide treatment group: $P < 0.01$: 3.0 vs. 0.03 and 0.3 versus 0.03). In fur-

Fig. 1. Dose-effect relationship for ACTH₁₋₂₄-induced excessive grooming (i.c.v. application). Mean $\pm$ S.E.M., $n=5$ per dose.

ther studies we used 0.3 μ g ACTH₁₋₂₄ as standard test dose and investigated the effect of systemic treatment with different doses of various psychoactive substances.

3.2. Neuroleptics and ACTH-induced excessive grooming

Haloperidol was chosen as an example of a 'classical' neuroleptic drug whereas clozapine and sulpiride were used as representatives of 'non-classical' neuroleptics. Haloperidol (0.01, 0.05, 0.1 and 0.5 mg/kg) and clozapine (0.1, 0.5, 1.0 and 5.0 mg/kg) were administered s.c. immediately prior to the i.c.v. injection of 0.3 μ g ACTH₁₋₂₄; whereas in the case of sulpiride (5.0, 50.0 and 100.0 mg/kg) a pretreatment interval of one or two hours was used as well.

There was a dose-dependent inhibition (fig. 2) of ACTH-induced grooming following the s.c. injection of haloperidol (between groups $F=164$, df 16; 3; $P<0.01$; t-test: differences between all groups) or clozapine (between groups $F=71.18$, df 15; 3; $P<0.01$; t-test: differences between all doses except between 1 and 5 mg/kg). At the highest doses tested, the neuroleptic/ACTH-treated rats showed significantly less grooming than even saline/saline-treated animals. Although there was no perfect linear relationship between

Fig. 2. Inhibition of ACTH₁₋₂₄-induced excessive grooming by neuroleptics. ACTH₁₋₂₄: 0.3 μ g/3 μ l i.c.v. Haloperidol and clozapine s.c. Mean $\pm$ S.E.M., $n=5$.

log dose and percentage inhibition, the curves indicate that the ED₅₀ for haloperidol s.c. was in the order of 0.08 mg/kg and that for clozapine s.c. in the order of 0.46 mg/kg. The treatment with sulpiride was ineffective and the ED₅₀ was at least greater than 100 mg/kg. The pretreatment interval between sulpiride and i.c.v. ACTH ranged from 0 to 2 h (data not shown).

3.3. Antidepressants and ACTH-induced excessive grooming

Amitriptyline was used as a representative of the 'classical' antidepressants whereas nomifensine and mianserin were taken as 'non-classical' antidepressants. The drugs were given immediately prior to the peptide injection: amitriptyline (1.0, 5.0, 10.0 and 50.0 mg/kg i.p.), nomifensine (0.1, 0.5, 1.0 and 5.0 mg/kg s.c.) and mianserin (0.5, 1.0, 5.0 and 10.0 mg/kg s.c.). The effect of these treatments on the grooming induced by 0.3 μ g ACTH₁₋₂₄ was then recorded. All three antidepressants inhibited dose-dependently (fig. 3) the display of excessive grooming. Amitriptyline (between groups $F=42$, df 16; 3; $P<0.01$; t-test: all groups differ); nomifensine (between groups $F=26$, df 16; 3; $P<0.05$; t-test no differences between 0.5 and 1, and 1 and 5 mg/kg); mianserin (between groups $F=16.61$, df 16; 3; $P<0.05$; t-test: no difference between 0.5 and 1.0, and 1.0 and 5.0 mg/kg). Again, with the highest doses tested, the amount of grooming was in the range

Fig. 3. Inhibition of ACTH₁₋₂₄-induced excessive grooming by antidepressants. ACTH₁₋₂₄: 0.3 µg/3 µl i.c.v. Nomifensine and mianserin s.c. Amitriptyline i.p. Mean ± S.E.M., n = 5.

of, or even lower than that of saline/saline-treated controls. The ED₅₀ as estimated from the log dose/percentage inhibition curves for amitriptyline, mianserin and nomifensine under these circumstances were of the order of 6.8, 5.0 and 1.9 mg/kg, respectively.

3.4. Novel box response

In order to investigate whether treatment with psychoactive drugs would affect the behavioral response of naive rats placed in the novel observation cages, a series of experiments was carried out to analyze the behavior of naive rats in the novel box in more detail, using the grooming test time schedule.

It was first studied whether the time of day was of significance to the behavioral response observed. Therefore, at times 8:00, 9:00, 10:00, 12:00 a.m., 1:00, 2:00 and 3:00 p.m. groups of 5 male non-cannulated naive rats were placed individually in the novel box and their behavior recorded between 15 and 65 min thereafter. The results are shown in fig. 4. As animal to animal variation was substantial, the experiment was repeated with larger groups of rats (10:00 a.m., n = 15; 2:00 p.m., n = 10). As is shown in fig. 5, the grooming, rearing and licking/sniffing activity at 10:00 a.m. was not significantly different from that seen at 2:00 p.m. However, in this experiment a significant reduction in motor activity and sit-

Fig. 4. Novel box response as a function of the time of day. The median values for a given behavior per group; n = 5.

ting behavior was observed at 2:00 p.m. as compared to 10:00 a.m. Concomitantly, there was a significant increase in sleeping scores at 2:00 p.m. (fig. 5). Irrespective of the meaning of these time-related changes in the response to a novel situation, it was decided to perform the observations at a fixed time of the day to allow valid comparisons between experiments. Accordingly, the experiments concerning the effect of acute systemic treatment with the psychoactive drugs on the behavioral response to a novel observation box were carried out at 10:00 a.m. Male rats received an

Fig. 5. Novel box response at 10:00-11:00 a.m. (n = 15) and 2:00-3:00 p.m. (n = 10). Data are expressed as median values; interquartile range in parentheses. Mann-Whitney U-test (two-tailed). * P ≤ 0.05, ** P ≤ 0.02.

i.c.v. cannula one week prior to the behavioral experiment. The rats were randomized over two treatment groups of 5 subjects each. One group received an s.c. or i.p. injection of saline followed immediately by an i.c.v. injection of saline (3 μ l). The other group received the drug systemically

and 15 min later the i.c.v. saline injection. The doses used were derived from their effectiveness in reducing ACTH-induced excessive grooming as found in the previous experiment and represented the estimated ED₅₀.

Immediately after the i.c.v. injection the rats were put in the novel box and behavior was recorded for a period of 50 min, beginning 15 min after placement in the box. The median scores for the different behavioral categories are given in fig. 6. As there were no significant differences between the saline/saline group of the various experiments, the scores are presented for only one group. However, all comparisons were made between drug/saline-treated rats and the corresponding saline/saline group.

Treatment with the neuroleptics haloperidol (0.08 mg/kg s.c.), clozapine (0.46 mg/kg s.c.) or sulpiride (100 mg/kg s.c.), resulted primarily in a marked increase in sitting ($P < 0.02$) accompanied by a significant decrease in sleeping. In addition, clozapine-treated rats showed a small but significant decrease in grooming activity ($P < 0.05$). Treatment with amitriptyline (6.8 mg/kg i.p.) also eliminated sleeping ($P < 0.02$), with a tendency to increase the sitting scores. The non-classical antidepressant mianserin (5.0 mg/kg s.c.) likewise eliminated sleeping ($P < 0.02$) and enhanced the amount of sitting scores ($P < 0.05$). The other non-classical antidepressant nomifensine (1.9 mg/kg s.c.), markedly enhanced the display of rearing, sniffing/licking and motor activity ($P < 0.02$, respectively) and completely suppressed sleeping ($P < 0.02$). The amount of grooming and sitting was not affected.

4. Discussion

Ferrari was the first to report on a behavioral syndrome in animals after intrathecal application of ACTH (Ferrari, 1958). In subsequent studies, Ferrari and co-workers focussed on the stretching and yawning syndrome, although they reported that, in rats and rabbits, the onset of this syndrome was preceded by excessive grooming (Ferrari et al., 1963). Quantifying the display of excessive grooming allowed reliable dose-response and

Fig. 6. Effect of neuroleptics and antidepressants on the response of rats to placement in a novel box. Data are expressed as median values. Mann-Whitney U-test (two-tailed). * $P < 0.05$, ** $P < 0.02$; $n = 5$ in each group. (A) Saline s.c., (B) haloperidol (0.08 mg/kg s.c.), (C) clozapine (0.46 mg/kg s.c.), (D) sulpiride (100 mg/kg s.c.), (E) nomifensine (1.9 mg/kg s.c.), (F) amitriptyline (6.8 mg/kg i.p.), (G) mianserin (5.0 mg/kg s.c.).

structure-activity studies to be done with the peptide-induced behavior (Gispen et al., 1975). In the present study also, the induction of excessive grooming depended very much on the peptide dose used. As these studies are in good agreement with those of other laboratories (reviewed by Gispen and Isaacson, 1981), the ACTH-induced excessive grooming behavior is shown to be a reliable and reproducible test for measuring the behavioral activity of ACTH.

There is much evidence indicating that this peptide effect is not mediated by the endocrine system (Gispen et al., 1975; Wiegant et al., 1979), but seems to result from a direct action of ACTH on brain structures (Colbern et al., 1977; Wiegant et al., 1977). Neuropharmacological experiments suggest that, in producing the behavioral response, ACTH affects distinct DA systems in the brain, presumably modulating the activity of DA neurons in the substantia nigra (Wiegant et al., 1977; Cools et al., 1978). Based both on anatomical projections of the forebrain dopamine systems and on the results of pharmacological and functional studies, Cools (1977) proposed that at least two distinct dopaminergic systems must be considered: an excitation-mediating dopaminergic system (DA_e receptors) and an inhibition-mediating dopaminergic system (DA_i receptors). It was suggested that ACTH modulates the activity of both dopaminergic systems and that the peptide-induced grooming is very sensitive to the balance between this DA_e and DA_i activity (Cools et al., 1978; Gispen and Isaacson, 1981). This suggestion was made because a shift in the balance induced by local application of specific agonists or antagonists of one of the functional distinct DA systems resulted in the suppression of ACTH-induced excessive grooming (Cools et al., 1978; Gispen et al., 1980). In addition, preliminary observations showed that clonidine, a potent α_2 -receptor agonist, suppressed ACTH-induced grooming (Gispen and Isaacson, 1981; Traber, unpublished data), suggesting a possible involvement of α -adrenergic mechanisms as well. Based on these assumptions, we tested in the present study whether psychoactive drugs with a presumed dopaminergic and/or noradrenergic mechanism of action could suppress ACTH-induced excessive grooming. One should

keep in mind, however, that such agents may have pre- and/or postsynaptic effects. Consequently there are conflicting reports with respect to their receptor specificity, etc. In addition, we considered whether changes in behavior resulting from the drug treatment per se could account for interference with ACTH-induced excessive grooming. Therefore, the drugs were tested in naive rats placed in novel boxes under conditions identical to those used for the grooming test using doses which were found to suppress ACTH-induced grooming by approximately 50%.

The 'novel box response' is a useful test to screen central effects of presumed psychoactive drugs and may even give a specific profile for a given class of centrally acting drugs provided one studies their effects over a wide dose range (Traber, in preparation). For instance the immobilization often seen after treatment with relatively high doses of classical neuroleptics is evidenced by the reduction of sleeping and the enhancement of sitting in the haloperidol-treated rats. Furthermore, the nomifensine treatment resulted in a picture reminiscent of that obtained with amphetamine (Traber, unpublished data; Fray et al., 1980). In animals so treated the reduction in sleep is not accompanied by an increase in sitting scores but by an increase in locomotion, rearing and sniffing/licking responses.

In the present study, the behavior seen in the novel box was dependent on the time of day when observation took place. Although no attempt was made to further analyze this correlation, one is tempted to speculate that such changes may reflect endogenous, time-dependent differences in the animal (for instance circadian differences in hypothalamo-pituitary-adrenal activity (Ader, 1975; Usatequi et al., 1976). Furthermore, we have preliminary evidence suggesting that the behavioral response to a novel box may also vary as a function of seasonal influences (Traber, in preparation). We have used the novel box response to investigate whether the suppression of ACTH-induced grooming by the various drugs could be explained simply by an overall behavioral change (i.e. sedation, activation, etc.). Although at the extremely high doses overall effects may add to the suppression of grooming by initiating competing behav-

ioral activity (sitting, haloperidol; motor activity, nomifensine), a more specific interaction seems to be responsible for the inhibition when doses at the ED_{50} level are used. The shift from sleeping to sitting—the most pronounced change seen in nearly all experiments with the psychoactive drugs—was not related to the suppression of grooming because sulpiride, which evokes a similar behavioral response in the novel box was hardly effective in the grooming test (even tested at high doses and after various pretreatment intervals). Also, the novelty-induced grooming was only slightly (clozapine) if at all (haloperidol) affected by the neuroleptics. The classical example of the neuroleptics tested, haloperidol, has a presumed preference for DA_e receptors (Cools, 1977), but in high concentrations it also affects α -adrenergic receptors (Cools, 1978). The non-classical examples clozapine and sulpiride presumably affect special classes of DA-receptors. Their selectivity is still under debate (Bürki et al., 1976; LeFur et al., 1980; Rebec et al., 1980; Jenner and Marsden, 1979). Only haloperidol and clozapine suppressed ACTH-induced grooming at low doses. The inhibition was already observed at doses which did not affect the behavior of the rats as studied in the novel box response test.

Although the sulpiride treatment certainly affected CNS structures as judged from its effectiveness in the novel box test, the poor penetration of sulpiride into the CNS might have interfered with the transport of the drug to the sites relevant for ACTH-induced grooming (see Woodruff et al., 1980).

On the other hand, the ineffectiveness may also be explained by assuming that sulpiride, like dopamine (Cools et al., 1978) does not lead to the shift in DA_e/DA_i activity necessary to block ACTH-induced excessive grooming.

The three antidepressants tested all reduced ACTH-induced grooming. They are reported to have different mechanisms of action. The 'classical' tricyclic amitriptyline seems to affect serotonergic and α -adrenergic mechanisms (Maj, 1981; LeFur, 1980). The non-classical antidepressant nomifensine is thought to increase DA and noradrenaline concentrations in the synaptic cleft (Brogden et al., 1979) and mianserin seems to have

mixed effects on α_2 - (Brown et al., 1980; Engberg and Svensson, 1981) and 5-HT-receptors (Maj et al., 1978; Maj, 1981). It may be that the interaction with α -adrenergic/dopaminergic systems is the common cause for the inhibition caused by these drugs, although an effect on serotonergic mechanisms cannot be excluded.

While the present experiments do not allow a firm conclusion, they certainly suggest that more is involved in the neuropharmacology of ACTH-induced excessive grooming than only the presumed DA systems containing opiate sensitive components (Cools et al., 1978; Gispen and Isaacson, 1981).

At present it is uncertain whether the treatment with the neuroleptics or antidepressants directly modified the effects of ACTH on DA neurons in the substantia nigra (Wiegant et al., 1977; Gispen and Isaacson, 1981) or whether they interacted with the neural substrate involved in ACTH-induced grooming at a level distinct from the peptide input.

References

- Ader, R., 1975, Neonatal stimulation and maturation of the 24-hour adrenocortical rhythm, *Progr. Brain Res.* 42, 340.
- Brakkee, J.H., V.M. Wiegant and W.H. Gispen, 1979, A simple technique for rapid implantation of a permanent cannula into the rat brain ventricular system, *Lab. Animal Sci.* 29, 78.
- Brogden, R.N., R.C. Heel, T.M. Speight and G.S. Avery, 1979, Nomifensine: A review of its pharmacological properties and therapeutic efficacy in depressive illness, *Drugs*, 18, 1.
- Brown, J., J.C. Doxey and S. Handley, 1980, Effects of α -adrenoceptor agonists and antagonists and of antidepressant drugs on pre- and postsynaptic α -adrenoceptors, *European J. Pharmacol.* 67, 33.
- Bürki, H.R., A.C. Sayers, W. Ruch and H. Asper, 1976, Effects of anticholinergics and clozapine on the activation of the striatal dopaminergic system in the rat by haloperidol. Neurochemical findings, *Arzneim. Forsch. (Drug Res.)* 26, 1094.
- Colbern, D., R. Isaacson, B. Bohus and W.H. Gispen, 1977, Limbic-midbrain lesions and ACTH-induced excessive grooming, *Life Sci.* 21, 393.
- Cools, A.R., 1977, Two functionally and pharmacologically distinct dopamine receptors in the rat brain, in: *Adv. Biochem. Psychopharmacol.*, Vol. 16, Nonstriatal Dopaminergic Neurons, eds. E. Costa and G.L. Gessa (Raven Press, New York) p. 215.

- Cools, A.R., 1978, Haloperidol and the significance of α -NE mediated control of a subpopulation of DA receptors for concepts such as supersensitivity and tolerance: A behavioral study on cats, *Life Sci.* 23, 2475.
- Cools, A.R., V.M. Wiegant and W.H. Gispen, 1978, Distinct dopaminergic systems in ACTH-induced grooming, *European J. Pharmacol.* 50, 265.
- Engberg, G. and T.H. Svensson, 1981, Mianserin: Direct activation of brain norepinephrine neurons by blockig α_2 -receptors, *Commun. Psychopharmacol.* 4, 233.
- Ferrari, W., 1958, Behavioural changes in animals after intracisternal injection with adrenocorticotrophic hormone and melonocyte stimulating hormone, *Nature* 181, 925.
- Ferrari, W., G.L. Gessa and L. Vargiu, 1963, Behavioral effects induced by intracisternally injected ACTH and MSH, *Ann. New York Acad. Sci.* 104, 330.
- Fray, P.J., B.J. Sahakian, T.W. Robbins, G.F. Koob and S.D. Iversen, 1980, An observational method for quantifying the behavioural effects of dopamine agonists: Contrasting effects of d-amphetamine and apomorphine, *Psychopharmacol.* 69, 253.
- Gispen, W.H. and R.L. Isaacson, 1981, ACTH-induced excessive grooming in the rat, *Pharmacol. Ther.* 12, 209.
- Gispen, W.H., D. Ormond, J. Ten Haaf and D. De Wied, 1980, Modulation of ACTH-induced grooming by (des-Tyr¹)- γ -endorphin and haloperidol, *European J. Pharmacol.* 63, 203.
- Gispen, W.H., V.M. Wiegant, H.M. Greven and D. De Wied, 1975, The induction of excessive grooming in the rat by intraventricular application of peptides derived from ACTH: Structure activity studies, *Life Sci.* 17, 645.
- Green, E.J., R.L. Isaacson, A.J. Dunn and T.H. Lanthorn, 1979, Naloxone and haloperidol reduce grooming occurring as an after effect of novelty, *Behav. Neural Biol.* 27, 546.
- Jenner, P. and C.D. Marsden, 1979, The substituted benzamides—a novel class of dopamine antagonists, *Life Sci.* 25, 479.
- Jolles, J., J. Rompa-Barendregt and W.H. Gispen, 1979, Novelty and grooming behavior in the rat, *Behav. Neural Biol.* 25, 563.
- Le Fur, G., 1980, A propos du mécanisme d'action supposé des antidépresseurs, *L'Encéphale* 6, 303.
- Le Fur, G., F. Guilloux and A. Uzan, 1980, In vivo blockade of dopaminergic receptors from different rat brain regions by classical and atypical neuroleptics, *Biochem. Pharmacol.* 29, 267.
- Maj, J., 1981, Serotonergic mechanisms of antidepressant drugs, *Pharmakopsychiat.* 14, 35.
- Maj, J., H. Sowinska, L. Baran, L. Gancarczyk and A. Rawlow, 1978, The central antiserotonergic action of mianserin, *Psychopharmacology* 59, 79.
- Rebec, G.V., T.C. Bashore, K.S. Zimmerman and K.D. Alloway, 1980, Neostriatal and mesolimbic neurons: dose-dependent effects of clozapine, *Neuropharmacology* 19, 281.
- Usatequi, R., C. Oliver, H. Vaudry and G. Lombardi, 1976, Immunoreactive α -MSH and ACTH levels in rat plasma and pituitary, *Endocrinology* 98, 189.
- Wiegant, V.M., A.R. Cools and W.H. Gispen, 1977, ACTH-induced excessive grooming involves brain dopamine, *European J. Pharmacol.* 41, 343.
- Wiegant, V.M., J. Jolles, D. Colbern, E. Zimmermann and W.H. Gispen, 1979, Intracerebroventricular ACTH activates the pituitary-adrenal system: Dissociation from a behavioral response, *Life Sci.* 25, 1791.
- Woodruff, G.N., S.B. Freedman and J.A. Poat, 1980, Why does sulpiride not block the effect of dopamine on the dopamine-sensitive adenylate cyclase?, *J. Pharm. Pharmacol.* 32, 802.