Pharmacology Biochemistry and Behavior, Vol. 64, No. 1, pp. 1–5, 1999

0091-3057/99 $–see front matter

PII S0091-3057(98)00243-3

Preliminary Evidence for an Involvement of the Cholinergic System in the Sedative Effects of Rolipram in Rats

JORDI S. SILVESTRE,[1] ANDRÉS G. FERNÁNDEZ[2] AND JOSÉ M. PALACIOS

Department of Pharmacology, Research Centre, Almirall-Prodesfarma, Cardener 68-74, Barcelona 08024, Spain

Received 22 August 1997; Revised 6 November 1998; Accepted 11 December 1998

SILVESTRE, J. S., A. G. FERNÁNDEZ AND J. M. PALACIOS. *Preliminary evidence for an involvement of the cholinergic system in the sedative effects of rolipram in rats.* PHARMACOL BIOCHEM BEHAV **64**(1) 1–5, 1999.—Rolipram is a specific cAMP phosphodiesterase type 4 (PDE4) inhibitor in the brain, which induces an increase in the intracellular levels of cAMP. Rolipram produces characteristic alterations in animal behavior, which have been suggested to be mediated mainly through an intracellular mechanism involving an increase in cAMP. However, specific mechanisms mediating the sedative effects of this compound have not yet been investigated. Because several lines of evidence indicate that the acetylcholine neural system may be involved in some effects of PDE4 inhibitors, the aim of this study was to elucidate whether the neurotransmitter acetylcholine is involved in the sedative effects induced by rolipram. The present study assessed the motor effects of rolipram in an exploratory behavioral test, the open field, in Wistar rats. The results show that rolipram (0.1–3.0 mg/kg SC) induced potent and dose-dependent hypoactivity, decreasing both locomotion and rearing. Physostigmine (0.03–0.3 mg/kg SC) potentiated a subeffective dose of rolipram (0.03 mg/kg SC), resulting in strong sedation, similar to that following higher doses of either rolipram or physostigmine alone, whereas the reduction in locomotor activity induced by rolipram (0.3 mg/kg SC) was completely reversed by scopolamine (0.03–0.3 mg/kg SC). These data provide preliminary evidence suggesting the involvement of the acetylcholinergic system in the sedative effects of rolipram. © 1999 Elsevier Science Inc.

Rolipram Acetylcholine Physostigmine Scopolamine Locomotor activity Sedation Open field Behavior Rat

ROLIPRAM is a selective phosphodiesterase type 4 (PDE4) inhibitor that preferentially inhibits cyclic adenosine 3′,5′-monophosphate (cAMP) phosphodiesterase in the brain, thus enhancing the intracellular availability of cerebral cAMP in the absence of direct stimulation of neurotransmitter receptors (21,22). The potency of rolipram and other PDE inhibitors for inhibition of rat brain cAMP phosphodiesterase in vitro is correlated with their efficacy in inducing a peculiar behavioral syndrome in rats characterized by hypoactivity, head twitches, forepaw shaking, grooming, and hypothermia (27). Indeed, these effects are mimicked by systemic administration of cAMP precursors, but not by precursors of cGMP (27). Hence, it has been suggested that the characteristic behavioral changes reflect the enhanced availability of cAMP in the brain induced in vivo by these PDE inhibitors. Interestingly, studies with tritiated rolipram have demonstrated a high-affinity site for the drug in rat brain membranes (22), and suggest the possibility that both the PDE4 catalytic activity site and the high-affinity binding site for rolipram are located in the same PDE4 enzyme (26). Although it has not yet been completely established whether the catalytic site and the binding site mediate the same pharmacological effect (20,26), a close relationship between behavioral responses and in vivo binding has been described for rolipram and other PDE4 inhibitors (20).

Rolipram exhibits antidepressant properties both in animals (16,29) and in humans (2,4), which have been proposed to be mediated by a presynaptic monoaminergic turnover-increasing effect resulting in enhanced postsynaptic stimula-

[1]Requests for reprints should be addressed to Dr. J. Silvestre, Prous Science, S.A., Provença 388, 08025 Barcelona, Spain.
[2]Present address: Laboratorios Salvat, S.A., Gall 30, 08950 Esplugues de Llobregat, Barcelona, Spain.

tion (12,29), as well as by an action beyond postsynaptic monoamine receptors and independent of the availability of endogenous monoamines (30,31). In addition, recent studies have suggested a heterogeneity for the effects of rolipram (9) whereby its different effects could be mediated by different mechanisms. Furthermore, an effect of rolipram on the synthesis or release of neurotransmitters such as noradrenaline (12,29) or acetylcholine (1) has been demonstrated.

The involvement of the neurotransmitter acetylcholine in the pharmacology of rolipram is an interesting possibility, and there is both direct and indirect experimental evidence supporting this suggestion (1,5,8,13). PDE4 inhibitors have some cognition-enhancing properties, and they have even been proposed for the treatment of milder forms or the early stages of dementia (13,14). Also, it has prudently been suggested that these compounds may produce cognition-enhancing actions via an enhancement of acetylcholine or dopamine release (13). Indeed, it has been demonstrated that rolipram is able to attenuate scopolamine-induced impairments in learning and memory (5,8), as well as to reverse experimentally induced amnesia and to enhance memory and learning in rodents (8,18), and it appears that a elevation in cAMP levels alone would be unable to completely explain these effects (5,8).

Thus, both behavioral (5,8) and biochemical data (1) suggest that acetylcholine could be involved in the behavioral effects of rolipram. It should be noted that other PDE4 inhibitors, such as denbufylline, are able to increase acetylcholine release in rat striatum in vivo (10), and in vitro studies have shown that analogues of cAMP are able to potentiate acetylcholine responses (6). In our laboratory it was observed that high doses of rolipram (10–100 mg/kg PO) produce cholinergic-like effects such as salivation, hypothermia, lacrimation, trembling, and diarrhoea in rodents (unpublished data).

Thus, although the behavioral effects of rolipram have been suggested to be mediated mainly by its ability to increase intracellular cAMP levels, both direct (1,6,10,12) and indirect (5,8,9,18) evidence strongly suggests the involvement of specific neurotransmitters, for example, acetylcholine, in some of the behavioral effects of rolipram and other PDE4 inhibitors.

The hypoactivity and sedative effects of rolipram are well documented. Acutely administered rolipram consistently decreases both locomotor activity and rearing in rats and mice (7,9,25,27,28). However, the specific mechanisms mediating these effects have not yet been reported or evaluated. Considering that an interaction between acetylcholine and dopamine appears to be involved in locomotor activity (3,15,24), this study was carried out to investigate the possible role of the cholinergic system in the sedative effects of rolipram. The effects of rolipram were assessed using an exploratory behavioral test, the open field (OF) in rats, and the role of acetylcholine was examined using the cholinesterase inhibitor physostigmine and the nonselective muscarinic receptor antagonist scopolamine.

METHOD

Animals

Male Wistar rats (207.3 ± 3.4g, Janvier, France) were housed in groups of six in wire-mesh cages at 21–22°C with a 12-h light:dark cycle (lights on 06:30; off 18:30 h). The animals had access to food and water ad lib during the 5-day adaptation period before beginning the study. The experimental protocol was in compliance with the European Community Council Directive of 24 November 1986 (86/609/EEC) for care and use of laboratory animals.

Drugs

Rolipram (synthesized in the Medicinal Chemistry Department of Almirall-Prodesfarma) was suspended in a vehicle composed of 0.5% methylcellulose and 0.1% Tween-80 in distilled water (TwMc). Physostigmine sulfate (Sigma, St. Louis, MO) and scopolamine hydrobromide (Sigma) were dissolved in saline. All doses refer to free-base weights. All injections were administered subcutaneously (SC) at a volume of 1 ml/kg.

Apparatus

The OF apparatus was a white-walled circular open field, 81.5 cm in diameter and 33.5 cm high. The floor was made up of white plywood. A slight white fluorescent circular light was hung 120 cm above the center of the apparatus. The subjects were placed individually in the center of the OF and locomotor activity (total distance traveled) and rearing (frequency) were automatically scored for 5 min. The OF apparatus was placed in an isolated and sound-proofed room contiguous to the observation room, and cleaned with water after each trial to remove any trace of odor. The subjects' behavior was recorded with a video camera mounted vertically above the apparatus for automatic and simultaneous analysis by means of an image analyzer program (SMART, Letica, Spain). Each animal was tested once only.

Drug Administration Studies

Compounds were administered in single drug studies at the following doses: rolipram (0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg), physostigmine (0.03, 0.1, and 0.3 mg/kg) and scopolamine (0.03, 0.1, and 0.3 mg/kg). All drugs were administered 30 min prior to testing, independently tested, and compared with their respective control groups.

In the drug interaction studies, scopolamine (0.03, 0.1, and 0.3 mg/kg) was administered 10 min prior to rolipram (0.3 mg/kg), which was administered 30 min prior to testing, while physostigmine (0.03, 0.1, and 0.3 mg/kg) was administered 10 min before the injection of 0.03 mg/kg of rolipram. Rats were randomly allocated to the following groups: (a) saline + vehicle; (b) saline + rolipram (0.3 or 0.03 mg/kg); and (c) drug (different doses) + rolipram (0.3 or 0.03 mg/kg). All interaction studies were performed independently of each other.

Statistical Analysis

The Kolmogorov-Smirnov test was used to assess the normality of the data, and the Cochran and Bartlett tests to assess homogeneity of variance. An analysis of variance (MANOVA) with planned between-group contrasts was used to evaluate treatment effects. The nonparametric Mann-Whitney test was used to calculate *U*-values for individual comparisons when the variables did not present homogeneity of variance, or when normality was not evident. In addition, correlational analysis between locomotor activity and rearing was calculated using the Pearson correlation coefficient (two tailed). The level of significance was set at $p < 0.05$.

RESULTS

Rolipram at doses of 0.1, 0.3, 1.0, and 3.0 mg/kg produced a significant and dose-dependent decrease in locomotor activity in the OF test, $F(1, 36) = 8.15$, $p < 0.01$; $F(1, 36) = 79.26$, $p < 0.001$; $F(1, 36) = 160.60$, $p < 0.001$; and $F(1, 36) = 192.84$, $p < 0.001$, respectively, whereas no effect was observed at the lowest dose of 0.03 mg/kg (Table 1). All doses of rolipram tested

TABLE 1
EFFECTS OF ROLIPRAM, PHYSOSTIGMINE, AND SCOPOLAMINE ON LOCOMOTOR ACTIVITY AND REARING IN THE OF TEST

Treatment (mg/kg SC)	*n*	Locomotor Activity	Rearing
Vehicle	7	4110 ± 194	18.1 ± 1.6
Rolipram 0.03	7	3684 ± 178	9.2 ± 1.6‡
0.1	7	2991 ± 382†	5.3 ± 0.7‡
0.3	7	1534 ± 186‡	1.1 ± 0.4‡
1.0	7	1100 ± 222‡	0.5 ± 0.5‡
3.0	7	829 ± 133‡	0.3 ± 0.3‡
Saline	6	3809 ± 154	19.3 ± 2.3
Physostigmine			
0.03	6	4122 ± 299	18.6 ± 2.7
0.1	6	3264 ± 184	6.0 ± 0.9‡
0.3	6	956 ± 126‡	0.0 ± 0.0‡
Saline	6	3950 ± 201	16.2 ± 2.4
Scopolamine			
0.03	6	4362 ± 211	15.2 ± 1.5
0.1	6	5222 ± 338*	9.8 ± 1.9*
0.3	6	6684 ± 732†	8.3 ± 1.8*

Both locomotor activity (total distance traveled expressed in cm) and rearing (frequency) were automatically scored for 5 min in OF test. Results are expressed as means ± SEM. Significant differences calculated by MANOVA using planned contrasts or Mann–Whitney nonparametric test: *$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ compared to their respective control group.

(0.03–3.0 mg/kg) produced a significant and dose-dependent decrease in rearing, $F(1, 36) = 23.78$, $p < 0.001$; $F(1, 36) = 48.43$, $p < 0.001$; $F(1, 36) = 108.44$, $p < 0.001$; $F(1, 36) = 188.60$, $p < 0.001$; and $F(1, 36) = 192.31$, $p < 0.001$, respectively. On the basis of these data, doses of 0.3 and 0.03 mg/kg of rolipram were selected for subsequent experiments as effective and subeffective doses, respectively. Furthermore, a positive relationship between locomotor activity and rearing was found, $r(40) = 0.61$, $p < 0.0001$.

A significant decrease in locomotor activity was observed only after administration of the highest dose of physostigmine (0.3 mg/kg), $F(1, 20) = 99.7$, $p < 0.001$, whereas no effects on locomotor activity were detected at the lower doses of 0.03 and 0.1 mg/kg (Table 1). Physostigmine also significantly decreased rearing at doses of 0.1 and 0.3 mg/kg, $F(1, 20) = 26.3$, $p < 0.001$; and $F(1, 20) = 55.5$, $p < 0.001$, respectively, but no effect was detected at the lowest dose. Furthermore, a positive relationship between locomotor activity and rearing was also found, $r(22) = 0.59$, $p < 0.01$. In agreement with the previous rolipram dose–response experiment, rolipram administered at the locomotor activity subeffective dose of 0.03 mg/kg to vehicle-pretreated rats did not affect locomotor activity (Tables 1 and 2), although in this case and in contrast with the previous results, a decrease in rearing was not observed. In comparison to the saline + vehicle group, a decrease in both locomotor activity and rearing was observed over the whole dose range of physostigmine administered prior to the subeffective dose of rolipram (Table 2). Locomotor activity was also decreased with the previously subeffective dose of 0.1 mg/kg of physostigmine as well as with the dose of 0.3 mg/kg when compared to the rolipram group, $F(1, 28) = 14.64$, $p < 0.01$; and $F(1, 28) = 203.65$, $p < 0.001$, respectively. However, the effects of physostigmine + rolipram on rearing were also potentiated, although with a similar profile to those observed in the previous physostigmine experiment (Table 2).

On the other hand, scopolamine, at doses of 0.1 and 0.3 mg/kg, produced a significant and dose-dependent increase in locomotor activity, $F(1, 20) = 4.40$, $p < 0.05$, and $F(1, 20) = 20.33$, $p < 0.01$, respectively, whereas rearing was decreased at doses inducing hyperactivity, $F(1, 20) = 5.40$, $p < 0.05$, and $F(1, 20) = 5.72$, $p < 0.05$, respectively. The lowest dose of scopolamine (0.03 mg/kg) failed to have any significant effect on either locomotor activity or rearing (Table 1). In addition, a negative relationship between locomotor activity and rearing was detected, $r(22) = -0.45$, $p < 0.05$, when scopolamine was administered alone. In the drug interaction experiment (Table 2), in accordance with prior experiments, 0.3 mg/kg of rolipram after saline pretreatment decreased locomotor activity, $F(1, 35) = 61.18$, $p < 0.001$, an effect that was significantly reversed by pretreatment with scopolamine at doses of 0.03, 0.1,

TABLE 2
EFFECTS OF PHYSOSTIGMINE ON A SUBEFFECTIVE DOSE OF ROLIPRAM (0.03 mg/kg) AND EFFECTS OF SCOPOLAMINE ON SEDATIVE EFFECTS OF ROLIPRAM (0.3 mg/kg) ON LOCOMOTOR ACTIVITY AND REARING IN THE OF TEST

Treatment (mg/kg SC)	*n*	Locomotor Activity	Rearing
Saline + vehicle	8	4220 ± 152	18.3 ± 1.3
Saline + ROL 0.03	8	3882 ± 162	14.2 ± 0.9
Physostigmine 0.03 + ROL 0.03	8	3460 ± 175§	11.7 ± 1.8§
0.1 + ROL 0.03	8	3020 ± 189†#	8.3 ± 1.6*#
0.3 + ROL 0.03	8	668 ± 94‡#	0.0 ± 0.1‡#
Saline + vehicle	8	4219 ± 180	17.5 ± 1.4
Saline + ROL 0.3	8	1961 ± 123#	3.8 ± 1.1#
Scopolamine 0.03 + ROL 0.3	8	2975 ± 237†#	4.8 ± 0.9#
0.1 + ROL 0.3	8	3981 ± 247‡	7.1 ± 1.4*#
0.3 + ROL 0.3	8	4006 ± 210‡	3.1 ± 0.5#

Both locomotor activity (total distance traveled expressed in cm) and rearing were automatically scored for 5 min in OF test. Results are expressed as means ± SEM. Significant differences calculated by MANOVA using planned contrasts or Mann–Whitney nonparametric test: *$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ compared to saline + rolipram groups (saline + ROL); and §$p < 0.01$, #$p < 0.001$ compared to saline + vehicle groups.

and 0.3 mg/kg, $F(1, 28) = 11.68$, $p < 0.01$; $F(1, 28) = 47.56$, $p < 0.001$, and $F(1, 28) = 46.44$, $p < 0.001$, respectively. As previously observed, rearing was also decreased by 0.3 mg/kg of rolipram, $F(1, 35) = 70.99$, $p < 0.001$; in contrast to locomotor activity, prior administration of scopolamine did not significantly affect the decrease in rearing induced by rolipram (Table 2), although some reversal was observed at the intermediate dose of 0.1 mg/kg, $F(1, 28) = 4.66$, $p < 0.05$.

DISCUSSION

Rolipram displayed a clear sedative effect in the OF test, as illustrated by the consistent and dose-dependent decrease in both locomotor activity and rearing. Our results agree with previously published data on the sedative properties of rolipram in both rats and mice (7,9,25,27,28). Also, in accordance with previous studies (15,19,24), scopolamine increased while physostigmine decreased locomotor activity in a dose-dependent manner. Furthermore, our results show that physostigmine at subeffective doses interacts with subeffective dose of rolipram, resulting a potentiation of hypoactivity. On the other hand, coadministration of scopolamine at a subeffective dose partially reversed and at higher doses completely annulled the effects of rolipram on locomotor activity (Table 2); however, no potentiation of the effect on rearing was observed. This could, in part, be an expected finding because scopolamine-induced rearing reduction may be due to its characteristic pattern on locomotor activity observed by scopolamine in the present study, as shown by means of a statistically significant locomotor activity and rearing relationship ($r = -0.45$, $r = 0.61$, and $r = 0.59$ by scopolamine, rolipram, and physostigmine, respectively). Thus, the distinct nature of rearing reduction induced by either rolipram, via a general activity reduction, or scopolamine, via a substitution from locomotor activity, would in part explain that result.

The present results show that subeffective doses of physostigmine and scopolamine are able to potentiate and to reverse, respectively, a subeffective and a sedative dose of rolipram. Taken together, these data indicate an interaction for rolipram with agents exerting opposite effects on the cholinergic system, which suggests that rolipram may produce hypoactivity in rats at least partially through the enhancement of cholinergic transmission in the brain.

The involvement of acetylcholine in the effects of rolipram has previously been suggested because rolipram was able to attenuate scopolamine-induced impairments in learning and memory in rodents (5,8) as well as to enhance the tremolors-induced in mice by the muscarinic agonist oxotremorine (5). Egawa and co-workers (5) have recently suggested that these effects of rolipram might result from the indirect potentiation of various transmitters, including cholinergic and noradrenergic systems, by an increase in cAMP via inhibition of PDE4 (5). Thus, although the behavioral effects of rolipram are thought to be mediated mainly through an intracellular mechanism involving an increase in cAMP (27,31), an extracellular action of rolipram cannot be ruled out. It is worth noting that recent studies have suggested the heterogeneity of the effects of rolipram whereby the various behavioral symptoms could be mediated by different mechanisms; for example, rolipram failed to potentiate head twitches, sniffing, and grooming induced by methamphetamine, whereas methamphetamine-induced hyperactivity and rearing were dose dependently suppressed by rolipram (9). Interestingly, it has recently been shown that repeated treatment with rolipram increases striatal choline acetyltransferase (ChAT) activity and decreases hippocampal cholinesterase activity in young adult rats (1). This study also showed that repeated treatment with rolipram in older rats increased both presynaptic ChAT activity and postsynaptic M_1 muscarinic receptor binding in frontal cortex and hippocampus, which were lower than those observed in young adult control rats. Furthermore, Asanuma and co-workers (1) also reported the potential of rolipram for increasing hippocampal acetylcholine contents.

It is well known that dopamine is the major neurotransmitter involved in the regulation of locomotor activity. However, there is no evidence for a direct effect of rolipram on dopamine transmission. Behavioral studies demonstrated that amphetamine, an indirect dopamine agonist, and imipramine, a tricyclic antidepressant, were unable to substitute for rolipram in a drug discrimination paradigm (23). Moreover, it has been demonstrated that rolipram does not affect central serotonergic transmission in rats (17). Hence, neither dopamine nor serotonin appear to be directly involved in the actions of rolipram.

Our results agree with previous studies showing that systemic administration of scopolamine induces hyperactivity (19). Likewise, it has been shown that physostigmine decreases locomotor activity and reverses scopolamine-induced hyperactivity (15,24). It has been suggested that there is a tonic inhibition of locomotor activity mediated by cholinergic neurons, which is attenuated when cholinergic activity is blocked by muscarinic receptor antagonists such as scopolamine (15). Furthermore, because scopolamine-induced hyperactivity is blocked by dopamine D_1 and D_2 receptor antagonists (24), it is assumed that acetylcholine acting at muscarinic receptors exerts an inhibitory effect on dopaminergic neurotransmission in the striatum (4). Similarly, it has been proposed that the cholinergic system could be involved in the regulation of the impulse flow of dopamine neurones in the substantia nigra and the ventral tegmental area (32).

Because PDE4 inhibitors are able to increase cerebral acetylcholine levels (1) and enhance acetylcholine release (10) and synthesis (1) in the brain, it can be assumed that some of the pharmacological and behavioral effects of rolipram are mediated by this neurotransmitter. Moreover, because acetylcholine appears to interact with dopamine in the regulation of locomotor activity, it is suggested that rolipram-induced hypoactivity may result from an indirect positive action on the dopaminergic system via the potentiation of cholinergic transmission. Furthermore, autoradiography reveals high rolipram binding site densities in the rat brain, largely in structures of the limbic system as well as in striatum (11). Thus, the brain location of the rolipram binding site, together with neurochemical data, suggests again that rolipram may affect acetylcholine release and/or functionality, and that its hypoactivity-inducing effects are probably mediated through an inhibition of striatal dopamine release by acetylcholine.

In conclusion, our results indicate that a relationship may exist between rolipram and the cholinergic system because: (a) subeffective doses of physostigmine, when combined with a subeffective dose of rolipram, were able to produce a strong hypoactivity; and (b) scopolamine prevented the rolipram-induced hypoactivity. The present results are the first behavioral evidence that rolipram-induced hypoactivity in rats may be modulated by the cholinergic system. However, considering both the complex nature of PDE4 inhibition by rolipram, which can be expected to exert a broad spectrum of actions in the brain, and the limited number of compounds tested in the present study, it will be necessary to study a wide range of cholinergic receptor agonists and antagonists to define the role of acetylcholine in the behavioral effects of rolipram and other PDE4 inhibitors.

REFERENCES

1. Asanuma, M.; Ogawa, N.; Kondo, Y.; Hirata, H.; Mori, A.: Effects of repeated administration of rolipram, a cAMP-specific phosphodiesterase inhibitor, on acetylcholinergic indices in the aged rat brain. Arch. Gerontol. Geriatr. 16:191–198; 1993.
2. Bobon, D.; Breulet, M.; Gerard-Vandenhove, M.-A.; Guiot-Goffioul, F.; Plomteux G.; Sastre-y-Hernández, M.; Schratzer, M.; Troisfontaines, B.; von Frenckell, R.; Wachtel, H.: Is phosphodiesterase inhibition a new mechanism of antidepressant action?. Eur. Arch. Psychiatry Neurol. Sci. 238:2–6; 1988.
3. DeBelleroche, J.; Bradford, H. F.: Biochemical evidence for the presence of presynaptic receptors on dopaminergic terminals. Brain Res. 142:53–68; 1978.
4. Eckmann, F.; Fichte, K.; Meya, U.; Sastre-y-Hernández, M.: Rolipram in major depression: Results of a double-blind comparative study with amitriptyline. Curr. Ther. Res. 43:291–295; 1988.
5. Egawa, T.; Mishima, K.; Matsumoto, Y.; Iwasaki, K.; Fujiwara, M.: Rolipram and its optical isomers, phosphodiesterase 4 inhibitors, attenuated the scopolamine-induced impairments of learning and memory in rats. Jpn. J. Pharmacol. 75:275–281; 1997.
6. Fu, W. M.: Potentiation of acetylcholine responses in *Xenopus* embryonic muscle cells by dibutyryl cAMP. Pflugers Arch. 425: 439–445; 1993.
7. Griebel, G.; Misslin, R.; Vogel, E.; Bourguingnon, J.-J.: Behavioral effects of rolipram and structurally related compounds in mice: Behavioral sedation of cAMP phosphodiesterase inhibitors. Pharmacol. Biochem. Behav. 39:321–323; 1991.
8. Imanishi, T.; Sawa, A.; Ichumaru, Y.; Miyashiro, M.; Kato, S.; Yamamoto, T.; Ueki, S.: Ameliorating effects of rolipram on experimentally induced impairments of learning and memory in rodents. Eur. J. Pharmacol. 321:273–278; 1997.
9. Iyo, M. M. D.; Maeda, Y.; Inada, T.; Kitao, Y.; Sasaki, H.; Fukui, S.: The effects of a selective cAMP phosphodiesterase inhibitor, rolipram, on methamphetamine-induced behavior. Neuropsychopharmacology 13:33–39; 1995.
10. Katsura, M.; Kuriyama, K.: Effects of [1,3-di-n-butyl-7-(2-oxopropyl)-xanthine] denbufylline), a low Km phosphodiesterase inhibitor, on striatal acetylcholine release in the rat: Analysis using cerebral microdialysis. Jpn. J. Pharmacol. 54:441–446; 1990.
11. Kaulen, P.; Brüning, G.; Schneider, H. H.; Sarterm, M.; Baumgartenm, H. G.: Autoradiographic mapping of a selective cyclic adenosine monophosphate phosphodiesterase in rat brain with the antidepressant [^{3}H]rolipram. Brain Res. 503:229–245; 1989.
12. Kehr, W.; Debus, G.; Neumeister, R.: Effects of rolipram, a novel antidepressant on monoamine metabolism in rat brain. J. Neural. Transm. 63:1–12; 1985.
13. Nicholson, C. D.: Pharmacology of nootropics and metabolically active compounds in relation to their use in dementia. Psychopharmacology (Berlin) 101:147–159; 1990.
14. Nicholson, C. D.; Challis, R. A. J.; Shahid, M.: Differential modulation of tissue function and therapeutic potential of selective inhibitors of cyclic nucleotide phosphodiesterase isoenzymes. Trends Pharmacol. Sci. 12:19–27; 1991.
15. O'Neill, M. F.; Fernández, A. G.; Gristwood, R. W.; Palacios, J. M.: Mecamylamine reverses physostigmine-induced attenuation of scopolamine-induced hyperactivity. J. Neural Transm. 96:9–18; 1994.
16. Porsolt, R. D.; Lenägre, A.; McArthur, R. A.: Pharmacological models of depression. In: Animal models in psychopharmacology: Advances in pharmacological sciences. Basel: Birkhñuser Verlag; 1991:137–159.
17. Przegalinski, E.; Bigajska, K.; Lewandowska, A.: The influence of rolipram on the central serotonergic system. Pharmacopsychiatria 14:162–166; 1981.
18. Randt, C. T.; Judge, M. E.; Bonnet, K. A.; Quartermain, D.: Brain cyclic AMP and memory in mice. Pharmacol. Biochem. Behav. 17:677–680; 1982.
19. Sanberg, P. R.; Henault, M. A.; Hagenmeyer-Houser, S. H.; Russell, K. H.: The topography of amphetamine and scopolamine-induced hyperactivity: Toward an activity print. Behav. Neurosci. 101:131–133; 1987.
20. Schmiechen, R.; Schneider, H. H.; Wachtel, H.: Close correlation between behavioural response and binding in vivo for inhibitors of the rolipram-sensitive phosphodiesterase. Psychopharmacology (Berlin) 102:17–20; 1990.
21. Schneider, H. H.: Brain cAMP response to phosphodiesterase inhibitors in rats killed by microwave irradiation or decapitation. Biochem. Pharmacol. 33:1690–1693; 1984.
22. Schneider, H. H.; Schmiechen, R.; Brezinski, M.; Seidler, J.: Stereospecific binding of the antidepressant rolipram to brain protein structures. Eur. J. Pharmacol. 127:105–115; 1986.
23. Schneider, H. H.; Yamaguchi, M.; Andrews, J. S.; Stephens, D. N.: Discriminative stimulus properties of the stereoisomers of the phosphodiesterase inhibitor rolipram. Pharmacol. Biochem. Behav. 50:211–217; 1995.
24. Shannon, H. E.; Peters, S. C.: A comparison of the effects of cholinergic and dopaminergic agents on scopolamine-induced hyperactivity in mice. J. Pharmacol. Exp. Ther. 255:549–553; 1990.
25. Smith, D. F.: Effects of lithium and rolipram enantiomers on locomotor activity in inbred mice. Pharmacol. Toxicol. 66:142–145; 1990.
26. Torphy, T. J.; Stadel, J. M.; Burman, M.; Cieslinski, L. B.; McLaughlin, M. M.; White, J. R.; Livi, G. P.: Coexpression of human cAMP-specific phosphodiesterase activity and high affinity rolipram binding in yeast. J. Biol. Chem. 267:1798–1804; 1992.
27. Wachtel, H.: Characteristic behavioral alterations in rats induced by rolipram and other selective adenosine cyclic 3′,5′-monophosphate phosphodiesterase inhibitors. Psychopharmacology (Berlin) 77:309–316; 1982.
28. Wachtel, H.: Neurotropic effects of the optical isomers of the selective adenosine cyclic 3′,5′-monophosphate phosphodiesterase inhibitor rolipram in rats in-vivo. J. Pharm. Pharmacol. 35:440–444; 1983.
29. Wachtel, H.: Potential antidepressant activity of rolipram and other selective cyclic adenosine 3′,5′-monophosphate phosphodiesterase inhibitors. Neuropharmacology 22:267–272; 1983.
30. Wachtel, H.: The second-messenger dysbalance hypothesis of affective disorders. Pharmacopsychiatry 23:27–32; 1990.
31. Wachtel, H.; Schneider, H. H.: Rolipram, a novel antidepressant drug, reverses the hypothermia and hypokinesia of monoamine-depleted mice by an action beyond postsynaptic monoamine receptors. Neuropharmacology 25:1119–1126; 1986.
32. Yeomans, J. S.: Role of tegmental cholinergic neurons in dopaminergic activation, antimuscarinic psychosis and schizophrenia. Neuropsychopharmacology 12:3–16; 1995.