ELSEVIER

European Journal of Pharmacology 449 (2002) 121–125

www.elsevier.com/locate/ejphar

Short communication

Topiramate antagonizes MK-801 in an animal model of schizophrenia

Stephen I. Deutsch [a,b,c,*], Richard B. Rosse [a,b], Eddie N. Billingslea [a], Alan S. Bellack [a,c], John Mastropaolo [a]

[a] *Mental Health Service Line, Veterans Integrated Service Network (VISN) 5, 849 International Drive, Suite 275, Linthicum, MD 21090, USA*
[b] *Department of Psychiatry, Georgetown University School of Medicine, 3800 Reservoir Road, NW, Washington, DC 20007, USA*
[c] *Department of Psychiatry, University of Maryland School of Medicine, 701 West Pratt Street, Suite 388, Baltimore, MD 21201, USA*

Received 26 June 2002; accepted 28 June 2002

Abstract

The phencyclidine (PCP) model of schizophrenia suggests that *N*-methyl-D-aspartate (NMDA) receptor hypofunction and its consequences may play an important role in the pathophysiology of this psychiatric disorder. Moreover, the schizophreniform psychosis caused by PCP resembles schizophrenia in all of the relevant domains of psychopathology, especially negative symptoms and cognitive dysfunction. Because of interest in the PCP model and possible NMDA receptor hypofunction in schizophrenia, animal behaviors elicited by PCP and its analogues have been characterized. These preclinical models may serve to identify candidate compounds that possess therapeutic efficacy in schizophrenia. Ideally, negative symptoms and cognitive dysfunction would also serve as therapeutic targets for these novel medications. In the current study, the ability of topiramate to attenuate the severity of a specific behavior elicited by MK-801 (dizocilpine), a high affinity analogue of PCP was studied in mice. Topiramate was chosen because it addresses two of the predicted pathological consequences of NMDA receptor hypofunction. Specifically, topiramate potentiates GABAergic neurotransmission and antagonizes the excitotoxic actions of glutamate at the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainate (KA) classes of glutamate-gated channels. Topiramate was shown to inhibit MK-801-elicited "popping" behavior in a complex dose-dependent manner.

Keywords: Topiramate; Schizophrenia; NMDA receptor; Popping

1. Introduction

Phencyclidine (PCP) can precipitate a schizophreniform psychosis in susceptible individuals that mimics schizophrenia in all of the relevant domains of psychopathology (Deutsch et al., 1989). Because of PCP's ability to antagonize noncompetitively the actions of glutamate at the *N*-methyl-D-aspartate (NMDA) class of glutamate receptors, the PCP model of schizophrenia has aroused interest in pathophysiological consequences of NMDA receptor hypofunction. Based on a model circuit that is proposed to exist in hippocampus and the cerebral cortex, consequences of NMDA receptor hypofunction are predicted to include diminished GABAergic tone and disinhibition of glutamatergic projections synapsing on α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainate (KA) receptors, distinct classes of glutamate-gated receptors (Coyle, 1996; Deutsch et al., 2001; Farber et al., 1998; Tamminga, 1998). Theoretically, disinhibition of glutamatergic projections to AMPA/kainate receptors would result in ongoing excitotoxic neuronal damage. This progressive neuronal damage might account for the advancing ventriculomegaly and psychosocial deterioration seen in at least a subgroup of patients with schizophrenia (Deutsch et al., 2001).

Current pharmacotherapeutic approaches to the treatment of schizophrenia do not address adequately the negative symptom domains and cognitive dysfunction. Until recently, these approaches emphasized selective antagonism of dopaminergic neurotransmission. The PCP model and possible NMDA receptor hypofunction have stimulated interest in developing new medication strategies. These experimental treatment strategies include potentiation of NMDA receptor-mediated neurotransmission, facilitation of GABAergic neurotransmission, and antagonism of AMPA/kainate receptors.

* Corresponding author. Mental Health Service Line, VISN 5, Department of Veterans Affairs Medical Center, 50 Irving Street, NW, Washington, DC 20422, USA. Tel.: +1-202-745-8156; fax: +1-202-745-8169.
E-mail address: Stephen.Deutsch@med.va.gov (S.I. Deutsch).

0014-2999/02/$ - see front matter © 2002 Published by Elsevier Science B.V.
PII: S0014-2999(02)02041-1

Currently, AMPA/kainate receptor antagonists are approved and marketed and under active development as medications for the treatment of seizure disorders and neuroprotection (Drapalski et al., 2001).

If NMDA receptor hypofunction is an important component of the pathophysiology of schizophrenia, animal models of NMDA receptor hypofunction caused by PCP or its related analogues (e.g., MK-801; dizocilpine) could serve as preclinical screening paradigms for the identification of novel pharmacotherapies (Deutsch et al., 1996a,b). In these procedures, candidate compounds would attenuate the severity of behaviors elicited by PCP or its analogues. The circuitry related to NMDA receptor hypofunction has inspired rational clinical trials, whose purpose is to correct the proposed neurotransmitter abnormalities along each link in the circuit. For example, in order to restore NMDA receptor-mediated neurotransmission, there have been trials of adjunctive administration of "glycinergic" interventions (e.g., milacemide and D-cycloserine); glycine is a co-agonist at the NMDA receptor complex (Rosse et al., 1990, 1991, 1996). Topiramate, a medication indicated as adjunctive therapy for adult and pediatric patients ages 2–16 years with partial-onset seizures and primary generalized tonic–clonic seizures, offers another potential avenue of intervention for schizophrenia. Topiramate possesses at least two desirable pharmacological properties: AMPA/kainate receptor antagonism and potentiation of GABA (Shank et al., 2000). Indeed, based on the predicted consequences of NMDA receptor hypofunction in schizophrenia, especially excessive and unregulated stimulation of AMPA/kainate receptors, topiramate has been administered to a patient with schizophrenia and persistent negative symptoms (Drapalski et al., 2001). In this case report, the addition of topiramate to a stable regimen of an atypical antipsychotic medication was associated with an improvement of negative symptoms. Although this result is contrary to the published report of Dursun and Deakin (2001), the efficacy of topiramate may be very dependent on dose, rate of titration, and target symptoms chosen as the primary outcome measures of efficacy. In our further exploration of topiramate in schizophrenia (Deutsch et al., 2002), improvement on the Positive and Negative Symptoms Scale (Kay et al., 1987), especially negative symptoms, was shown with a very slow titration schedule and limitation of the upper dose to about 100 mg/day. Additionally, schizophrenia is probably a very heterogeneous disorder with respect to etiology and pathophysiology; thus, only a subgroup of patients may benefit from the addition of topiramate to their regimen of antipsychotic medications.

In the current study, the ability of topiramate to attenuate a well-characterized behavior elicited by MK-801 was studied (Rosse et al., 1995). MK-801, a high-affinity analogue of PCP that binds to the same hydrophobic channel domain of the NMDA receptor complex as PCP, is known to elicit irregular episodes of intense jumping behavior in mice (termed popping). Since the initial demonstration that both conventional and atypical antipsychotic medications attenuate the severity of popping behavior elicited by MK-801 (Deutsch and Hitri, 1993), the "popping" paradigm has been used to identify novel candidate compounds for the treatment of schizophrenia (Deutsch et al., 1996a,b). The ability of topiramate to attenuate behavioral effects of MK-801 would be consistent with therapeutic efficacy. Ideally, therapeutic targets of topiramate would include negative symptoms and cognitive dysfunction.

2. Materials and methods

2.1. Subjects

Experimentally naïve male NIH Swiss mice (an outbred strain obtained from the National Cancer Institute, Frederick, MD) weighing 20–30 g were used. Mice were housed in hanging clear Plexiglas cages in groups of five and maintained on a cycle of 12 h of light followed by 12 h of darkness in an American Association for the Accreditation of Laboratory Animal Care (AAALAC)-approved animal facility. The mice had free access to food and water. The animals were weighed individually prior to drug administration and behavioral testing. In each of the experimental conditions, group sizes ranged from 6 to 18 mice, with an average group size of 12.

Because animal subjects were employed in these experiments, all experimental protocols had to be approved by our institutional review board prior to being initiated. All experiments were conducted in accordance to these protocols.

2.2. Drug

MK-801 (dizocilpine; Research Biochemical International, Natick, MA) was dissolved in 0.9% saline and prepared on the day of the experiment. Groups of mice were injected intraperitoneally with MK-801 (or its vehicle) in a volume of 0.01 ml/g of body weight 5 min prior to the 30-min monitoring period for the assessment of popping behavior. Similarly, topiramate (2,3:4,5-bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate; RWJ Pharmaceutical Research Institute) was dissolved in 0.9% saline; it was injected in a volume of 0.01 ml/g of body weight 10 min prior to the injection of MK-801.

2.3. Computerized assessment of MK-801-elicited popping

The recording of MK-801-elicited popping behavior was divided into two phases: a baseline period of 5 min and an outcome recording period of 30 min, which immediately followed an injection of either MK-801 or its vehicle. The automated system for measuring MK-801-elicited mouse popping is based on the detection and measurement of vertical displacements of a platform related to mouse move-

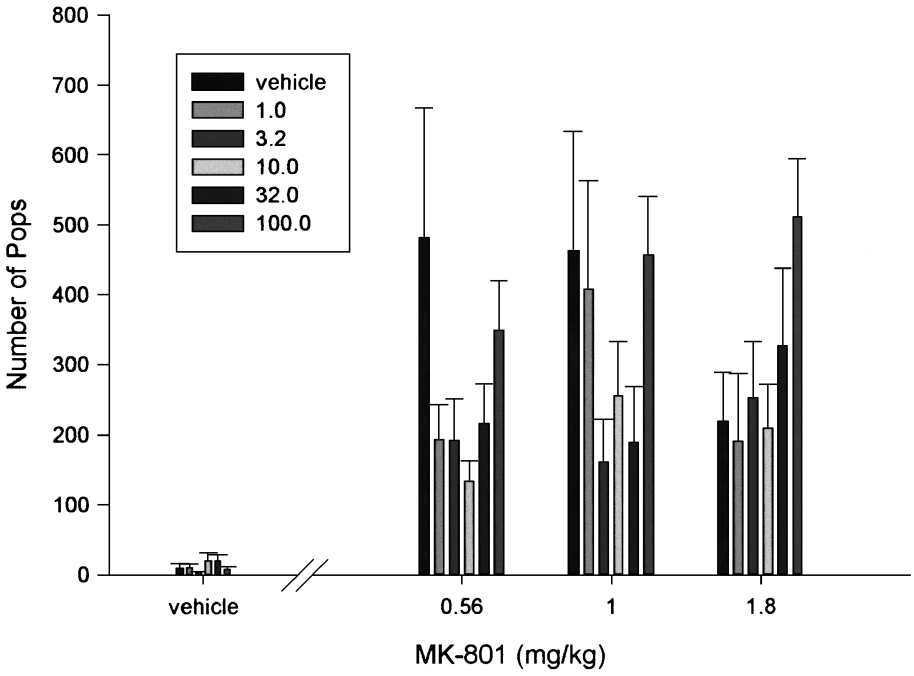

Fig. 1. This figure illustrates the mean number of "pops" (± SEM) in groups of (average group size was 12) mice pretreated with either vehicle or one of several doses of topiramate (1.0, 3.2, 10, 32 or 100 mg/kg, ip) 10 min before an injection of vehicle or one of three doses of MK-801 (0.56, 1.0 or 1.8 mg/kg, ip).

ments (Rosse et al., 1995). The vertical displacements resulting from mouse "pops" are detected and converted to electrical signals (S72-25 Type A Transducer Coupler and S75-01 Modified Contour Following Integrator; Coulbourn Instruments, Allentown, PA, USA), and are then transformed into a digital signal (L25-12 A/D Converter; Coulbourn Instruments). The chamber which houses the animals for the experimental session, measured 16.5 cm long, 8.9 cm wide, and 8.9 cm high. A discrete count of popping is defined as a vertical displacement of the platform of more than 150% of body weight. The computer is able to determine the total number of popping counts, force (in gram equivalents) of individual pops, and duration of an episode of popping (in seconds). Reverberations or "aftershock" movements of the platform after jumps are removed automatically by the system in the manner used in the measurement of startle responses in laboratory animals (Coulbourn Instruments).

3. Results

A two-way analysis of variance revealed a significant main effect ($F(3,293) = 13.204$, $P < 0.001$) for MK-801 and a significant main effect ($F(5,293) = 2.888$, $P = 0.015$) for topiramate. The two-way interaction was not significant. Post-hoc least significant differences tests revealed that at the 1.8 mg/kg dose of MK-801, the vehicle, 1.0, 3.2 and 10 mg/kg doses of topiramate dose were significantly different from the 100 mg/kg dose. In addition, at the 0.56 mg/kg dose of MK-801, the vehicle group was significantly different from the groups given 1.0, 3.2, 10 and 32 mg/kg. As can be seen in Fig. 1, when MK-801 was administered in combination with the topiramate vehicle, popping was elicited. As has been demonstrated previously (Deutsch et al., 1996a,b), at the highest dose of MK-801 (1.8 mg/kg), popping begins to decrease relative to lower doses. In addition, the figure illustrates that all doses of topiramate tested were effective in reducing MK-801-elicited popping. However, at the highest dose combination (1.8 mg/kg of MK-801 and 100 mg/kg of topiramate), popping increased.

4. Discussion

The dopaminergic model of schizophrenia has led to effective treatments for the positive symptoms of this disorder (e.g., hallucinations). Unfortunately, even when full remission of positive symptoms is achieved, schizophrenia patients are often profoundly dysfunctional, manifesting persistence of negative symptoms (e.g., flattening of affect and social withdrawal) and cognitive dysfunction. Because the model of psychosis elicited by PCP includes manifestation of symptoms in all of the domains of psychopathology, a strategy for the pharmacotherapy of schizophrenia is emerging, whose pharmacological mechanism of action is designed specifically to address NMDA receptor hypofunction (Coyle, 1996; Deutsch et al., 2001; Farber et al., 1998; Tamminga, 1998). In the current investigation, we employed an animal model of NMDA receptor hypofunction to provide a rationale for exploring

topiramate as a pharmacotherapeutic agent for the treatment of schizophrenia.

In the current study, topiramate was effective in attenuating the severity of popping behavior elicited by MK-801 in mice. MK-801 noncompetitively interferes with NMDA receptor-gated neurotransmission by binding to a hydrophobic domain within the ionophore. Thus, MK-801 is a pharmacological strategy for creating a state of NMDA receptor hypofunction in the living intact animal (Rosse et al., 1995). As reviewed above, based on the PCP model of schizophrenia, NMDA receptor hypofunction and its "downstream" consequences are thought to play very significant roles in the pathophysiology of schizophrenia. It is conceivable that the NMDA receptor hypofunction caused by MK-801 in mice, which is reflected in the behavioral outcome measure of "popping," relates in some way to the induction of psychosis by PCP. In any event, the ability to attenuate the severity of a behavior linked to NMDA receptor hypofunction would be a desirable pharmacological property of a candidate compound for development as a medication for the treatment of schizophrenia. Of course, candidate compounds identified in specific preclinical screening strategies may be shown to lack antipsychotic efficacy in patients; thus, there is a need to screen compounds in multiple behavioral procedures (e.g., attenuation of both dopamimetic-elicited and MK-801/PCP-elicited behaviors). Some of the "failures" of promising candidate compounds in clinical trials may reflect the involvement of multiple neurotransmitter systems in pathophysiology, and such issues as dose range and rate of dose titration, bioavailability and distribution, and complex pharmacokinetic interactions. Moreover, a compound like CPP, a competitive NMDA receptor antagonist, may attenuate MK-801-elicited popping but still possess psychotomimetic properties. This may be due to the ability of CPP to block channel opening and, thereby, the accessibility of MK-801 to its hydrophobic domain (Deutsch et al., 1996b). In fact, CPP was reported to have psychotomimetic side effects in man (Kristensen et al., 1992). The NMDA-receptor antagonist CPP abolishes neurogenic "wind-up pain" after intrathecal administration in humans. Ultimately, the psychotomimetic effect may relate more to the potency of NMDA receptor antagonism, irrespective of the mechanism of this antagonism (Lodge et al., 1994).

Topiramate possesses several properties that should encourage its exploration and possible development as a medication for the treatment of schizophrenia. It is readily available after peripheral administration, achieving levels in plasma and whole brain that are in the concentration range for blocking seizure activity in rodent models of epilepsy (Shank et al., 2000). With respect to addressing the potential consequences of NMDA receptor hypofunction, at least two of the pharmacological properties of topiramate may be relevant (Shank et al., 2000). Topiramate was reported to enhance GABA-gated chloride ion flux in mouse cerebellar cells in a manner that differs from that of benzodiazepines and barbiturates (Brown et al., 1993; White et al., 2000). Moreover, topiramate has complex and temporally biphasic effects on kainate-evoked membrane currents in cultured rat hippocampal neurons (Gibbs et al., 2000). Initially, within the first 2 to 4 min of a bath application of topiramate (100 μM) to these cultured neurons, kainate-evoked currents were reduced by 20% to 40%. However, upon prolonged exposure of the cultured rat hippocampal neurons (i.e., >10 min), the magnitude of the inhibitory effect on excitatory amino acid-induced currents increased and persisted during a 2- to 4-h washout period. A common mechanism that could account for topiramate's actions on both GABA and AMPA/kainate receptor-gated neurotransmission has been suggested, involving an effect of topiramate on the phosphorylation of intracellular domains of one or more receptor subunit polypeptides (Shank et al., 2000). Essentially, positive (i.e., GABA) or negative (i.e., AMPA/kainate) allosteric modulation of neurotransmission is proposed to result from topiramate-induced changes in the phosphorylation state of the receptor-gated channel. In any event, the data support the continued exploration of topiramate for the treatment of NMDA receptor hypofunction and its consequences in patients with schizophrenia.

Acknowledgements

The VISN 5 Mental Illness Research, Education, and Clinical Center (MIRECC; Alan S. Bellack, PhD, Director) supported this work.

References

Brown, S.D., Wolf, H.H., Swinyard, E.A., Twyman, R.E., White, H.S., 1993. The novel anticonvulsant topiramate enhances GABA-mediated chloride flux. Epilepsia 34 (Suppl. 2), 122.

Coyle, J.T., 1996. The glutamatergic dysfunction hypothesis for schizophrenia. Harv. Rev. Psychiatr. 3, 241–253.

Deutsch, S.I., Hitri, A., 1993. Measurement of an explosive behavior in the mouse, induced by MK-801, a PCP analogue. Clin. Neuropharmacol. 16 (3), 251–257. Jun.

Deutsch, S.I., Mastropaolo, J., Schwartz, B.L., Rosse, R.B., Morihisa, J.M., 1989. A "glutamatergic hypothesis" of schizophrenia: rationale for pharmacotherapy with glycine. Clin. Neuropharmacol. 12 (1), 1–13. Feb.

Deutsch, S.I., Rosse, R.B., Paul, S.M., Tomasino, V., Koetzner, B.A., Morn, C.B., Mastropaolo, J., 1996a. 7-Nitroindazole and methylene blue, inhibitors of neuronal nitric oxide synthase and no-stimulated guanylate cyclase, block MK-801 elicited behaviors in mice. Neuropsychopharmacology 15, 37–43.

Deutsch, S.I., Rosse, R.B., Riggs, R.L., Koetzner, L., Mastropaolo, J., 1996b. The competitive NMDA antagonist CPP blocks MK-801-elicited popping behavior in mice. Neuropsychopharmacology 15, 329–331.

Deutsch, S.I., Rosse, R.B., Schwartz, B.L., Mastropaolo, J., 2001. A revised excitotoxic hypothesis of schizophrenia: therapeutic implications. Clin. Neuropharmacol. 24, 43–49.

Deutsch, S.I., Rosse, R.B., Schwartz, B.L., Marvel, C.L., Dirks, B., Drapalski, A.L., 2002. Biol. Psychiatry 51, 113s.

Drapalski, A.L., Rosse, R.B., Peebles, R.R., Schwartz, B.L., Marvel, C.L., Deutsch, S.I., 2001. Topiramate improve deficit symptoms in a patient

with schizophrenia when added to a stable regimen of antipsychotic medication. Clin. Neuropharmacol. 24, 290–294.

Dursun, S.M., Deakin, J.F., 2001. Augmenting antipsychotic treatment with lamotrigine or topiramate in patients with treatment-resistant schizophrenia: a naturalistic case-series outcome study. J. Psychopharmacol. 15, 297–301.

Farber, N.B., Newcomer, J.W., Olney, J.W., 1998. The glutamate synapse in neuropsychiatric disorders. Prog. Brain Res. 116, 421–437.

Gibbs, J.W., Sombati, S., DeLorenzo, R.J., Coulter, D.A., 2000. Cellular actions of topiramate: blockade of kainate-evoked inward currents in cultured hippocampal neurons. Epilepsia 41 (Suppl. 1), S10–S16.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Kristensen, J.D., Svensson, B., Gordh Jr., T., 1992. The NMDA-receptor antagonist CPP abolishes neurogenic 'wind-up pain' after intrathecal administration in humans. Pain 51, 249–253.

Lodge, D., Jones, M., Fletcher, E., 1994. Non-competitive antagonists of *N*-methyl-D-aspartate. In: Collingridge, G.L., Watkins, J.C. (Eds.), The NMDA Receptor, 2nd ed. Oxford Univ. Press, Oxford, pp. 105–131.

Rosse, R.B., Schwartz, B.L., Leighton, M.P., Davis, R.E., Deutsch, S.I., 1990. An open-label trial of milacemide in schizophrenia: an NMDA intervention strategy. Clin. Neuropharmacol. 13, 348–354.

Rosse, R.B., Schwartz, B.L., Davis, R.E., Deutsch, S.I., 1991. An NMDA intervention strategy in schizophrenia with "low-dose" milacemide. Clin. Neuropharmacol. 14, 268–272.

Rosse, R.B., Mastropaolo, J., Koetzner, L., Morn, C.B., Sussman, D.M., Deutsch, S.I., 1995. Computerized measurement of MK-801-elicited hyperactivity and popping in mice. Clin. Neuropharmacol. 18, 448–457.

Rosse, R.B., Fay-McCarthy, M., Kendrick, K., Davis, R.E., Deutsch, S.I., 1996. D-Cycloserine adjuvant therapy to molindone in the treatment of schizophrenia. Clin. Neuropharmacol. 19, 444–450.

Shank, R.P., Gardocki, J.F., Streeter, A.J., Maryanoff, B.E., 2000. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. Epilepsia 41 (Suppl. 1), S3–S9.

Tamminga, C.A., 1998. Schizophrenia and glutamatergic transmission. Crit. Rev. Neurobiol. 12, 21–36.

White, H.S., Brown, S.D., Woodhead, J.H., Skeen, G.A., Wolf, H.H., 2000. Topiramate modulates GABA-evoked currents in murine cortical neurons by a nonbenzodiazepine mechanism. Epilepsia 41 (Suppl. 1), S17–S20.