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Effects of antidepressants on phencyclidine-induced enhancement of immobility in a forced swimming test in mice

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Abstract

We have previously found that repeated phencyclidine (PCP) treatment enhances the immobility induced by forced swimming and suggested that this behavioral change could be used as a model of the negative symptoms, particularly depression, of schizophrenia. The present study attempted to examine the effects of antidepressants on the depressive states (immobility) induced by forced swimming in mice repeatedly treated with PCP, compared with those in mice repeatedly treated with saline. In mice repeatedly treated with saline, desipramine (5 and 10 mg/kg) and imipramine (5 and 10 mg/kg) significantly attenuated immobility, whereas mianserin (5–20 mg/kg) and clomipramine (10 and 50 mg/kg) had no affect. In mice repeatedly treated with PCP, the enhancing effect of PCP on immobility was attenuated by mianserin (5–20 mg/kg) at doses which did not have any effect in saline-treated mice, and by desipramine at higher doses (20 and 50 mg/kg). However, imipramine (5–20 mg/kg) and clomipramine (10–50 mg/kg) did not affect PCP-induced enhancement of immobility. In the biochemical study, the content of 5-hydroxyindoleacetic acid (5-HIAA) and the 5-HIAA/5-hydroxytryptamine (5-HT) ratio in the prefrontal cortex in mice repeatedly treated with PCP, but not with saline, following the forced swimming test were significantly increased, compared with those in the corresponding control mice (which did not perform the test). The present findings suggest that the depressive states induced by the forced swimming in mice repeatedly treated with PCP are less sensitive to acute treatment with tricyclic antidepressants, and this may be due to increase in 5-HT turnover. Antidepressants such as mianserin, which have the 5-HT_2 receptor antagonist properties, may be useful for the treatment of negative symptoms of schizophrenia.

Keywords: Phencyclidine; Antidepressant; Schizophrenia, negative symptom; Depression; 5-HT (5-hydroxytryptamine, serotonin); Forced swimming test; (Mouse)

1. Introduction

Schizophrenic patients show symptoms that are regarded as positive (e.g., hallucinations, delusions, disordered thinking and paranoia) (Andreasen, 1990; Dickerson et al., 1991; Peralta et al., 1992) and negative (e.g., apathy, manifested as deficits in social interaction, emotional expression, and motivation) (Kukla and Gold, 1991; Troisi et al., 1991; Fenton and McGlashan, 1992). Schizophrenic patients also exhibit depression (Barnes et al., 1989), and it is difficult to distinguish between depressive symptoms and the negative symptoms of schizophrenia. It has been reported that antidepressants have been used in stable schizophrenics and schizoaffective patients who continued to show negative symptoms (Lindenmayer, 1995; Siris et al., 1991). However, earlier research suggests that when an antidepressant is the only medication given, some patients experience an increase in delusion, hallucinations, and disorganization (Baldessarini and Willmuth, 1968; Siris et al., 1978). Thus, the association between depressive features and certain negative schizophrenic symptoms remains unclear.

In humans, phencyclidine (PCP)-induced psychosis manifests with both positive and negative symptoms (Javitt, 1987; Hurlbut, 1991; Javitt and Zukin, 1991; Volkow and Fowler, 1992), as well as depressive symptoms. Thus, PCP may provide a good animal model of schizophrenia that

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includes positive-like and negative-like symptoms. We have previously found that repeated PCP treatment enhances immobility in a forced swimming test in mice and that this effect is reduced by atypical antipsychotics, risperidone and clozapine, but not by a typical antipsychotic, haloperidol. This is consistent with clinical findings, suggesting that this model may be useful as an animal model of the negative symptoms of schizophrenia (Noda et al., 1995).

Forced swimming, regarded as acute inescapable stress, produces immobility in rodents (Porsolt et al., 1977a,b, 1978). This immobility appears to be selectively sensitive to several antidepressants and to be reversed by acute antidepressant treatment, suggesting that this behavioral change is depression (Porsolt et al., 1977a,b, 1978).

To determine whether the depressive states in mice repeatedly treated with PCP are similar to those in mice repeatedly treated with saline, the present study attempted to examine the effects of antidepressants on the forced swimming-induced immobility in mice repeatedly treated with PCP, compared with those in mice repeatedly treated with saline. In addition, 5-hydroxytryptamine (5-HT) metabolism in the brain following the forced swimming was assessed, since Borsini (1995) has suggested that the 5-HTergic neuronal system plays an important role in depression.

2. Materials and methods

All experiments were performed in accordance with the Guidelines for Animal Experiments of Nagoya University School of Medicine.

2.1. Animals and environments

Male mice of the *ddY* strain (Japan SLC, Shizuoka, Japan), weighing 25–27 g at the beginning of the experiments were used. The animals were housed in plastic cages and were kept in a regulated environment (23 ± 1°C, 50 ± 5% humidity), with a 12/12 h light-dark cycle (light on at 8:00 a.m.). Food (CE2, Clea Japan, Tokyo, Japan) and tap water were available ad libitum.

2.2. Drugs

The following compounds were purchased from commercial sources: desipramine hydrochloride (Sigma, St. Louis, MO, USA), clomipramine hydrochloride (Sigma), imipramine hydrochloride (Sigma), and mianserin hydrochloride (Funakoshi, Tokyo, Japan). Phencyclidine (1-(1-phenylcyclohexyl) piperidine hydrochloride; PCP) was synthesized by us. All compounds were dissolved in a 0.9% saline or distilled water solution.

Other agents were obtained from standard commercial sources.

2.3. Forced swimming test

2.3.1. First measurement of immobility

On the 1st day, mice were individually placed in a transparent glass cylinder (19 cm high, 14.5 cm in diameter), which contained water at about 25°C to a depth of about 15 cm, and forced to swim for 3 min. The duration of immobility (immobility time) was measured (the first measurement), with a SCANET MV-10 AQ apparatus (Toyo Sangyo Co., Toyama, Japan). The mice were matched according to this first measurement of immobility, and then divided into various treatment groups.

2.3.2. Drug treatment

On the 2nd day, drug treatment was commenced and thereafter, saline or PCP (10 mg/kg s.c.) was administered once a day for 14 days according to our previous report (Noda et al., 1995).

2.3.3. Second measurement of immobility

On the 16th day (24–27 h after the last administration of PCP or saline), each mouse was placed in water again for 3 min, and the immobility time was recorded (the second measurement of immobility). Desipramine, imipramine, clomipramine, and mianserin were orally administered 1 h before this second measurement was taken.

Control animals received the vehicle only.

2.4. Measurement of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) contents

Animals were killed by decapitation immediately after the forced swimming test. The brain was then rapidly removed and the prefrontal cortex dissected out on an ice-cold plate. Each tissue sample was quickly frozen and stored in a deep freezer at −80°C until assayed.

The contents of 5-HT and 5-HIAA were determined using high-performance liquid chromatography with electrochemical detector according to a modification of the method of Nitta et al. (1992). Each frozen tissue sample was weighed, then homogenized with an ultrasonic cell disrupter (160 W, Model UCD-200TM, Cosmo Bio, Tokyo, Japan) in 350 μl of 0.2 M perchloric acid for the tissue sample containing isoproterenol (internal standard). The homogenate was placed in ice for 30 min and then centrifuged at $18\,500 \times g$ for 15 min at 4°C. The supernatant was mixed with 1 M sodium acetate to adjust the pH to 3.0 and then injected into a liquid chromatography system equipped with a reversed-phase ODS column (4.6×150 mm, Eicompak MA-5 ODS (diameter of stationary phase grains; 5 μm), Eicom, Kyoto, Japan) and an electrochemical detector (Model ECD-100, Eicom). The column temperature was maintained at 25°C and the detector potential was set at +750 mV. The mobile phase was 0.1 M citric acid and 0.1 M sodium acetate, pH 3.9, containing 14% methanol, 160 mg/l sodium-*l*-octanesulfonate and 5 mg/l EDTA: the flow rate was 1 ml/min.

2.5. Statistical analysis

Statistical differences among values for individual groups were determined with the Dunnett multiple comparisons test (behavioral experiment) and with analysis of variance (ANOVA) followed by the Dunnett multiple comparisons test (biochemical experiment).

3. Results

3.1. Effects of antidepressants on the forced swimming-induced immobility in mice repeatedly treated with saline

The administration of mianserin (5–20 mg/kg p.o.) and clomipramine (10 and 50 mg/kg p.o.) 1 h before the second measurement of immobility in saline-treated mice, had no effect (Fig. 1). However, desipramine (5 and 10 mg/kg p.o.) and imipramine (5 and 10 mg/kg p.o.) significantly reduced immobility time (Fig. 1).

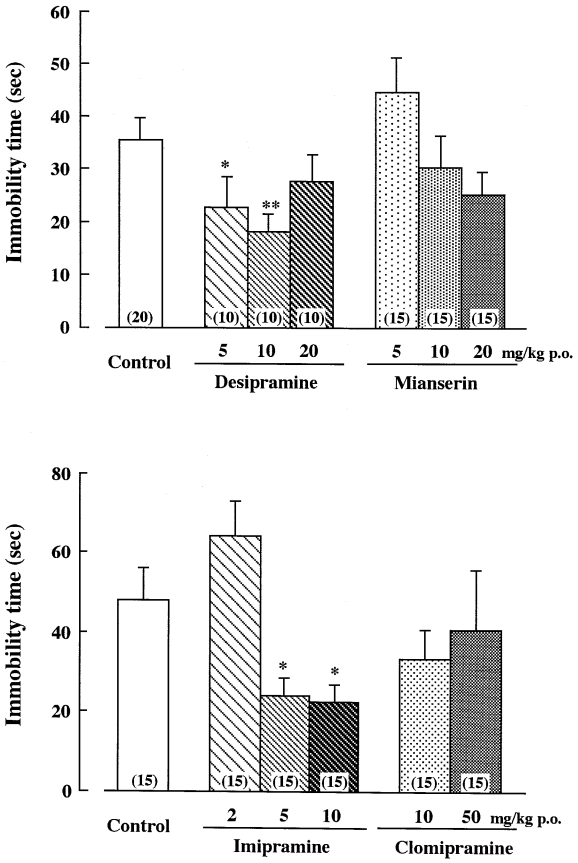

Fig. 1. Effects of desipramine, mianserin, imipramine and clomipramine on forced swimming-induced immobility in mice. In the repeated saline-treated mice, desipramine (5–20 mg/kg), mianserin (5–20 mg/kg), imipramine (2–10 mg/kg) and clomipramine (10 and 50 mg/kg) were administered orally 1 h before the second measurement of immobility. The animals then performed the post-test. Numbers in parentheses show the number of animals tested. * $P < 0.05$, ** $P < 0.01$ vs. control group.

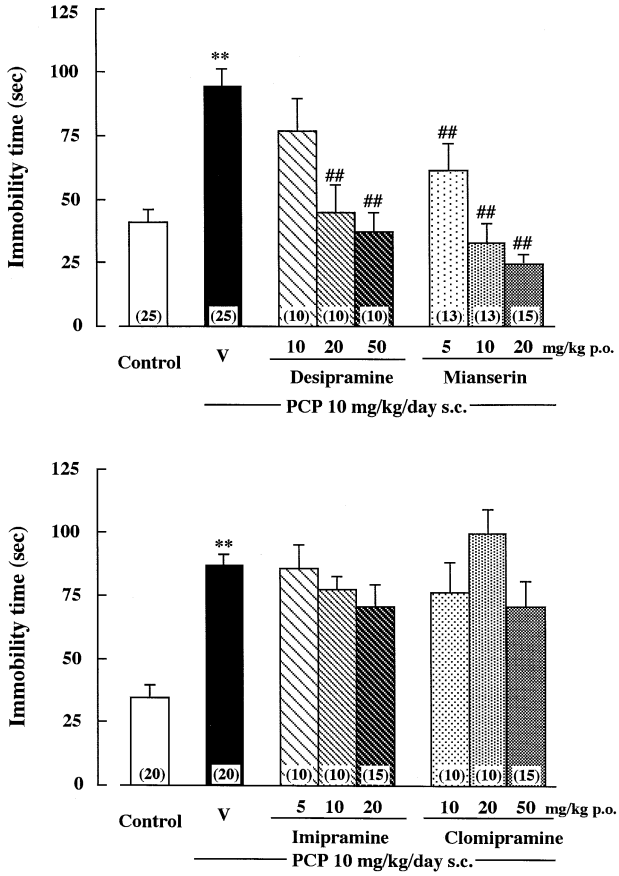

Fig. 2. Effects of desipramine, mianserin, imipramine, and clomipramine on the PCP-induced enhancement of immobility in mice. In the repeated PCP-treated mice, desipramine (10–50 mg/kg), mianserin (5–20 mg/kg), imipramine (5–20 mg/kg) and clomipramine (10–50 mg/kg) were administered orally 1 h before the second measurement of immobility. The animals then performed the post-test. V: vehicle. Numbers in parentheses show the number of animals tested. ** $P < 0.01$ vs. control group. ## $P < 0.01$ vs. repeated PCP-treated group.

3.2. Effects of antidepressants on the PCP-induced enhancement of immobility in the forced swimming test in mice

In mice repeatedly treated with PCP, immobility time was significantly prolonged (Fig. 2). When such mice received mianserin (5–20 mg/kg p.o.) 1 h before the second measurement of immobility, the enhanced effect of PCP on immobility was significantly attenuated at doses which did not have any effect in the saline-treated mice (Figs. 1 and 2). Desipramine also attenuated the enhancing effect of PCP, but the minimal effective dose of desipramine was over 4 times higher than that in mice repeatedly treated with saline.

On the other hand, imipramine (5–20 mg/kg) and clomipramine (10–50 mg/kg) did not attenuate the effect of PCP (Fig. 2).

Table 1
Changes in 5-HT and 5-HIAA contents in the prefrontal cortex of mice repeatedly treated with saline and PCP

Treatment	*n*	5-HT [a]	5-HIAA [a]	5-HIAA/5-HT ratio
Non-forced swimming control				
Repeated saline	8	344.3 ± 16.1	443.3 ± 11.3	1.30 ± 0.05
Repeated PCP	8	295.6 ± 48.9	383.5 ± 57.2	1.32 ± 0.03
Forced swimming				
Repeated saline	6	315.6 ± 33.9	361.1 ± 48.6	1.17 ± 0.14
Repeated PCP	6	295.6 ± 21.8	558.1 ± 41.6 [b]	1.93 ± 0.15 [c]

The contents of 5-HT and 5-HIAA ([a] ng/g wet tissue) were determined with a high-performance liquid chromatography system with an electrochemical detector, as described in the text. Control mice were not given the forced swimming test. [b] $P < 0.05$, [c] $P < 0.01$ vs. the corresponding control mice.

3.3. Changes in 5-HT and 5-HIAA contents

The contents of 5-HT and 5-HIAA in the prefrontal cortex of mice repeatedly treated with saline and PCP following the forced swimming test are shown in Table 1. The content of 5-HIAA ($F(3,24) = 3.7175$, $P < 0.05$) and the 5-HIAA/5-HT ratio ($F(3,24) = 11.613$, $P < 0.01$) were significantly increased by the forced swimming in mice repeatedly treated with PCP, but not with saline, compared with those in the corresponding control mice (which did not perform the test).

4. Discussion

Since acute treatment with many antidepressants reduces forced swimming-induced immobility, the immobility has been proposed as an animal model of depression. Thus, it is commonly used as a screening method for antidepressants (Porsolt et al., 1977a,b, 1978). Our results, which support those of previous studies (Porsolt et al., 1977a, 1978), indicate that desipramine, a noradrenaline reuptake inhibitor, and imipramine, a noradrenaline and 5-HT reuptake inhibitor, attenuated the forced swimming-induced immobility in mice repeatedly treated with saline. However, clomipramine, a 5-HT reuptake inhibitor, and mianserin, a 5-HT_2 and α_2-adrenoceptor antagonist, both clinically effective antidepressants, failed to do so. The inconsistent results obtained for clomipramine and mianserin are somewhat unclear. However, there is some evidence that the immobility is sensitive to agents which modify the activity of central catecholaminergic neuronal systems (e.g., desipramine or imipramine) but is relatively insensitive to agents which act primarily on central 5-HTergic neuronal systems (e.g., mianserin or clomipramine) (Danysz et al., 1988). It has been reported that mianserin shows antidepressant activity via 5-HT_2 receptor antagonism (Hand et al., 1991), rather than a blockade of α_2-adrenoceptors (Elliott et al., 1983), and is not active in the forced swimming test (Maj et al., 1992; Nixon et al., 1994). Thus, the present results obtained in saline-treated mice suggest that our procedure would be less suitable as a screening test for clomipramine or mianserin.

PCP induces a psychotomimetic state that closely resembles schizophrenia; PCP psychosis, unlike amphetamine psychosis, incorporates both the positive and negative symptoms of schizophrenia (Contreras et al., 1986; Sanger and Joly, 1991; Javitt and Zukin, 1991). We have previously reported that the immobility in the forced swimming test is enhanced by repeated, but not by single, treatment with PCP (10 mg/kg for 14 days), suggesting that this behavioral change could be used as a model of the negative symptoms, particularly the depression, of schizophrenia (Noda et al., 1995). In the present study, immobility was significantly enhanced in mice repeatedly treated with PCP in agreement with our previous report (Noda et al., 1995). It is unlikely that the enhancing effect of PCP on the immobility in the forced swimming test was due to motor dysfunction, such as decreased locomotor activity and ataxia, since we have already found that the repeated PCP treatment did not affect locomotor activity under the same treatment conditions as those used for the forced swimming test (Noda et al., 1995). Further, this effect of PCP was observed over 24 h after the final injection of PCP, and was well maintained for 21 days after the withdrawal of the drug (Noda et al., 1995). These findings therefore indicate that the enhancing effect of PCP on the immobility was not due to an acute effect of PCP, such as the induction of motor dysfunction.

PCP has been reported to interact with many neurotransmitters, including dopamine and 5-HT (Javitt and Zukin, 1991). Further, PCP, as well as dizocilpine, is also known to interact with a PCP binding site within the NMDA ionophore receptor complex (Johnson et al., 1987). In animals, PCP induces a characteristic behavioral syndrome, with hyperlocomotion and stereotyped behaviors, which is thought to result, at least in part, from an inhibition of dopamine reuptake or, to a lesser extent, from a stimulation of dopamine release. In contrast to the enhancing effect of PCP on the immobility, repeated methamphetamine treatment under the same treatment conditions of PCP failed to modify the forced swimming-induced immobility in mice, and haloperidol, a dopamine D_2 receptor antagonist, failed to attenuate this effect of PCP (Noda et al., 1995). Thus, it is unlikely that this effect of PCP on the immobility is due to overstimulation of dopaminergic systems.

It has been suggested that a disturbance in the balance of 5-HT- and dopamine-mediated neurotransmission might underlie schizophrenia (Meltzer, 1989); increased 5-HTergic activity relative to dopaminergic activity might lead to negative symptoms while the converse might contribute to positive symptoms. This hypothesis is based, in part, on the evidence that 5-HT_2 receptor antagonists such as ritanserin (Duinkerke et al., 1993) and mianserin (Mizuki et al., 1992) reduce negative symptoms. These clinical findings were consistent with our previous and present results that the enhancing effect of PCP on the immobility in the forced swimming test is attenuated by ritanserin, risperidone or clozapine, which have 5-HT_2 receptor antagonist properties (Noda et al., 1995) and by mianserin at the doses which did not have any effect on immobility in mice repeatedly treated with saline. The ameliorating effect of mianserin in this model would reflect its clinical effectiveness and may be mediated, in part at least, via 5-HTergic systems since mianserin has a blocking action not only on presynaptic α-adrenoceptors, but also on 5-HT_2 receptors. Further, the present biochemical experiment showed that the content of 5-HIAA and the 5-HIAA/5-HT ratio in the prefrontal cortex were increased following forced swimming in mice repeatedly treated with PCP, but not with saline, compared with those in the corresponding control mice, suggesting that the forced swimming following repeated PCP treatment resulted in an increase in the turnover of 5-HT in the prefrontal cortex, and supporting that the hypothesis that increased 5-HTergic activity relative to dopaminergic activity might lead to negative symptoms. The mechanisms of the increases in the turnover of 5-HT in the prefrontal cortex induced by the forced swimming following repeated PCP treatment have yet to be elucidated. It has been observed that dizocilpine increases the metabolism of 5-HT (Löscher et al., 1991) and PCP inhibits 5-HT reuptake (Hiramatsu et al., 1989), suggesting that PCP activates 5-HTergic systems through PCP binding site within the NMDA ionophore receptor complex and/or through the inhibition of 5-HT reuptake. Thus, it is possible that the present biochemical changes may be produced through its action on the NMDA ionophore receptor complex. However, this point must be considered with caution, as other neuropharmacology of PCP and association with stress (forced swimming) remains to be further clarified.

The hypothesis that 5-HTergic neuronal systems play a role in mediating the therapeutic effect of antidepressant treatments has been well documented in the last two decades (for review see Blier et al., 1990). However, there is evidence that other neuronal systems, such as the noradrenergic, the dopaminergic, and the glutamatergic neuronal systems, might also be involved. Desipramine which is thought to block the reuptake of noradrenaline, attenuated the PCP-induced enhancement of immobility; however, the minimal effective dose was over 4 times higher than that in mice repeatedly treated with saline. Tennant et al. (1981) have reported that desipramine, but not imipramine, is effective to prevent withdrawal syndrome in patients of PCP abuse, demonstrating that chronic PCP abuse induces depletion of the neurotransmitter noradrenaline. Thus, attenuation of noradrenergic neuronal systems may be involved, in part, in the PCP-induced enhancement of the immobility in the forced swimming test. However, the roles played by noradrenergic neuronal systems in mediating this enhancement remain to be elucidated.

There is some evidence that adjunctive treatments with specific 5-HT reuptake inhibitors can be beneficial to schizophrenic patients. However, neither clomipramine, a selective 5-HT reuptake inhibitor, nor imipramine, a 5-HT/noradrenaline reuptake inhibitor, had an effect in our PCP model. The clinical effectiveness of 5-HT reuptake inhibitors has demonstrated that reuptake inhibition of 5-HT may result in down-regulation of postsynaptic 5-HT receptors after adequate treatment, thus causing the overall effects of the agents to be similar to a 5-HT receptor blockade. Further, forced swimming following repeated PCP treatment resulted in an increase in the turnover of 5-HT in the prefrontal cortex. Thus, it is postulated that the main reason for the lack of effect of both drugs on the enhancing effect of PCP is due to their acute pharmacological action: 5-HT reuptake inhibition which results in more enhancement of 5-HTergic transmission. Further studies are necessary to fully clarify the effects of repeated tricyclic antidepressant treatment on this PCP model.

In conclusion, the present findings suggest that the depressive states which follow repeated PCP treatment, unlike those following repeated saline treatment, are less sensitive to acute treatment with tricyclic antidepressants, and this may be due to an increase, at least in part, in 5-HT turnover in the prefrontal cortex induced by forced swimming following repeated PCP treatment. Antidepressants such as mianserin, which have the 5-HT_2 receptor antagonist properties, may be useful for the treatment of negative symptoms of schizophrenia, taking together with our previous report that this effect of PCP on the immobility is reversed by ritanserin, risperidone, and clozapine which have the 5-HT_2 receptor antagonist properties.

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References

Andreasen, N.C., 1990, Methods for assessing positive and negative symptoms, Mod. Probl. Pharmacopsychiatry 24, 73.

Baldessarini, R.J. and R.L. Willmuth, 1968, Psychotic reactions during amitriptyline therapy, Can. Psychoatr. Assoc. J. 13, 571.

Barnes, T.R.E., D.A. Curson, P.F. Liddle and M. Patel, 1989, The nature and prevalence of depression in chronic schizophrenic in-patients, Br. J. Psychiatry 154, 486.

Blier, P., C. De Montigny and Y. Chaput, 1990, A role for the serotonin system in the mechanism of action of antidepressant treatments: preclinical evidence, J. Clin. Psychiatry 51 (Suppl. 4), 14.

Borsini, F., 1995, Role of the serotonergic system in the forced swimming test, Neurosci. Biobehav. Rev. 19, 377.

Contreras, P.C., K.C. Rice, A.E. Jacobson and T.L. O'Donohue, 1986, Stereotyped behavior correlates better than ataxia with phencyclidine-receptor interactions, Eur. J. Pharmacol. 121, 9.

Danysz, W., A. Plaznik, W. Kostowski, E. Malatynska, T.V.C. Jarbe, A.J. Hiltunen and T. Archer, 1988, Comparison of desipramine, amitriptyline, zimelidine and alaproclate in six animal models used to investigate antidepressant drugs, Pharmacol. Toxicol. 62, 42.

Dickerson, F.B., N.B. Ringel and J.J. Boronow, 1991, Neuropsychological deficits in chronic schizophrenics. Relationship with symptoms and behavior, J. Nerv. Ment. Dis. 179, 744.

Duinkerke, S.J., P.A. Botter, A.A.I. Jansen, P.A.M. Van Donegen, A.J. Van Haaften, A.J. Boom, J.H.M. Van Laarhoven and H.L.S.M. Busard, 1993, Ritanserin, a selective 5-HT2/1C antagonist, and negative symptoms in schizophrenia: a placebo-controlled double-blind trial, Br. J. Psychiatry 163, 451.

Elliott, H., K. McLean, D. Sumner and J. Reid, 1983, Absence of an effect of mianserin on the actions of clonidine or methyldopa in hypertensive patients, Eur. J. Pharmacol. 24, 15.

Fenton, W.S. and T.H. McGlashan, 1992, Testing system for assessment of negative symptoms in schizophrenia, Arch. Gen. Psychiatry 49, 179.

Hand, T., G. Marek and L. Seiden, 1991, Comparison of the effects of mianserin and its enantiomers and metabolites on a behavioral screen for antidepressant activity, Psychopharmacology 105, 453.

Hiramatsu, M., A.K. Cho and T. Nabeshima, 1989, Comparison of the behavioral and biochemical effects of the NMDA receptor antagonists, MK-801 and phencyclidine, Eur. J. Pharmacol. 166, 359.

Hurlbut, K.M., 1991, Drug-induced psychoses, Emerg. Med. Clin. North. Am. 9, 31.

Javitt, D.C., 1987, Negative schizophrenic symptomatology and the PCP (phencyclidine) model of schizophrenia, Hillside J. Clin. Psychiatry 9, 12.

Javitt, D.C. and S.R. Zukin, 1991, Recent advances in the phencyclidine model of schizophrenia, Am. J. Psychiatry 148, 1301.

Johnson, J.W., L.D. Snell and R.S. Morter, 1987, *N*-Methyl-D-aspartate enhanced ^{3}H-TCP binding to rat cortical membranes: effects of divalent cations and glycine, in: Proceedings of the Second U.S.-French Sponsored International Seminar: Sigma and Phencyclidine-like Compounds as Molecular Probes in Biology, eds. E.F. Domino and J.M. Kamenka (NPP Books, New York/Ann Arbor, MI) p. 259.

Kukla, F. and R. Gold, 1991, Negative schizophrenic symptoms and their detection, Fortschr. Neurol. Psychiatr. 59, 60.

Lindenmayer, J.P., 1995, New pharmacotherapeutic modalities for negative symptoms in psychosis, Acta Psychiatr. Scand. 91, 15.

Löscher, W., R. Annies and D. Honack, 1991, The *N*-methyl-D-aspartate receptor antagonist MK-801 induces increases in dopamine and serotonin metabolism in several brain regions of rats, Neurosci. Lett. 128, 191

Maj, J., Z. Rogóź, G. Skuza and H. Sowińska, 1992, Effects of MK-801 and antidepressant drugs in the forced swimming test in rats, Eur. Neuropsychopharmacol. 2, 37.

Meltzer, H.Y., 1989, Clinical studies on the mechanism of action of clozapine: the dopamine-serotonin hypothesis of schizophrenia, Psychopharmacology 99, S18.

Mizuki, Y., N. Kajimura, S. Kai, M. Suetsugi, I. Ushijima and M. Yamada, 1992, Effects of mianserin in chronic schizophrenia, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 16, 517.

Nitta, A., Y. Furukawa, K. Hayashi, M. Hiramatsu, T. Kameyama and T. Nabeshima, 1992, Denervation of dopaminergic neurons with 6-hydroxydopamine increases nerve growth factor content in rat brain, Neurosci. Lett. 144, 152.

Nixon, M.K., M. Hascoet, M. Bourin and M.C. Colombel, 1994, Additive effects of lithium and antidepressants in the forced swimming test: further evidence for involvement of the serotoninergic system, Psychopharmacology 115, 59.

Noda, Y., K. Yamada, H. Furukawa and T. Nabeshima, 1995, Enhancement of immobility in a forced swimming test by subacute or repeated treatment with phencyclidine: a new model of schizophrenia, Br. J. Pharmacol. 116, 2531.

Peralta, V., J. De-Leon and M.J. Cuesta, 1992, Are there more than two syndromes in schizophrenia? A critique of the positive-negative dichotomy, Br. J. Psychiatry 161, 335.

Porsolt, R.D., A. Bertin and M. Jalfre, 1977a, Behavioural despair in mice: a primary screening test for antidepressants, Arch. Int. Pharmacodyn. 229, 327.

Porsolt, R.D., M. Le Pichon and M. Jalfre, 1977b, Depression: a new animal model sensitive to antidepressant treatments, Nature 266, 730.

Porsolt, R.D., G. Anton, N. Blavet and M. Jalfre, 1978, Behavioural despair in rats: a new model sensitive to antidepressant treatments, Eur. J. Pharmacol. 47, 379.

Sanger, D.J. and D. Joly, 1991, Effects of NMDA receptor antagonists and sigma ligands on the acquisition of conditioned fear in mice, Psychopharmacology 104, 27.

Siris, S.G., D.P. Van Kammen and J.P. Docherty, 1978, Use of antidepressant drugs in schizophrenia, Arch. Gen. Psychiatry 35, 1368.

Siris, S.G., P.C. Bermanzohn, A. Gonzalez, S.E. Mason, C.V. White and M.A. Shuwall, 1991, The use of antidepressants for negative symptoms in a subset of schizophrenic patients, Psychopharmacol. Bull. 27, 331.

Tennant Jr., F.S., R.A. Rawson and M. Mccann, 1981, Withdrawal from chronic phencyclidine (PCP) dependence with desipramine, Am. J. Psychiatry 138, 845.

Troisi, A., A. Pasini, G. Berasni, M. DiMauro and N. Ciani, 1991, Negative symptoms and visual behavior in DSM-III-R prognostic subtypes of schizophreniform disorder, Acta Psychiatr. Scand. 83, 391.

Volkow, N.D. and J.S. Fowler, 1992, Neuropsychiatric disorders: investigation of schizophrenia and substance abuse, Semin. Nucl. Med. 22, 254.