ELSEVIER

European Journal of Pharmacology 332 (1997) 115–119

ejp

Short communication

Effects of AMPA receptor positive modulators on amphetamine- and dizocilpine-induced locomotion

Kimberly E. Vanover *

Department of Pharmacology, CoCensys Inc., 213 Technology Drive, Irvine, CA 92618, USA

Received 17 April 1997; revised 19 June 1997; accepted 20 June 1997

Abstract

Two allosteric α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor positive modulators, 1-(1,3-benzodioxol-5-ylcarbonyl)piperidine (1-BCP) and 1-(quinoxalin-6-ylcarbonyl)piperidine (CX516), and the antipsychotic drug, haloperidol, were tested for their ability to inhibit hyperactivity induced by amphetamine and dizocilpine in mice. Haloperidol (0.03–1.0 mg/kg) and 1-BCP (20.0–120.0 mg/kg) attenuated hyperactivity induced by both amphetamine and dizocilpine, with higher potency against amphetamine. CX516 (30.0–170.0 mg/kg), however, failed to attenuate amphetamine- and dizocilpine-induced hyperactivity up to a dose which decreased spontaneous locomotor activity. These results indicate that AMPA receptor positive modulators may not be uniform with regard to their effects on dopamine-mediated behaviors and their antipsychotic potential. © 1997 Elsevier Science B.V.

Keywords: AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid); Antipsychotic; Behavior; Dopamine; (Mouse); Schizophrenia

1. Introduction

Recent reviews regarding potential mechanisms of schizophrenia agree that an interaction of the dopamine and glutamate neurotransmitter systems likely underlie the disease (Iversen, 1995; Olney and Farber, 1995). Noncompetitive NMDA receptor antagonists such as phencyclidine and dizocilpine (MK-801) have been shown (Freed et al., 1984; Carboni et al., 1989; Rao et al., 1989; Javitt and Zukin, 1991), like the indirect dopamine receptor agonist amphetamine (Snyder, 1976; Zetterström et al., 1983; Carboni et al., 1989; Kuczenski and Segal, 1989; Arnt, 1995), to increase extracellular dopamine concentrations in brain, increase locomotor activity, and exhibit psychotomimetic effects.

It could be argued that administration of a glutamate receptor agonist might reverse the neurochemical and behavioral effects of the noncompetitive NMDA receptor antagonists and/or indirect dopamine receptor agonists and, thus, might have therapeutic potential for the treatment of schizophrenia. Indeed, glycine, an NMDA receptor complex co-agonist acting at the strychnine-insensitive glycine site, and D-cycloserine, a partial agonist at the glycine site, have been reported to improve negative symptoms (e.g., flattened effect and social withdrawal) in schizophrenia (Javitt et al., 1994; Goff et al., 1995). It is possible that enhancing glutamate function via non-NMDA receptors may also have a potential beneficial effect for schizophrenia. Recent reports suggested potential antipsychotic effects of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor positive modulators based on results which showed blockade of methamphetamine-induced activity by the AMPA receptor positive modulators BDP-29 and CX516 in rats (Johnson et al., 1996; Larson et al., 1996). However, the role of glutamate in schizophrenia remains unclear with preclinical evidence also suggesting that antagonism of glycine/NMDA receptor sites (Bristow et al., 1995, 1996) or antagonism of AMPA receptors (Willins et al., 1992, 1993; Hauber and Andersen, 1993; Burns et al., 1994; Bubser et al., 1995) may have antipsychotic-like behavioral effects.

In order to further evaluate AMPA receptor interactions with dopaminergic systems, two allosteric AMPA receptor positive modulators were examined in amphetamine- and dizocilpine-induced locomotor hyperactivity paradigms in mice. The compounds examined included 1-(1,3-benzodioxol-5-ylcarbonyl)piperidine (1-BCP; BDP; Staubli et al., 1994) and 1-(quinoxalin-6-ylcarbonyl)piperidine (CX516;

* Tel.: (1-714) 753-6100; Fax: (1-714) 753-6151; e-mail: kim@rat.ucsd.edu

PII S0014-2999(97)01103-5

BDP-12; Arai et al., 1996). The effects of the AMPA receptor modulators were compared to those of the dopamine receptor antagonist and antipsychotic drug haloperidol. Further, the effects of all compounds on spontaneous locomotion were determined.

2. Materials and methods

2.1. Animals

Male NSA mice (20–30 g; Harlan Sprague–Dawley, San Diego, CA, USA) were used as subjects. Mice ($n = 4$/cage) were housed in polycarbonate cages containing sterilized bedding material (Sani-Chips, P.J. Murray, Montville, NJ, USA). Housing rooms were maintained at 23°C (±2.5°C) on a 12 h:12 h light:dark cycle (lights on 7 a.m.). Water and food (Harlan Teklad, Madison, WI, USA) were continuously available in the home cage.

2.2. Apparatus

Locomotor activity cages (20 × 20 × 30 cm, Omnitech Electronics, Columbus, OH, USA) were equipped with 8 photocell beams left to right and 8 beams front to back for monitoring horizontal activity and 8 beams front to back for monitoring vertical activity. Data were collected using Digipro computer software (Omnitech Electronics).

2.3. Procedure

In a darkened room, locomotor activity was monitored for 15 min after the appropriate injection(s). Vehicle or a dose of a test compound was administered (at an appropriate pretreatment interval, previously determined) alone or in combination with 3.0 mg/kg D-amphetamine (15 min before the session) or 0.3 mg/kg dizocilpine (15 min before the session). Each dose or dose combination was tested in a separate group of mice ($n = 8$/group).

2.4. Data analysis

The measure for horizontal locomotor activity was total distance traveled (cm) during the 15 min session. Means and standard errors were calculated. To measure the effects of a test drug on amphetamine hyperactivity, dizocilpine hyperactivity and spontaneous locomotion, a two-way analysis of variance (ANOVA) was conducted for main effects of group (+amphetamine, +dizocilpine, or alone) and dose (of test drug) and interactions between group and dose. For significant main effects of dose, post-hoc Bonferroni comparisons were conducted to compare individual doses to the vehicle control.

2.5. Drugs

Haloperidol, dizocilpine maleate and D-amphetamine sulfate were purchased from Research Biochemicals International (Natick, MA, USA) and dissolved in 10% Tween-80, 0.9% saline and deionized water, respectively. 1-BCP and CX516 were synthesized at CoCensys and were dissolved in 10% Tween-80. Drugs were administered i.p. in a volume of 0.1 ml/10 g body weight. Where applicable, doses referred to the salt form.

3. Results

In mice pretreated with haloperidol (0.03–1.0 mg/kg; Fig. 1), treatment of amphetamine (3.0 mg/kg) and dizocilpine (0.3 mg/kg) differed from spontaneous locomotion with a significant main effect of group ($F(2,105) = 24.833$, $P < 0.001$). In addition, haloperidol caused a dose-related decrease in locomotor activity with a significant main effect of dose ($F(4,105) = 24.580$, $P < 0.001$). The interaction between group and dose was also significant ($F(8,105) = 3.303$, $P = 0.002$), suggesting that haloperidol had different effects across treatment groups. Indeed, post hoc analyses revealed that haloperidol more potently attenuated amphetamine hyperactivity (0.1 mg/kg versus vehicle, $P < 0.05$; 0.3 versus vehicle, $P < 0.05$; 1.0 versus vehicle, $P < 0.05$) than dizocilpine hyperactivity (1.0 versus vehicle, $P < 0.05$) or spontaneous locomotion (0.3 versus vehicle, $P < 0.05$; 1.0 versus vehicle, $P < 0.05$).

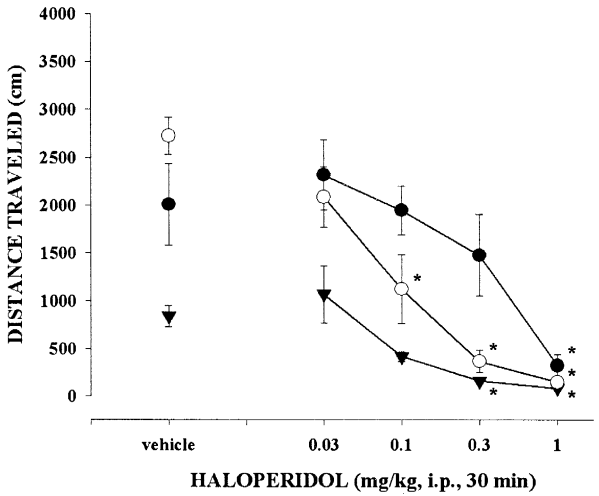

Fig. 1. Dose–response functions of haloperidol in three locomotor assays in mice. Distance traveled is shown as a function of dose. Open circles represent vehicle or test drug in combination with 3.0 mg/kg amphetamine. Closed circles represent vehicle or test drug in combination with 0.3 mg/kg dizocilpine. Closed inverted triangles represent drug effects on spontaneous locomotion (i.e., vehicle or drug administered alone). Each point represents the mean of the data collected and vertical bars represent their standard errors. Statistical significance ($P < 0.05$) of a dose compared to its vehicle control is also indicated (*).

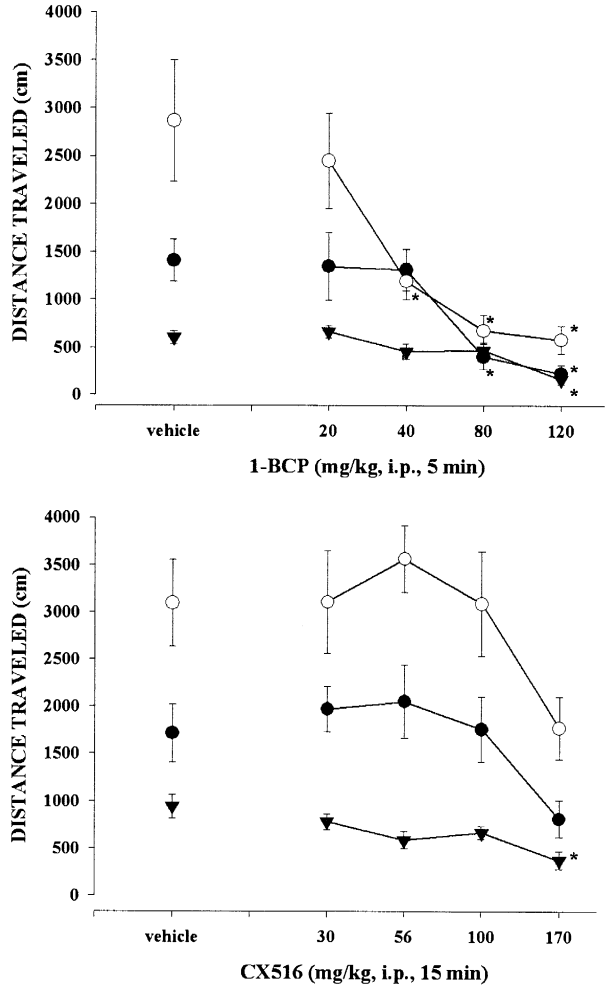

Fig. 2. Dose–response functions of 1-BCP (upper panel) and CX516 (lower panel) in locomotor assays in mice. Other details as in Fig. 1.

The AMPA receptor positive modulator, 1-BCP (20.0–120.0 mg/kg; Fig. 2, upper panel), had a profile similar to haloperidol with a significant main effect for group ($F(2,105) = 21.912$, $P < 0.001$), a significant main effect for dose ($F(4,105) = 14.782$, $P < 0.001$) and a significant interaction between group and dose ($F(8,105) = 3.499$, $P = 0.001$). Also consistent with the effects observed with haloperidol, 1-BCP was more potent in attenuating amphetamine hyperactivity (40.0 versus vehicle, $P < 0.05$; 80.0 versus vehicle, $P < 0.05$; 120.0 versus vehicle, $P < 0.05$) than dizocilpine hyperactivity (80.0 versus vehicle, $P < 0.05$; 120.0 versus vehicle, $P < 0.05$) or spontaneous locomotion (120.0 versus vehicle, $P < 0.05$).

CX516 (30.0–170.0 mg/kg; Fig. 2, lower panel), on the other hand, appeared to have no effect in the mouse hyperactivity paradigms. Although there was a significant main effect for group ($F(2,105) = 62.549$, $P < 0.001$) and a significant main effect for dose ($F(4,105) = 5.406$, $P = 0.001$), the interaction between group and dose was not significant ($F(8,105) = 0.872$, $P = 0.542$). Therefore, non-specific effects on locomotor behavior were likely the cause of the decrease in spontaneous locomotor activity at 170.0 mg/kg CX516 (170.0 versus vehicle, $P < 0.05$) and the non-significant tendency to decrease amphetamine- and dizocilpine-induced hyperactivity at the same dose.

4. Discussion

Consistent with previous reports, amphetamine and dizocilpine increased locomotor activity and these increases were attenuated by haloperidol (Hoffman, 1992; Arnt, 1995; Corbett et al., 1995). Haloperidol attenuated amphetamine at lower doses than it attenuated dizocilpine. It has previously been suggested that more potent antagonism of dopaminergic behavioral effects compared to antagonism of dizocilpine may be indicative of a classical neuroleptic profile, whereas atypical antipsychotics, such as clozapine and olanzapine, are more potent against dizocilpine (Corbett et al., 1995).

It was reported previously that the AMPA receptor potentiators, BDP-29 and CX516, attenuated methamphetamine-induced hyperactivity in rats (Johnson et al., 1996; Larson et al., 1996). Similarly, the present experiment demonstrated attenuation of both amphetamine- and dizocilpine-induced hyperactivity by 1-BCP in mice. Although 1-BCP was much less potent than haloperidol, a profile similar to that of haloperidol was observed, with higher potency against amphetamine than against dizocilpine. Further, 1-BCP attenuated dizocilpine-induced hyperactivity at a dose which had no effect on spontaneous locomotion, whereas haloperidol decreased dizocilpine-induced locomotor effects only at a dose which also significantly reduced spontaneous activity. This suggests that 1-BCP may be more specific than haloperidol in the attenuation of dizocilpine. The data suggest that 1-BCP may have therapeutic potential as antipsychotic drug. Due to the potential neuroleptic-like profile, however, further testing is warranted to examine the potential of this compound for inducing extrapyramidal side-effects typically observed concomitantly with neuroleptic efficacy.

In contrast, the present experiment failed to replicate effects on locomotor activity by CX516. CX516 had no effect on amphetamine- or dizocilpine-induced hyperactivity in mice up to a dose (170.0 mg/kg) which significantly decreased spontaneous locomotion. The difference between the previous report of attenuation of methamphetamine hyperactivity by CX516 (Johnson et al., 1996) and the current lack of effects may be due to differences in procedures. For example, the present study used non-habituated mice as subjects whereas the previous study used rats habituated to the activity chamber. In addition, the present experiment used a shorter session time (15 min) than that used by Johnson and colleagues (90 min). Further, there may be a difference in a compound's ability to attenuate the behavioral effects of methamphetamine compared to amphetamine and/or dizocilpine.

It is unclear why one, but not both, AMPA receptor potentiators exhibited attenuation of hyperactivity induced by amphetamine and dizocilpine in the present paradigm. Perhaps differences in receptor kinetics, bioavailability, or AMPA receptor subtypes underlie the behavioral differences. However, both 1-BCP and CX516 have been shown to similarly increase excitatory postsynaptic potential amplitude in hippocampal slices with CX516 10-fold more potent than 1-BCP (Staubli et al., 1994; Arai et al., 1996). In addition, CX516 has been shown to be more potent than 1-BCP in facilitating performance in a two-odor discrimination task in rats (Larson et al., 1995; Staubli et al., 1994). Alternatively, there may be some non-AMPA related mechanism of 1-BCP which is not shared by CX516 that may mediate the interaction with dopaminergic and/or NMDA glutamatergic systems in mice. Further research with 1-BCP and additional AMPA receptor positive modulators will be necessary to clarify the neurochemical mechanisms which mediate the in vivo effects of 1-BCP.

Whereas there may be a possible role for AMPA receptors in the neurochemical mechanisms underlying schizophrenia and for the treatment of the disease, the nature of such a role remains unclear. Antipsychotic-like potential of 1-BCP was observed in the present experiment, but this effect was not shared by CX516. In addition, the utility of 1-BCP may be limited due to its lack of potency compared to haloperidol. Further studies evaluating the potential antipsychotic-like effects of other AMPA receptor positive modulators as well as the potential extrapyramidal side-effects of 1-BCP and similar compounds are warranted to elucidate AMPA receptor involvement in mechanisms and treatment of schizophrenia.

Acknowledgements

I thank Dr. R. Carter, Dr. J. Hawkinson and Dr. P. Wood for their helpful comments, M. Huber and Z. Kazeminezhad for their technical assistance and Dr. Y. Wang and J. McLellan for the syntheses of 1-BCP and CX516.

References

Arai, A., Kessler, M., Rogers, G., Lynch, G., 1996. Effects of a memory-enhancing drug on DL-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor currents and synaptic transmission in hippocampus. J. Pharmacol. Exp. Ther. 278, 627–638.

Arnt, J., 1995. Differential effects of classical and newer antipsychotics on the hypermotility induced by two dose levels of D-amphetamine. Eur. J. Pharmacol. 283, 55–62.

Bristow, L.J., Landon, L., Saywell, K.L., Tricklebank, M.D., 1995. The glycine/NMDA receptor antagonist, L-701,324 reverses isolation-induced deficits in prepulse inhibition in the rat. Psychopharmacology 118, 230–232.

Bristow, L.J., Flatman, K.L., Hutson, P.H., Kulagowski, J.J., Leeson, P.D., Young, L., Tricklebank, M.D., 1996. The atypical neuroleptic profile of the glycine/*N*-methyl-D-aspartate receptor antagonist, L-701-324, in rodents. J. Pharmacol. Exp. Ther. 277, 578–585.

Bubser, M., Tzschentke, T., Hauber, W., 1995. Behavioural and neurochemical interactions of the AMPA antagonist GYKI 52466 and the non-competitive NMDA antagonist dizocilpine in rats. J. Neural Transm. Gen. Sect. 101, 115–126.

Burns, L.H., Everitt, B.J., Kelley, A.E., Robbins, T.W., 1994. Glutamate–dopamine interactions in the ventral striatum: Role in locomotor activity and responding with conditional reinforcement. Psychopharmacology 115, 516–528.

Carboni, E., Imperato, A., Perezzani, L., Di Chiara, G., 1989. Amphetamine, cocaine, phencyclidine and nomifensine increase extracellular dopamine concentrations preferentially in the nucleus accumbens of freely moving rats. Neuroscience 28, 653–661.

Corbett, R., Camacho, F., Woods, A.T., Kerman, L.L., Fishkin, R.J., Brooks, K., Dunn, R.W., 1995. Antipsychotic agents antagonize non-competitive *N*-methyl-D-aspartate antagonist-induced behaviors. Psychopharmacology 120, 67–74.

Freed, W.J., Bing, L.A., Wyatt, R.J., 1984. Effects of neuroleptics on phencyclidine (PCP)-induced locomotor stimulation in mice. Neuropharmacology 23, 175–181.

Goff, D.C., Tsai, G., Manoach, D.S., Coyle, J.T., 1995. Dose-finding trial of D-cycloserine added to neuroleptics for negative symptoms in schizophrenia. Am. J. Psychiatry 152, 1213–1215.

Hauber, W., Andersen, R., 1993. The non-NMDA glutamate receptor antagonist GYKI 52466 counteracts locomotor stimulation and anticataleptic activity induced by the NMDA antagonist dizocilpine. Naunyn-Schmiedebergs Arch. Pharmacol. 348, 486–490.

Hoffman, D.C., 1992. Typical and atypical neuroleptics antagonize MK-801-induced locomotion and stereotypy in rats. J. Neural. Transm. 89, 1–10.

Iversen, S.D., 1995. Interactions between excitatory amino acids and dopamine systems in the forebrain: Implications for schizophrenia and Parkinson's disease. Behav. Pharmacol. 6, 478–491.

Javitt, D.C., Zukin, S.R., 1991. Recent advances in the phencyclidine model of schizophrenia. Am. J. Psychiatry 148, 1301–1308.

Javitt, D.C., Zylberman, I., Zukin, S.R., Heresco-Levy, U., Lindenmayer, J.-P., 1994. Amelioration of negative symptoms in schizophrenia by glycine. Am. J. Psychiatry 151, 1234–1236.

Johnson, S.A., Larson, J., Luu, N.T., Lutz, D.L., Rogers, G., Lynch, G., 1996. Antagonism of methamphetamine-induced hyperactivity in rats by specific facilitation of AMPA-receptor-mediated glutamatergic transmission (657.12). Soc. Neurosci. Abstr. 22, 1676.

Kuczenski, R., Segal, D., 1989. Concomitant characterization of behavioral and striatal neurotransmitter response to amphetamine using in vivo microdialysis. J. Neurosci. 9, 2051–2065.

Larson, J., Lieu, T., Petchpradub, V., LeDuc, B., Ngo, H., Rogers, G.A., Lynch, G., 1995. Faciliatation of olfactory learning by a modulator of AMPA receptors. J. Neurosci. 15, 8023–8030.

Larson, J., Quach, C.N., LeDuc, B.Q., Nguyen, A., Rogers, G.A., Lynch, G., 1996. Effects of an AMPA receptor modulator on methamphetamine-induced hyperactivity in rats. Brain Res. 738, 353–356.

Olney, J.W., Farber, N.B., 1995. Glutamate receptor dysfunction and schizophrenia. Arch. Gen. Psychiatry 52, 998–1007.

Rao, T.S., Kim, H.S., Lehmann, J., Martin, L.L., Wood, P.L., 1989. Differential effects of phencyclidine (PCP) and ketamine on mesocortical and mesostriatal dopamine release in vivo. Life Sci. 45, 1065–1072.

Snyder, S.H., 1976. The dopamine hypothesis of schizophrenia: Focus on the dopamine receptor. Am. J. Psychiatry 133, 197–202.

Staubli, U., Rogers, G., Lynch, G., 1994. Facilitation of glutamate receptors enhances memory. Proc. Natl. Acad. Sci. USA 91, 777–781.

Willins, D.L., Wallace, L.J., Miller, D.D., Uretsky, N.J., 1992. α-Amino-3-hydroxy-5-methylisoxazole-4-proprionate/kainate receptor antagonists in the nucleus accumbens and ventral pallidum decrease the

hypermotility response to psychomotor stimulant drugs. J. Pharmacol. Exp. Ther. 260, 1145–1151.

Willins, D.L., Narayanan, S., Wallace, L.J., Uretsky, N.J., 1993. The role of dopamine and AMPA/kainate receptors in the nucleus accumbens in the hypermotility response to MK801. Pharmacol. Biochem. Behav. 45, 881–887.

Zetterström, T., Sharp, T., Marsden, C.A., Ungerstedt, U., 1983. In vivo measurement of dopamine and its metabolites by intracerebral dialysis: Changes after D-amphetamine. J. Neurochem. 41, 1769–1773.