JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 1997, 48, 2, 263—275

I. ŻEBROWSKA-ŁUPINA, T. PIETRASIEWICZ, G. OSSOWSKA, T. ŁUPINA*, B. KLENK-MAJEWSKA

ACTH 4—9 ANALOGUE FACILITATES THE ANTIIMMOBILITY EFFECT OF ANTIDEPRESSANTS AND DOPAMINE AGONISTS IN SWIMMING RATS

Department of Clinical Pharmacology and Department of Pulmonology*, Medical Academy, Lublin, Poland

Evidence exists that the 4—10 or 4—9 fragments of adrenocorticotropic hormone (ACTH) produce some behavioral effects in animals and in humans. The present study was designed to investigate whether ACTH 4—9 interferes with the effects of antidepressants: fluoxetine (FLU), fluvoxamine (FOX), selegiline (SEL) or dopamine agonists: piribedil (PRB) or quinpirol (QPR) in forced swimming test and in open field in rats. ACTH 4—9 was given in a single dose (25, 50 or 100 μg/kg) or for 7 days (50 μg/kg/day), alone or together with antidepressants or dopamine agonists. It was shown that ACTH 4—9 alone did not influence the behavior of rats. However, when given in a single dose, ACTH 4—9 potentiated the antiimmobility effect of all antidepressants and dopamine agonists. ACTH 4—9 given for 7 days, facilitated only the effect of selegiline. The results suggest a functional interaction of ACTH 4—9 with serotonergic and dopaminergic brain mechanisms of drugs action.

Key words: *ACTH 4—9, fluoxetine, fluvoxamine, selegiline, piribedil, quinpirol, forced swimming, open field.*

INTRODUCTION

A number of recent investigations have shown that ACTH or its fragments, particularly 4—10 or 4—9 sequence of ACTH (corresponding to Met-Glu-His-Phe-Arg-Trp) affect central nervous functions in animals (1—8) and humans (9—15).

ACTH and ACTH 4—9 are involved in some aspects of motivation, concentration, learning and memory processes (1, 16) and also in behavior related to fear in animals (3).

Behavioral effects of ACTH — related neuropeptides in humans have been labelled mainly with reference to attentional processes, but also to general arousal, activation, mood and sensory sensitivity (9, 13, 17).

ACTH or ACTH 4—9 seems to be useful in the treatment of panic disorders (11), seizures (6, 18, 19) or in neurophaties induced by cisplatin or by diabetes, because of neurotrophic activity of this hormone (4, 5, 20, 21).

Recently some studies are undertaken on the usefulness of ACTH or its fragments in the treatment of schizophrenia with depression (22).

In our previous investigations the potentiation of amitryptyline, imipramine and nomifensine effects by ACTH was observed in rats in forced swimming test (23), which is a behavioral model sensitive to antidepressant treatment (24, 25).

The present study was designed to investigate whether ACTH 4—9, a centrally active peptide fragment of ACTH with little corticotropic activity, interferes with three other antidepressants: fluoxetine (FOX), fluvoxamine (FVA) or selegiline (SEL) in forced swimming rats. Interaction of ACTH 4—9 with two dopamine agonists: piribedil (PRB) and quinpirol (QPR) was also examined.

MATERIALS AND METHODS

Studies were conducted on male Wistar rats weighing 180—220 g at the beginning of the experiment. Rats were housed 8 per cage under standard laboratory condition, with free access to granular standard diet and tap water. All experiments were performed between 9 a.m. and 1 p.m.

Forced swimming test (24, 25)

Rats were individually plunged in vertical cylinders containing 20 cm depth of water at 25°C for 15 min. 24 h or seven days later and 1 h after the last drug treatment, the rats were replaced into the same cylinders again and the total duration of immobility was measured for 5 min.

Exploratory activity (26)

The number of squares traversed or rearings were scored for 3 min in the "open field" apparatus (divided into 25 equal squares), using photoelectric counter. Testing was always performed 55 min after the single or last injection of the drug and 5 min before the forced swimming test.

The drugs used were: fluoxetine hydrochloride (Lilly, France), fluvoxamine maleate (Cédex, France), selegiline hydrochloride (Chinoin, Hungary), piribedil methanosulfonate (Euthérapie, France), quinpirole hydrochloride (Lilly, USA) and [Met(0)^4, D-Lys^8, Phe^9] adrenocorticotropic hormone fragment 4—9 (ACTH 4—9, Sigma, USA). All drugs, as water solutions or suspensions in 3% solution of Tween 80, were administrated ip. ACTH 4—9 was dissolved in distilled water and injected sc.

All data are presented as means ±SEM. The statistical significance of the differences between groups was assessed by a one — way ANOVA followed by the Dunnet's test.

RESULTS

Influence of ACTH 4—9 on the effect of antidepressant drugs in the forced swimming test

a) Acute treatment

ACTH 4—9 administrated sc in a single dose of 50 μg/kg or 100 μg/kg did not change the duration of the immobility in the forced swimming rats (*Fig. 1, 2*).

FOX in a single dose of 5, 10 or 20 mg/kg and FVA 10, 25 or 50 mg/kg given alone did not influence the time of immobility (*Fig. 1*). On the contrary SEL injected in a single dose of 7.5 or 10 mg/kg significantly decreased the duration of immobility by 20% or 43% respectively (*Fig. 2*).

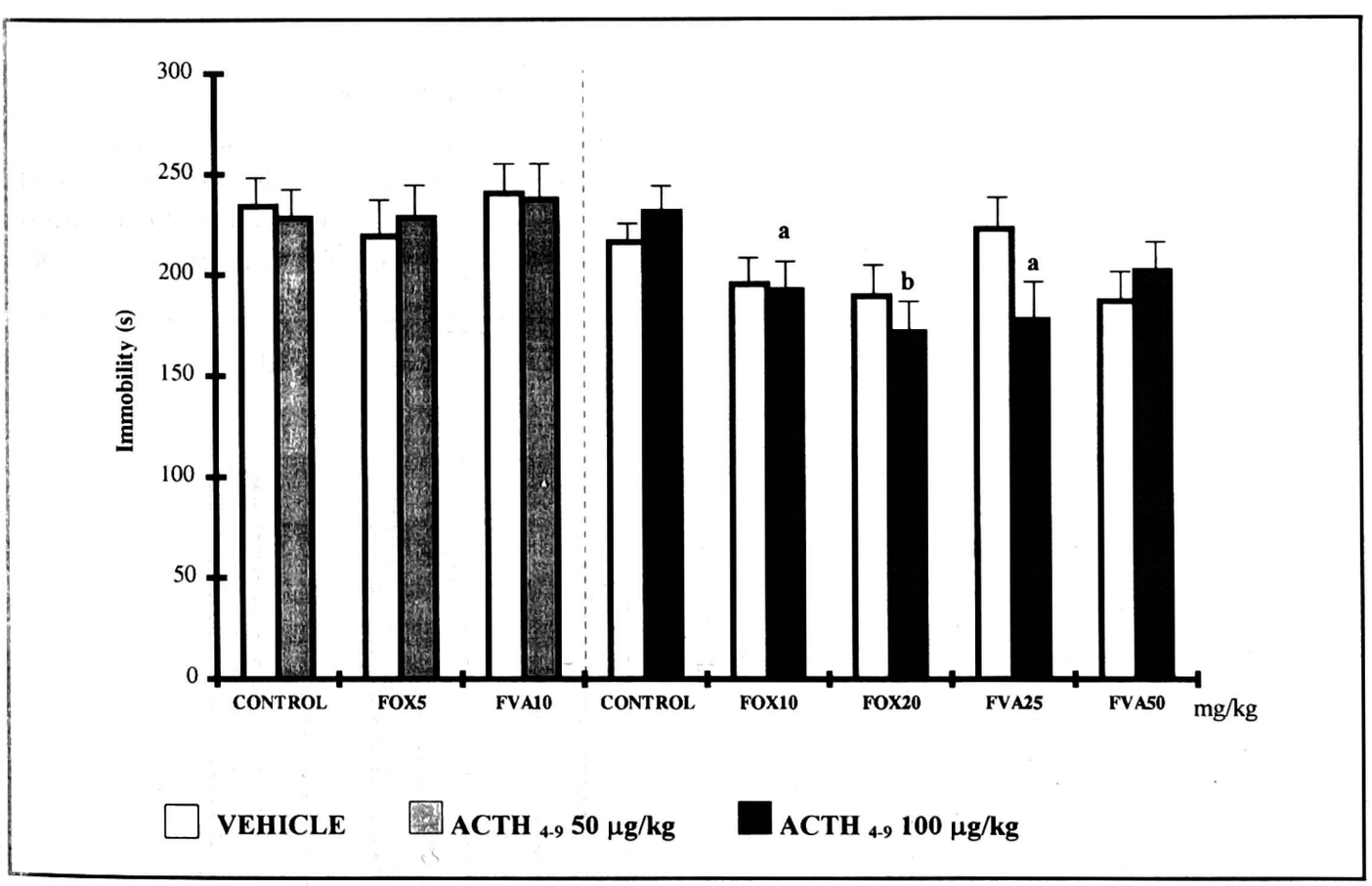

Fig. 1. The influence of ACTH 4—9 given in a single dose on the effect of fluoxetine (FOX) or fluvoxamine (FVA) in the forced swimming rats. ACTH 4—9 was injected sc simultaneously with FOX or FVA given ip. 1 h before the test. a — $p < 0.05$, b — $p < 0.01$ vs resp. control. N = 8.

After joint treatment with ACTH 4—9 in a dose of 100 μg/kg, but not 50 μg/kg, and FOX 10 or 20 mg/kg or FVA 25 mg/kg, significant reduction of immobility time was observed (*Fig. 1*). SEL (7.5 or 10 mg/kg) co-administered with ACTH 4—9 100 μg/kg reduced the time of immobility more potently

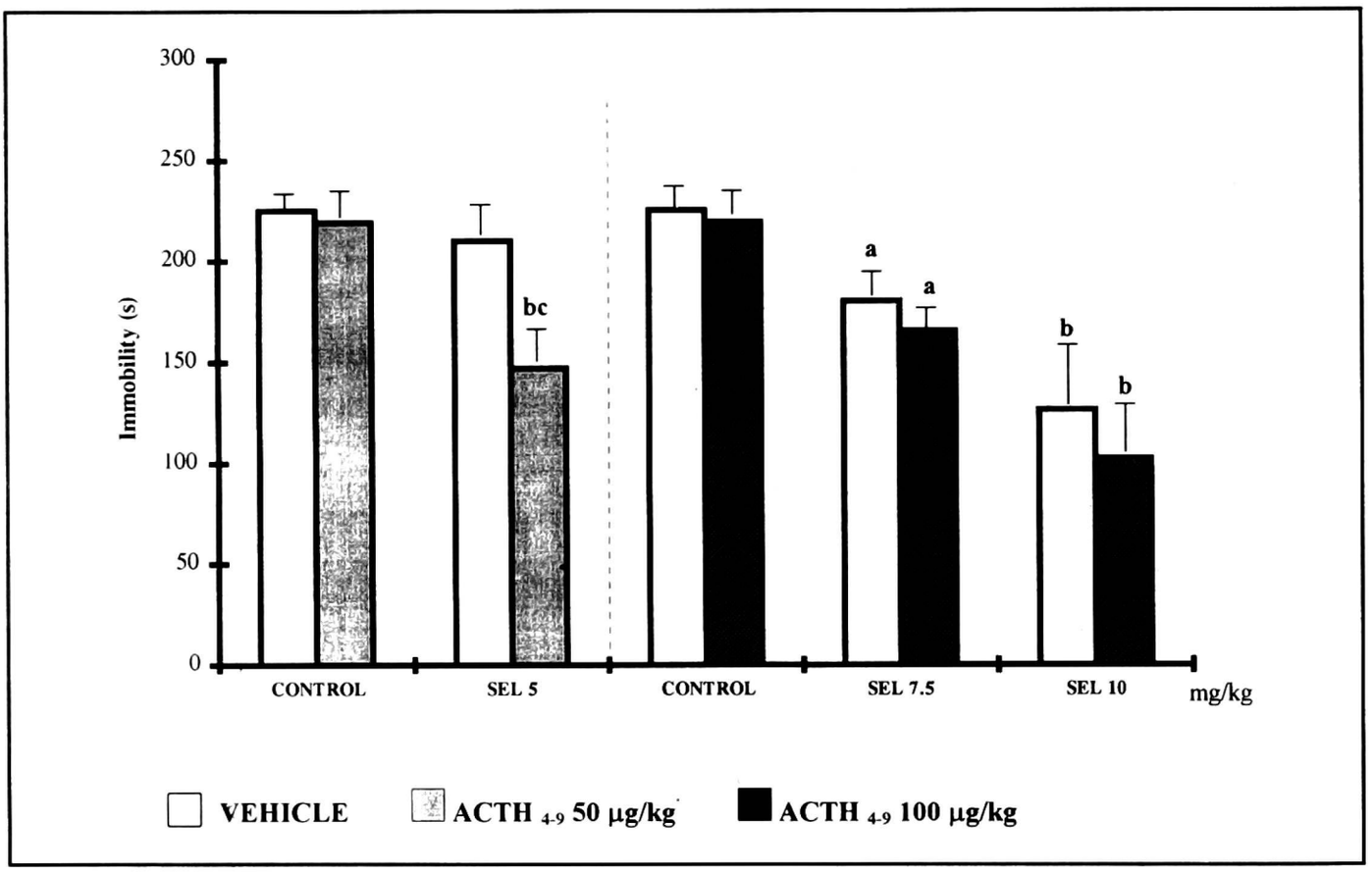

Fig. 2. The influence of ACTH 4—9 given in a single dose on the effect of selegiline (SEL) in the forced swimming rats. ACTH 4—9 was injected sc simultaneously with SEL given ip. 1 h before the test. a — $p < 0.05$, b — $p < 0.001$ vs resp. control, c — $p < 0.05$ vs SEL alone. N = 8.

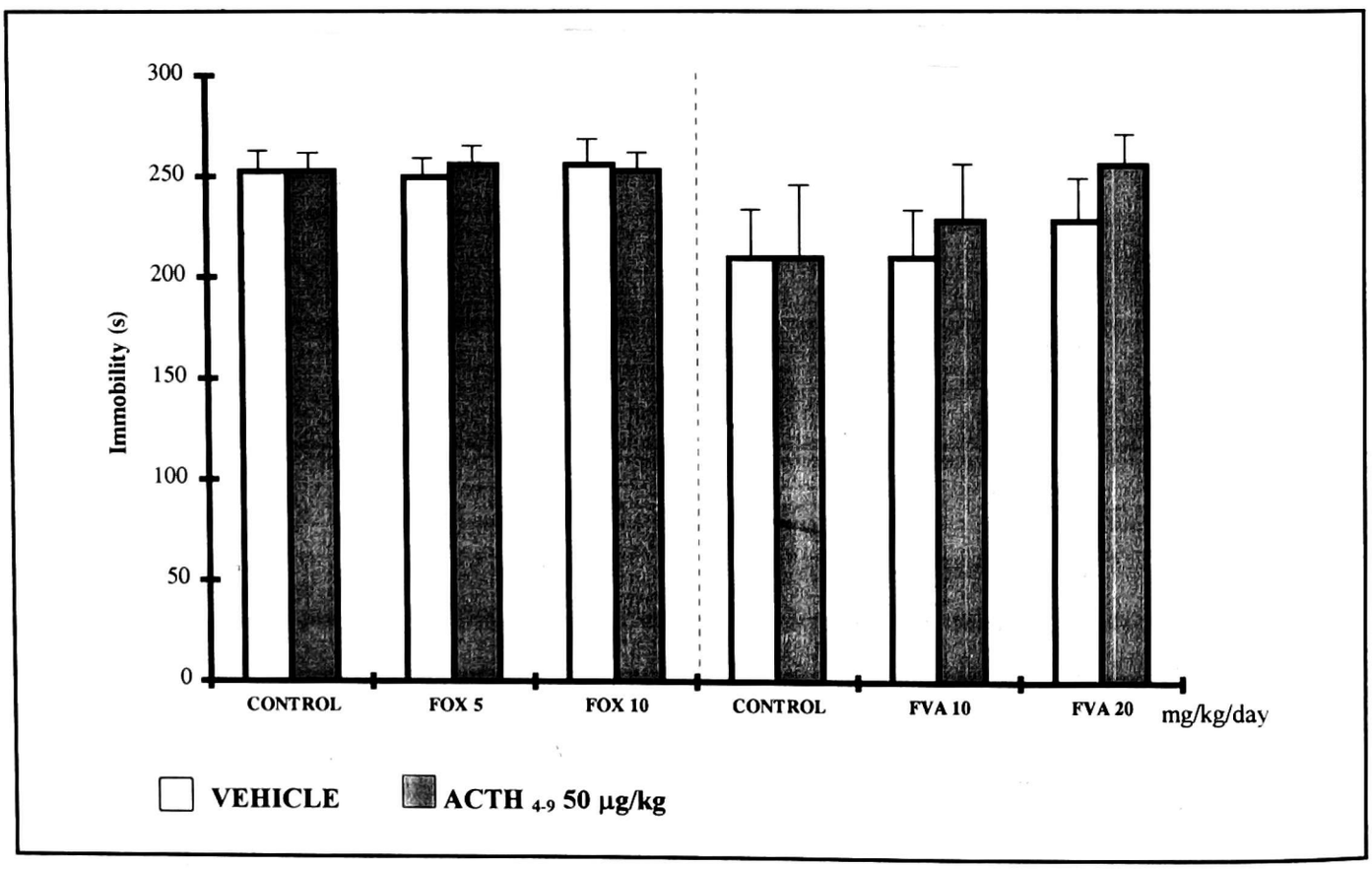

Fig. 3. The effect of prolonged treatment with ACTH 4—9 on the effect of fluoxetine (FOX) or fluvoxamine (FVA) in the forced swimming rats. ACTH 4—9 was injected sc simultaneously with FOX or FVA given ip. Both drugs were administrated for 7 days. The test was conducted 1 h after the last dose of the drug. N = 8.

(by 27% or 56% resp.). SEL given in a dose of 5 mg/kg (inactive alone) together with ACTH 4—9 50 μg/kg decreased significantly the duration of immobility — by 27% (*Fig. 2*).

b) Prolonged treatment

ACTH 4—9 injected sc in a dose of 50 μg/kg/day for 7 consecutive days, alone or together with FOX (5 or 10 mg/kg/day) or FVA (10 or 20 mg/kg/day) did not influence the duration of immobility in the swimming rats (*Fig. 3*).

On the contrary, in the rats receiving SEL (2.5 or 5 mg/kg/day) for 7 days, alone or together with ACTH 4—9, significant and even more potent, than after SEL alone, reduction of immobility time was observed (*Fig. 4*).

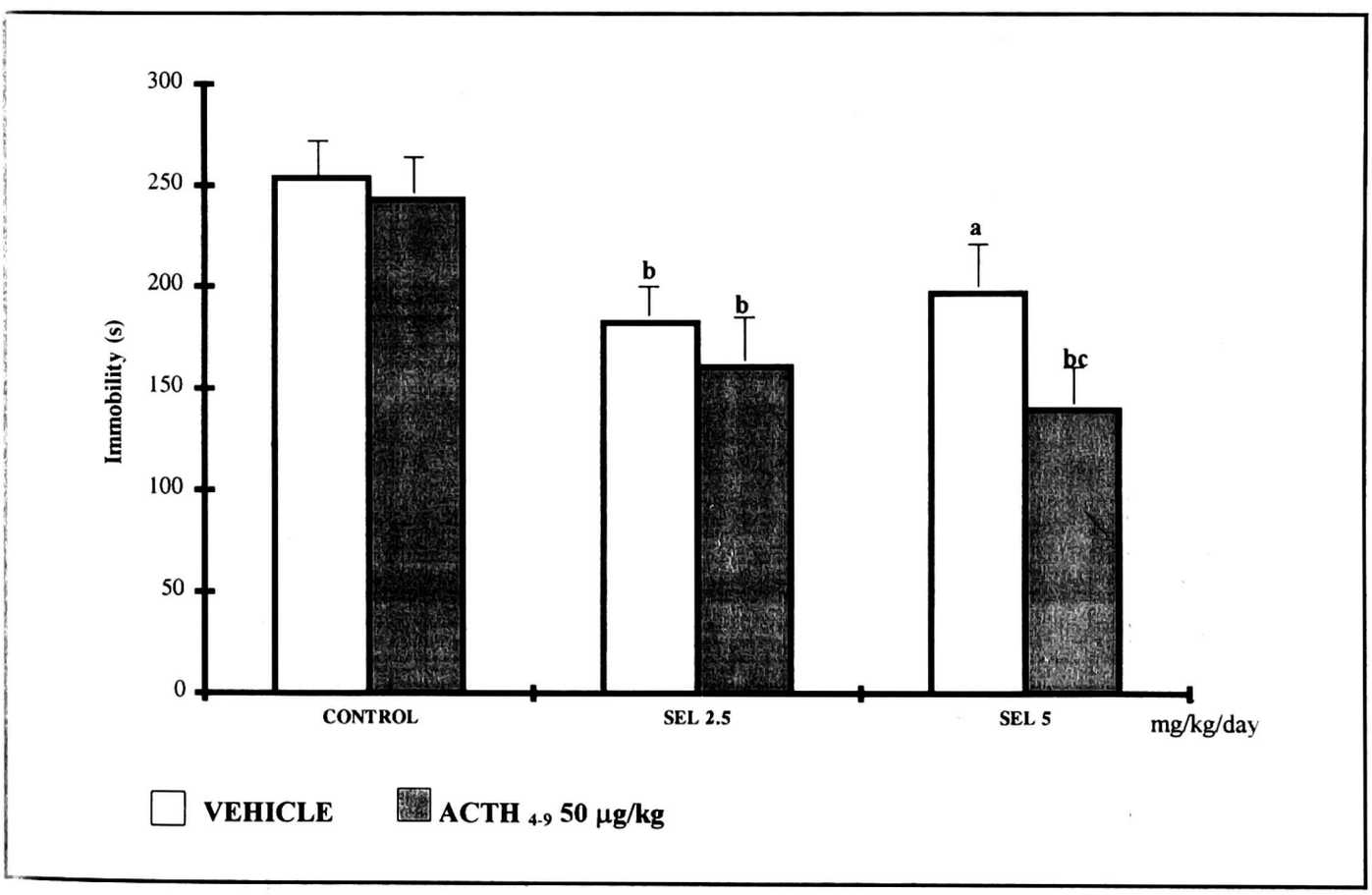

Fig. 4. The effect of prolonged treatment with ACTH 4—9 on the effect of selegiline (SEL) in the forced swimming rats. ACTH 4—9 was injected sc simultaneously with SEL given ip. Both drugs were administrated for 7 days. The test was conducted 1 h after the last dose of the drug. a — $p < 0.05$, b — $p < 0.001$, c — $p < 0.05$ vs SEL alone. $N = 8$.

Influence of ACTH 4—9 on the effect of dopamine agonists in the forced swimming test

a) Acute treatment

PRB administrated alone in a single dose of 25 or 50 mg/kg did not change the time of immobility in control rats. On the contrary, QPR given in a single

dose of 0.25 or 0.5 mg/kg reduced significantly the duration of immobility by about 40% (*Fig. 5*).

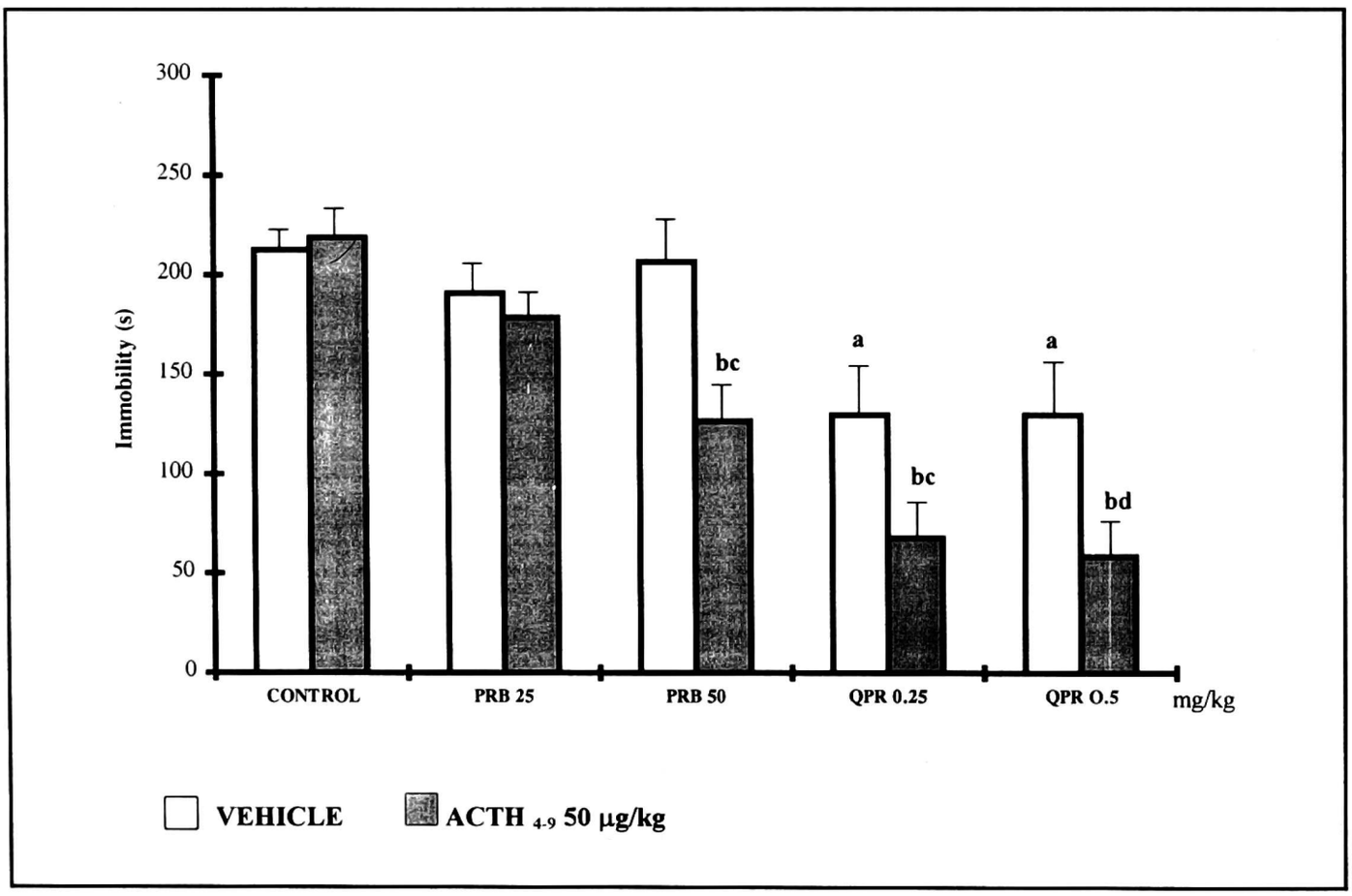

Fig. 5. The influence of ACTH 4—9 given in a single dose on the effect of piribedil (PRB) or quinpirol (QPR) in the forced swimming rats. ACTH 4—9 was injected sc simultaneously with PRB or QPR given ip. 1 h before the test. a — $p < 0.05$, b — $p < 0.001$ vs resp. control, c — $p < 0.05$, d — $p < 0.01$ vs resp. drug alone. N = 8.

After co-administration of ACTH 4—9 (50 µg/kg) with PRB (50 mg/kg) the significant reduction (by 40%) of immobility time was noted (*Fig. 5*). In rats receiving joint treatment of ACTH 4—9 and QPR (0.25 and 0.5 mg/kg) significant potentiation of QPR effect was observed (immobility time was shorter by 50% and 55% resp.) (*Fig. 5*).

b) Prolonged treatment

In rats receiving PRB or QPR for 7 days, in both doses used, alone or together with ACTH 4—9 50 µg/kg/day the similar reduction (by 20—30%) of immobility time was observed (*Fig. 6*).

Influence of ACTH 4—9 on the effect of antidepressant drugs and dopamine agonists in open field test

ACTH 4—9 administered in a single dose (25, 50 or 100 μg/kg) or for 7 days (50 μg/kg/day) did not change the exploratory activity of rats (*Tab. 1, 2*).

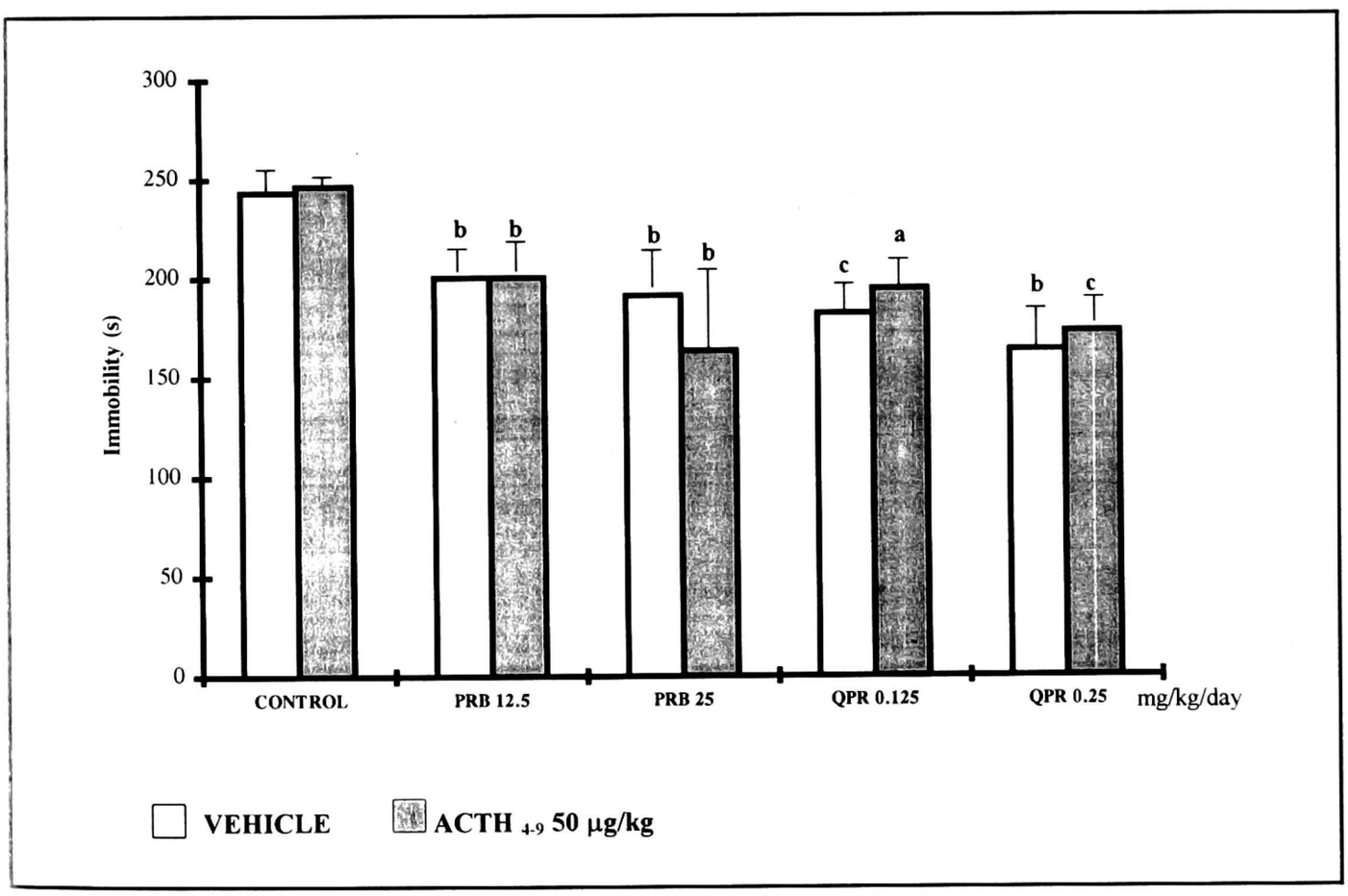

Fig. 6. The effect of prolonged treatment with ACTH 4—9 on the effect of piribedil (PRB) or quinpirol (QPR) in the forced swimming rats. ACTH 4—9 was injected sc simultaneously with PRB or QPR given ip. Both drugs were administrated for 7 days. The test was conducted 1 h after the last dose of the drug. a — $p < 0.05$, b — $p < 0.001$, c — $p < 0.05$ vs resp. control. N = 8.

Antidepressant drugs (but not dopamine agonists) given in a single, especially higher, dose reduced the motility of rats. ACTH 4—9 did not modify this effect of antidepressants. ACTH 4—9 induced hyper-motility of rats, receiving concomitantly QPR 0.5 mg/kg.

FOX given for 7 days (10 mg/kg/day) decreased but QPR (in both doses) increased the exploratory activity. ACTH 4—9 given for 7 days did not influence the effect of antidepressants and PRB, but it normalised the motility of rats receiving concomitantly QPR (in both doses) for 7 days (*Tab. 1, 2*).

Table 1. Effects of combined treatment with ACTH (4—9) and antidepressants or dopamine agonists, given in a single dose, on exploratory activity

Treatment — mg/kg (for ACTH (4—9) — μg/kg)	Mean number ±SEM	
	Squares traversed	Rearings
Solvent	23.8±4.4	6.5±1.0
ACTH (4—9) 25	20.8±1.6	4.3±1.0
ACTH (4—9) 50	18.8±4.7	4.6±1.1
ACTH (4—9) 50	15.6±2.6	4.9±0.7
FOX 10	10.7±4.1*	4.3±1.3
FOX 20	7.2±1.5*	2.0±0.8*
ACTH (4—9) 50+FOX 10	7.9±1.7	0.6±0.3*
ACTH (4—9) 50+FOX 20	7.1±0.7	2.5±1.2
FVA 25	12.5±3.3	2.3±0.6*
FVA 50	3.9±1.3*	0.8±0.4*
ACTH (4—9) 50+FVA 25	8.0±2.4	2.1±0.8
ACTH (4—9) 50+FVA 50	9.3±2.8	3.0±0.6
SEL 7.5	12.3±4.3	5.0±1.6
SEL 10	12.4±2.5*	3.5±0.6*
ACTH (4—9) 50+SEL 7.5	15.0±3.0	4.6±1.2
ACTH (4—9) 50+SEL 10	18.3±2.5	3.5±0.6
PRB 25	23.0±3.1	3.4±0.7
PRB 50	28.8±2.9	5.3±1.4
ACTH (4—9) 50+PRB 25	25.6±4.1	3.8±1.0
ACTH (4—9) 50+PRB 50	28.0±3.9	3.6±0.9
QPR 0.25	19.1±1.8	7.2±0.9
QPR 0.5	18.7±2.1	5.1±0.7
ACTH (4—9) 50+QPR 0.25	20.4±1.6	6.8±1.4
ACTH (4—9) 50+QPR 0.5	35.8±2.9*	6.7±1.4

ACTH 4-9 was injected sc simultaneously with other drugs given ip 55 min before the test. Asterisk indicates significant change ($p<0.05$) as compared to the control (solvent or drug alone receiving group) value. N = 8 rats.

Table 2. Effects of combined treatment with ACTH (4—9) and antidepressants or dopamine agonists, given for 7 days, on exploratory activity

Treatment — mg/kg/day (for ACTH (4—9) — μg/kg)	Mean number ±SEM	
	Squares traversed	Rearings
Solvent	16.8±3.3	3.8±0.8
ACTH (4—9) 50	12.0±2.0	3.8±0.9
FOX 5	7.5±1.7	2.5±0.9
FOX 10	4.7±0.8*	0.8±0.3*
ACTH (4—9) 50+FOX 5	13.9±3.4	2.2±0.7
ACTH (4—9) 50+FOX 10	8.6±2.3	3.0±1.2
FVA 10	10.5±2.8	4.1±1.4
FVA 20	10.0±1.7	1.7±0.8
ACTH (4—9) 50+FVA 10	8.7±2.2	1.7±0.7
ACTH (4—9) 50+FVA 20	15.0±4.2	2.4±0.6
SEL 2.5	17.4±3.0	6.1±1.5
SEL 5	10.3±2.1	2.9±0.8
ACTH (4—9) 50+SEL 2.5	10.9±1.5	3.7±0.3
ACTH (4—9) 50+SEL 5	14.1±4.9	3.1±0.6
PRB 12.5	10.7±2.8	4.9±0.9
PRB 25	12.6±1.6	4.1±0.6
ACTH (4—9) 50+PRB 12.5	8.0±0.9	5.1±1.7
ACTH (4—9) 50+PRB 25	12.7±2.0	4.7±1.4
QPR 0.125	27.5±2.4*	4.9±0.9
QPR 0.25	26.0±3.0*	6.2±0.7*
ACTH (4—9) 50+QPR 0.125	14.2±2.6*	3.1±0.6
ACTH (4—9) 50+QPR 0.25	13.8±2.7*	3.6±0.6*

ACTH 4-9 was injected sc simultaneously with other drugs given ip for 7 days. The test was conducted 55 min after the last dose of the drug. For other explanations see *Table 1.*

DISCUSSION

The present results demonstrate that ACTH 4—9 given alone, in a single dose of 50 or 100 μg/kg, or for 7 days in a dose of 50 μg/kg/day, did not influence the behavior of rats in the forced swimming or in open field test.

Only SEL and QPR administered in a single dose but also SEL, QPR and PRB given for 7 days reduced significantly the immobility time in a swim test. ACTH 4—9 (in single dose) facilitated the antiimmobility effect of all antidepressants: FOX, FVA and SEL and dopamine agonists: PRB and QPR. The potentiation of activating effect of SEL by ACTH 4—9 was also observed when both drugs were given for 7 days.

The present results correspond with our previous and with other studies where it was shown that ACTH potentiated the activating effect of tricyclic antidepressants in Porsolt's forced swimming test in rats (23, 27). The results of the present study indicate that ACTH 4—9 may also increase in this test the activity of non-tricyclic antidepressants: FOX, FVA or SEL and also the effect of dopamine agonists: PRB and QPR. Interaction between ACTH 4—9 and all drugs used seems to be specific, unrelated to locomotor activity level, as it was observed in open field test.

Evidence exists that ACTH 4—9, which is ACTH fragment centrally active, (but not stimulating the release of adrenal hormones) may have anxiolytic activity (3, 11) and other behavioral effects in animals (1, 3, 16) and in humans (9, 13, 16, 22). The anxiolytic effect seems to be also involved in the interaction of ACTH 4—9 with antidepressants and dopaminomimetics, activating the behavior in forced swimming rats, observed in this study.

On the other hand, ACTH-related neuropeptides act as a blocking of suppressive functions, during habituation or selective attention for instance (9). Disinhibitory effects mediated by structures of the limbic system may be responsible for improvement of sustained attention following the administration of ACTH-related peptides (1, 9).

Moreover, the effects of ACTH peptides, acute or after subchronical application, on diverse aspects of mood as depressiveness, feelings of competence and sociability have been investigated in human (1, 28, 29). Applying ACTH 4—9 analogue, ORG 2766, a decrease of anxiety and depression and an increase of behavior related to communication and sociability in mentally retarded subjects (9, 28—30) was reported.

In the swimming test in rats we were not able to observe the similarity between ACTH 4—9 and antidepressant drugs action. However ACTH 4—9 administrated in a single dose or in the case of SEL given also for 7 days, potentiated the activity of antidepressants and dopaminomimetics in the forced swimming rats.

Various peptide hormones have been described as capable of influencing the number and function of brain neurotransmitter receptors (1, 2). Co-administration of ACTH but also ACTH 4—9 and desipramine has been reported to accelerate onset of the attenuation of α_2-adrenoceptors response in nucleus accumbens (31), β-adrenoceptors in the frontal cortex (2, 32) and dopamine receptors in the mesolimbic area (33).

The mechanism of interaction observed in this study seems to be related to any changes induced by ACTH 4—9 in the sensitivity of brain catecholamine or serotonine receptors participated in the activating effect of investigated drugs.

In this and in our previous and other studies the interaction of ACTH or its fragments with DA mechanisms of antidepressants seems to be the most visible (12, 23, 33). There are also proofs that ACTH or its fragments could activate dopamine receptors (34, 35) or modulate their sensitivity (33, 36—38) in the different structures of brain.

The role of the own anxiolytic and/or disinhibiting effect of ACTH 4—9 and other mechanisms related with observed effects can not be also excluded.

REFERENCES

1. De Wied D, Jolles J. Neuropeptides derived from pro-opiocortin: behavioral, physiological and neurochmical effects. *Physiol Rev* 1982; 62: 976—1059.
2. Enna SJ, Duman RS. β-adrenergic receptor regulation and antidepressants: the influence of adrenocorticotropin. *J Neural Transm* 1983; 57: 297—307.
3. File SE. Contrasting effects of ORG 2766 and alpha-MSH on social and exploratory behavior in the rat. *Peptides* 1981; 2: 255—260.
4. Murry R, Mc Lane JA, Gruener G. Effects of ORG 2766, a neurotrophic ACTH 4—9 analogue, in neuroblastoma cells. *Ann NY Acad Sci* 1993; 679: 270—275.
5. Sporel-Özakat RE, Edwards PhM, Van der Hoop RG, Gispen WH. An ACTH — (4—9) analogue, Org 2766, improves recovery from acrylamide neuropathy in rats. *Eur J Pharmacol* 1990; 186: 181—187.
6. Wamil A, Croiset G, Kleinrok Z, de Wied D. Beneficial effects of ACTH 4—10 on pilocarpine induced seizures. *Neurosci Res Commun* 1989; 4: 109—116.
7. Hock FJ, Gerhards HJ, Wiemer G, Usinger P, Geiger R. Learning and memory processes of an ACTH 4—9 analog (Ebiratiole; HOE 427) in mice and rats. *Peptides* 1988; 9: 575—581.
8. Greven HM, De Wied D. The influence of peptides derived from ACTH on performance. Structure activity studies. In: Drug effects on neuroendocrine regulation, E. Zimmerman, WH Gipsen, BH Marks, D De Wied (eds). *Prog Brain Res* 1973, 39, pp. 429—442.
9. Born J, Fehm HL, Voight KH. ACTH and attention in humans: a review. *Neuropsychobiology* 1986; 15: 165—186.
10. Born J, Kern W, Pietrowsky R, Sitting W, Fehm HL. Fragments of ACTH affect electrophysiological signs of controlled stimulus processing in humans. *Psychopharmacology* 1989; 99: 439—444.
11. Den Boer JA, Westenberg HGM, Mastenbroek B, van Ree JM. The ACTH (4—9) analog Org 2766 in panic disorder: a preliminary study. *Psychopharmacol Bull* 1989; 25: 204—208.

12. Dornbush RL, Shapiro B, Freedman AM. Effects of an ACTH short chain neuropeptide in man. *Am J Psychiat* 1981; 138: 962—964.
13. Gaillard AWK. ACTH analogs and human performance. In: Endogenous Peptides and Learning and Memory Processes, J Martinez, R Jensen, RB Messing, H Rigter, JL Mc Gaugh (eds). New York, Academic Press, 1981, pp. 181—196.
14. Nicholson AN, Stone BM, Jones SJ. Studies on the possible central effects in man of a neuropeptide (ACTH 4—9 analogue). *Eur J Clin Pharmacol* 1984; 27: 561—565.
15. Bohus B. Effects of ACTH-like neuropeptides on animal behavior and man. *Pharmacology* 1979; 18: 113—122.
16. Spruijt BM. Org 2766 enhances social attention in aging rats: a longitudinal study. *Neurobiol Aging* 1992; 13: 153—158.
17. Beckwith BE, Sandman CA. Central nervous system and peripheral effects of ACTH, MSH and related neuropeptides. *Peptides* 1982; 3: 411—420.
18. Pantella K, Bachman DS, Sandman CA. Trial of an ACTH (4—9) analog in children with intractable seizures. *Neuropediatrics* 1982; 13: 59—62.
19. Willing RP, Lagenstein I. Use of ACTH fragments in children with infantile spasms. *Neuropediatrics* 1982; 13: 55—58.
20. Strand FL, Rose KJ, King JA, Segarra AC, Zuccarell LA. ACTH modulation of nerve development and regeneration. *Prof Neurobiol* 1989; 33: 45—85.
21. Wolterink G, Vos PE, van Ree JM. ACTH neuropeptides and recovery after brain damage. *Eur Neuropsychopharmacol* 1993; 3: 198—199.
22. Pużyński S. Drugs used in the experimental treatment of psychiatric disorders. In Experimental and Clinical Psychopharmacology (in Polish), W Kostowski, S Pużyński (eds). Warszawa, PZWL, 1986, pp. 347—383.
23. Pietrasiewicz T, Żebrowska-Łupina I. Studies on the interaction of antidepressant drugs with adrenocorticotropic hormone or prednisone in rats. *Pol J Pharmacol* 1996; 48: 145—152.
24. Porsolt RD, Anton G, Blavet N, Jalfre M. Behavioural despair in rats: a new model sensitive to antidepressant treatments. *Eur J Pharmacol* 1978; 47: 379—381.
25. Porsolt RD, Bertin A, Blaved N, Deniel M, Jalfre M. Immobility induced by forced swimming in rats: effects of agents which modify central catecholamine and serotonin activity. *Eur J Pharmacol* 1979; 57: 201—210.
26. Fontenay M, Le Cornec J, Zaczyńska M, Debarle MC, Simon P, Boissier JR. Probléms posés par l'utilisation de trois testes de comportement du rat pour l'étude des medicament psychotropes. J *Pharmacol* (*Paris*) 1970; 1: 243—254.
27. Volosin M, Cancela LM, Molina VA. Influence of adrenocorticotropic hormone on the behaviour in the swim test of rats treated chronically with desipramine. *J Pharm Pharmacol* 1988; 40: 74—76.
28. Ferris SH, Reisberg B, Gershon S. Neuropeptide effects on cognition in the elderly. In Poon, Aging in the 1980's: Selected Contemporary Issues in the Psychology of Aging. American Psychological Association. Washington, DC, 1980.
29. Sandman CA, Walker BB, Lawton CA. An analog of MSH/ACTH 4—9 enhances interpersonal and environmental awareness in mentaly retarded adults. *Peptides* 1980; 1: 109—114.
30. D'Elia G, Frederiksen SO, Bengtsson BO. Early visual information processing in depressive patients treated wit ORG 2766 (an ACTH 4—9 analogue). *Neuropsychobiology* 1985; 13: 63—68.
31. Volosin M, Cancella LM, Molina VA. ACTH accelerates the attenuation of alpha 2 — adrenoceptors response in nucleus accumbens following chronic despiramine. *Meth Find Exp Clin Pharmacol* 1992; 14: 189—192.
32. Kendall DA, Duman R, Slopis J, Enna SJ. Influence of adrenocorticotropic hormone and yohimbine on antidepressant-induced declines in rat brain neurotransmitter receptor binding and function. *J Pharmacol Exp Ther* 1982; 222: 566—571.

33. Volosin M, Cancella LM, Laino C, Massci M, Molina VA. Adrenocorticotropic hormone influences the development of adaptive changes in dopamine autoreceptors induced by chronic administration of desipramine. *Neuropharmacology* 1991; 7: 719—725.
34. Wolterink G, Van Zanten E, Kamsteeg H, Radhakishun FS, Van Ree JM. Functional recovery after destruction of dopamine systems in the nucleus accumbens of rats. II. Facilitation by the ACTH (4—9) analog ORG 2766. *Brain Res* 1990; 507: 101—108.
35. Wiegant VM, Cools AR, Gispen WH. ACTH-induced excessive grooming involves brain dopamine. *Eur J Pharmacol* 1977; 41: 343—345.
36. Bazzani C, Nardi MG, Ferrante F, Bertolini A, Guarini S. Dopamine D_1 receptors are involved in the ACTH-induced reversal of hemorrhagic shock. *Eur J Pharmacol* 1994; 253: 303—306.
37. Versteeg DHG, De Crom MPG, Mulder AH. ACTH (1—24) and α-MSH antagonize dopamine receptor-mediated inhibition of striatal dopamine and acetylcholine release. *Life Sci* 1986; 38: 835—840.
38. Telegdy G, Kadar T, Balazs M. Involvement of neurotransmitter and neuropeptides in behavioural action of some neurohormones. *Pol J Pharmacol* Pharm 1990; 42: 537—547.

Received: January 24, 1997
Accepted: April 4, 1997

Author's address: I. Żebrowska-Łupina, Department of Clinical Pharmacology, Medical Academy, ul Jaczewskiego 8, 20-090 Lublin, Poland.