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Interaction of stress and strain on glutamatergic neurotransmission: relevance to schizophrenia

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Abstract

Psychosis caused by phencyclidine (PCP) stimulated interest in characterizing rodent behaviors elicited by PCP and its analogues. We have shown that MK-801 antagonizes electrically precipitated seizures (defined as tonic hindlimb extension) and elicits episodes of intense jumping behavior, referred to as "popping," in mice. Moreover, 24 h after stress, MK-801's ability to antagonize electrically precipitated seizures is reduced in outbred NIH Swiss mice. Inbred BALBc mice are more resistant to electrically precipitated seizures than the NIH Swiss strain, and are more sensitive to both MK-801's anticonvulsant effect and ability to elicit popping. In the current experiments, we examined the influence of stress and genetic mouse strain on both MK-801's ability to antagonize electrically precipitated seizures and elicit popping. Stress significantly reduced the threshold voltage for precipitation of seizures in BALBc mice and the anticonvulsant properties of MK-801 in both strains. These data show that factors relevant to schizophrenia and its exacerbation (i.e., acute stress and genetics) influence *N*-methyl-D-aspartic acid (NMDA) receptor-mediated neurotransmission in intact mice. The BALBc inbred strain of mouse may possess advantages in preclinical screening paradigms designed to assess NMDA receptor agonist interventions for disorders such as schizophrenia. Specifically, stressed BALBc mice showed the greatest behavioral sensitivity to MK-801 with regard to electrically precipitated seizures in the incremental electroconvulsive shock (IECS) paradigm, whereas unstressed BALBc showed the greatest behavioral sensitivity to MK-801 in the "popping" paradigm, relative to BALBc and NIH Swiss mice in the appropriate comparison conditions.

Keywords: Mouse strains; NMDA receptor; MK-801; Phencyclidine; Schizophrenia

1. Introduction

Phencyclidine (PCP), a noncompetitive allosteric antagonist of the *N*-methyl-D-aspartic acid (NMDA) receptor complex, precipitates a schizophreniform psychosis that mimics naturally occurring schizophrenia in all of the relevant domains of psychopathology. This phenomenologic similarity between the psychosis induced by PCP and schizophrenia led to the formulation of a "glutamatergic deficiency" or "NMDA receptor hypofunction (NRH)" hypothesis of schizophrenia (Coyle, 1996; Deutsch et al., 1989; Javitt and Zukin, 1991; Tamminga, 1998). Moreover, interest in the NRH hypothesis stimulated the quantitative characterization of rodent behaviors elicited by PCP or its analogues. These behaviors could serve as preclinical outcome measures for the identification of candidate antipsychotic medications, whose actions attenuate the intensity of behaviors linked to NRH. For example, MK-801 has been shown to disrupt prepulse inhibition (PPI) in rodents, which is proposed as a model of the sensory gating abnormality observed in patients with schizophrenia (Varty et al., 2001). Importantly, differences in sensitivity to disruption of PPI have been demonstrated among genetically inbred strains of rodents, suggesting that genetic factors modulate sensory gating (Varty et al., 2001). Disruption of PPI occurs

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commonly in patients with schizophrenia and closely related biological relatives, and is proposed to be a fundamental pathophysiological mechanism responsible for many of the attentional and cognitive disturbances manifested in patients with schizophrenia. The study of behaviors linked to NRH would extend many of the current preclinical screening paradigms for potential antipsychotic medications, which are largely limited to the identification of compounds whose primary actions involve antagonism of dopamine.

In prior work, we showed that MK-801 ([+]-5-methyl-10,11-dihydro-5*H*-dibenzo [*a*,*d*] cyclohepten-5,10-IMINE; dizocilpine), a noncompetitive "open-channel" blocker of NMDA receptors that binds with higher affinity to the same hydrophobic channel domain as PCP, elicits explosive episodes of jumping behavior (termed "popping") and antagonizes electrically precipitated seizures in a dose-dependent fashion in NIH Swiss mice, an outbred strain (Rosse et al., 1995). Moreover, 24 h after exposure of mice to a single session of cold water swim stress, the ability of MK-801 (dizocilpine) to antagonize electrically precipitated seizures was reduced (Deutsch et al., 1997a,b). Thus, this may represent a model for stress-associated alterations of NMDA receptor-mediated neurotransmission in the intact animal (Norris et al., 1994). Further, we have shown that genetically inbred strains of mice differ in their sensitivity to the ability of MK-801 to antagonize electrically precipitated seizures and elicit "popping." Both outcome measures identified the BALBc strain of mouse as the most sensitive to the behavioral effects of MK-801 of several strains tested. Thus, genetic factors influence NMDA receptor-mediated neurotransmission, and these inbred strain differences may lead to the identification of genes in mice (Quantitative Trait Loci [QTL]) that are homologous to genes in humans conferring proneness to psychosis or schizophrenia (Routman and Cheverud, 1994; Zeng, 1994).

In the current investigation, we examined how stress and strain differences interact to alter behavioral sensitivity to MK-801 in these two in vivo models of NMDA receptor-mediated neurotransmission. Specifically, groups of mice from the highly sensitive inbred BALBc and outbred NIH Swiss strain were assigned to either the stress or nonstress pretreatment prior to behavioral testing. It would be important to know if the heightened behavioral sensitivity of the BALBc strain to MK-801, relative to NIH Swiss mice, would be differentially influenced by stress in the two behavioral outcome measures.

2. Materials and methods

2.1. Subjects

Experimentally naïve male NIH Swiss mice (an outbred strain obtained from the National Cancer Institute, Frederick, MD) and male mice from one inbred strain (BALBc, obtained from the Charles River Laboratories, Wilmington, MA) matched for their age (7 to 8 weeks) and 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 AALAC approved animal facility. The mice had free access to food and water. The animals were weighed individually prior to drug administration and behavioral testing. Each dose of MK-801 and its vehicle were tested in groups of 15 mice from each strain in Experiment 1 and groups of 25–28 mice in Experiment 2.

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. Stress procedure (all experiments)

Mice were forced to swim in cold (6 °C) water in a Plexiglass container for up to 10 min, 24 h prior to testing the ability of MK-801 to antagonize electrically precipitated seizures or elicit popping behavior.

2.3. Incremental eletroconvulsive shock (IECS) procedure (Experiment 1)

In the IECS procedure, a Hittman electroconvulsive shock generator (Medcraft model B24-III) was utilized to administer 0.3 s of voltage via earclip electrodes. To determine threshold voltages for the precipitation of tonic hindlimb extension, the procedure began with 70 V and was increased in 10 V increments every 2 s until the maximal tonic hindlimb extension occurred or 170 V was reached. A voltage of 180 was recorded for animals that did not seize or show tonic hindlimb extension (Deutsch et al., 1997b).

2.4. Computerized assessment of MK-801-elicited popping (Experiment 2)

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 movements (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 "after-shock" movement 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).

2.5. Drugs (all experiments)

MK-801 (dizocilpine; Research Biochemical International, Natick, MA) was dissolved in 0.9% saline and prepared on the day of the experiment. Groups of stressed and nonstressed mice were injected intraperitoneally with MK-801 (or its vehicle) in a volume of 0.01 ml/g of body weight either 30 min prior to the IECS procedure or 5 min prior to the 30-min monitoring period for the assessment of popping behavior.

3. Results

3.1. Experiment 1

A three-way analysis of variance (ANOVA) performed on threshold voltages revealed a significant main effect for strain [$F(1,276) = 69.43$; $P < .001$], dose [$F(4,276)=42.19$; $P < .001$] and stress [$F(1,276) = 45.41$; $P < .001$]. Also, there was a significant Strain × Stress × Dose (three-way) interaction [$F(4,276) = 5.315$, $P=.001$]. Subsequent post hoc analyses showed that, compared to nonstressed NIH Swiss mice, nonstressed BALBc mice had significantly higher threshold voltages for the elicitation of seizures in the vehicle condition and at 0.18 and 0.32 mg/kg of MK-801 [$F(1,25) = 11.59$, $P < .01$; $F(1,26) = 60.93$, $P < .01$; $F(1,25) = 11.29$, $P < .01$, respectively]. The nonsignificant difference between BALBc and NIH Swiss mice at the two highest doses (0.56 and 1.0 mg/kg) in the nonstressed condition could be due to a ceiling effect (i.e., maximal protection from seizures is scored as a 180 V). In stressed animals, the two strains did not differ in the vehicle condition and at 0.32 mg/kg of MK-801, but the BALBc strain had significantly higher threshold voltages for the elicitation of seizures at 0.18, 0.56, and 1.0 mg/kg of MK-801 [$F(1,24) = 5.28$, $P < .05$; $F(1,27) = 7.69$, $P < .01$; $F(1,26) = 7.14$, $P < .05$, respectively]. Comparing nonstressed and stressed BALBc mice, significantly higher threshold voltages for the elicitation of seizures were revealed in nonstressed mice only in the vehicle and 0.18 mg/kg groups [$F(1,29) = 15.89$, $P < .001$; $F(1,25) = 13.29$, $P < .01$, respectively]. Finally, comparing nonstressed and stressed NIH Swiss mice, significantly higher threshold voltages for the elicitation of seizures were revealed for nonstressed animals at the 0.18-, 0.56-, and 1.0-mg/kg doses of MK-801 [$F(1,25) = 7.49$, $P < .05$; $F(1,27) = 12.26$, $P < .01$; $F(1,28) = 8.48$, $P < .01$, respectively] (Fig. 1).

3.2. Experiment 2

A three-way ANOVA performed on the number of pops during the 30-min observation period revealed significant main effects for strain [$F(1,359) = 4.50$, $P < .05$] and dose [$F(2,359) = 17.60$, $P < .01$], but not for stress. There was a significant Strain × Dose (two-way) interaction. Subsequent post hoc tests revealed that in the NIH Swiss strain, nonstressed animals showed a significant increase in popping at 0.32 and 0.56 mg/kg, relative to vehicle-injected animals [$F(1,59) = 10.88$, $P < .01$; $F(1,89) = 4.88$, $P < .01$, respectively]. This was also true for the NIH Swiss strain of mice in the stress condition [$F(1,59) = 4.25$, $P < .05$; $F(1,89) = 3.01$, $P < .05$, respectively]. This effect of MK-801 dose was apparent in BALBc mice as well [nonstressed: $F(1,59) = 7.02$, $P < .01$; $F(1,89) = 5.82$, $P < .01$;

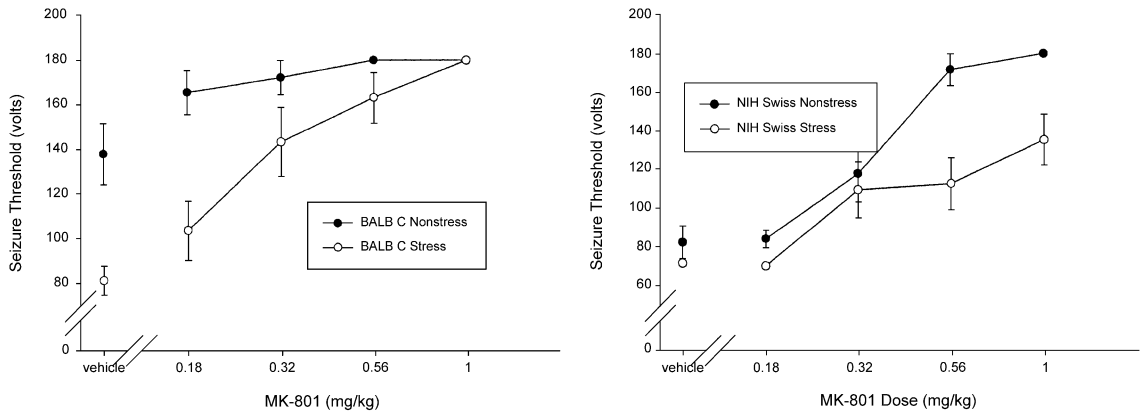

Fig. 1. The left panel depicts the mean (±S.E.M.) threshold voltage to electrically precipitate seizures for groups of nonstressed (closed circles) or stressed (open circles) BALBc mice 30 min following the injection of saline (vehicle) or one of several doses of MK-801 (0.18, 0.32, 0.56, or 1.0 mg/kg). The right panel depicts the mean (±S.E.M.) threshold voltage to electrically precipitate seizures for groups of nonstressed (closed circles) or stressed (open circles) NIH Swiss mice 30 min following the injection of saline (vehicle) or one of several doses of MK-801 (0.18, 0.32, 0.56, or 1.0 mg/kg).

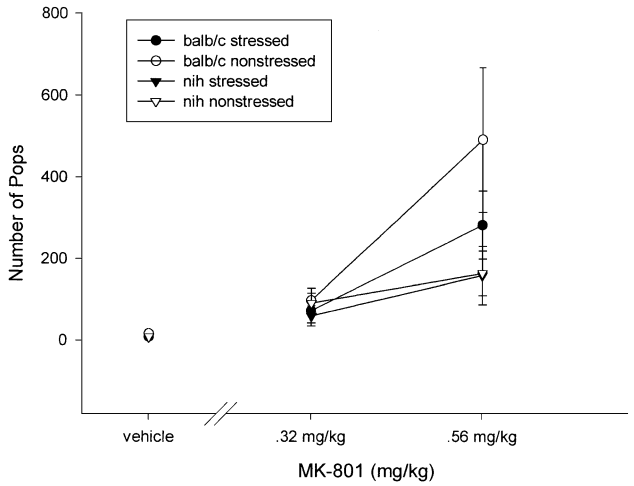

Fig. 2. The mean number of "pops" (±S.E.M.) for groups of nonstressed (open symbols) and stressed (closed symbols) BALBc (circles) and NIH Swiss (inverted triangles) mice during a 30-min recording period that occurred 5 min after the injection of vehicle or MK-801 (0.32 or 0.56 mg/kg).

stressed: $F(1,59)=4.23$, $P<.05$; $F(1,89)=7.08$, $P<.01$]. No other post hoc comparisons were significant (Fig. 2).

4. Discussion

Specifically, as has been reported elsewhere, genetically inbred strains of mice differ in terms of their sensitivity or proneness to the elicitation of seizures by chemical or electrical precipitation (Deutsch et al., 1998). In the current experiment, we replicated our earlier finding that nonstressed BALBc mice require a higher threshold voltage for the elicitation of tonic hindlimb extension than the outbred NIH Swiss strain. Interestingly, in the stressed condition, the threshold voltage for the elicitation of seizures in the BALBc mice was lowered to the level of both stressed and nonstressed NIH Swiss mice. However, despite the more profound effect of stress on threshold voltage for the elicitation of seizures in the vehicle condition for the BALBc mice, MK-801 afforded greater protection, relative to stressed NIH Swiss mice. This demonstrates that stressed BALBc mice are more sensitive to the effects of MK-801. Furthermore, these data show that genetic factors influencing sensitivity to the behavioral effects of MK-801/PCP interact with acute stress; in the case of electrically precipitated seizures, this interaction resulted in a heightened sensitivity of BALBc mice to the anticonvulsant effects of MK-801. It would appear that the interaction of stress with this genetically inbred strain makes this heightened sensitivity even more apparent. In view of the shared pharmacological actions of MK-801 and PCP, these data show that in the IECS paradigm, BALBc mice may offer advantages in terms of preclinical screening of novel antipsychotic medications. Moreover, these data support studies designed to identify QTLs, including the precise chromosomal localization of genes contributing to sensitivity to MK-801/PCP. The homologous genes on the human chromosome may contribute to the precipitation of schizophreniform psychosis in susceptible individuals in particular, and psychosis-proneness in general.

With respect to Experiment 2, the data revealed an interaction between strain and dose of MK-801. Thus, the ability of MK-801 to elicit popping behavior is greater in the BALBc strain of mouse compared to the NIH Swiss strain. These data are consistent with a heightened sensitivity of BALBc mice to the behavioral effects of MK-801. This heightened sensitivity could result from a greater proportion of the NMDA receptor-associated channels in the activated or open-configuration, greater affinity of the hydrophobic channel domain for MK-801, or a combination of these two possibilities. Interestingly, the MK-801-elicited popping paradigm was not able to demonstrate a significant main effect for stress; thus, these data suggest that there may be important advantages for using multiple behavioral paradigms to evaluate the interactive effects of stress, strain, and dose, and screen for potentially novel antipsychotic medications. For example, 7-nitroindazole, a neuronally selective nitric oxide synthase (NOS) inhibitor, was shown to potentiate the ability of MK-801 to antagonize the precipitation of electrically precipitated seizures, whereas 7-nitroindazole antagonized MK-801's ability to elicit mouse popping behavior (Deutsch et al., 1996). The latter effect was contrary to what was predicted based on 7-nitroindazole's potentiation of the antiseizure effect of MK-801. Ultimately, these findings may reflect differences in receptor polypeptide subunit composition and the extent to which these pharmacologically distinctive receptors are phosphorylated and glycosylated in discrete anatomic regions of the brain. Furthermore, they reflect the complex allosteric modulation of glutamate and glycine's coordinated ability to promote channel opening and ionic conductance. In addition, this highlights the need to have a battery of behavioral, pharmacological, and genetic variables to manipulate when exploring potential antipsychotics. The availability of a variety of behavioral paradigms associated with NMDA receptor antagonism, including effects on mouse popping, protection against electrically precipitated seizures, and disruption of PPI and impairment of sensory gating, should afford powerful tools to examine these issues.

Because PCP and its analogues are unquestionably relevant to schizophrenia, it is critical to have preclinical paradigms to explore the effects of these compounds, perturbations to the relevant neurotransmitter systems, and interventions that alleviate their effects. In the current experiments, we again demonstrated the usefulness of IECS and "popping" as intact animal models that can be used to detect both the effects of the PCP analogue, MK-801, and alterations in glutamatergic neurotransmission. The present data demonstrate that the dose–response relationship for the anticonvulsant properties of MK-801 is altered by the genetics of the animal under study and the previous experi-

ence with an environmental stress. Specifically, MK-801 is more effective as an anticonvulsant in the BALBc mice and both the BALBc and NIH Swiss mice are less protected from seizures 24 h after a cold water swim stress.

The variables influencing NMDA receptor-mediated neurotransmission in the intact mouse (i.e., stress and genetic mouse strain) in the current investigation were selected based on their relevance to schizophrenia. Specifically, stress is known to cause acute exacerbation of illness (e.g., Myin-Gerneys et al., 2001), and schizophrenia is a familial disorder whose basal rate of occurrence is higher in closely related biological relatives of an index proband with the disorder (Deutsch et al., 1997a,b). Based on the psychotomimetic properties of PCP, an intuitive prediction might suggest that because of the ability of stress to exacerbate psychosis, the behavioral sensitivity of stressed mice to MK-801 would be increased. However, because of the location of the PCP binding site within the hydrophobic channel domain of the NMDA receptor-associated ionophore and the fact that binding is dependent on the open configuration of this channel, diminished behavioral sensitivity to MK-801 may be consistent with a reduction in the population of NMDA receptor-associated ionophores assuming the open configuration or NRH.

As shown by the IECS paradigm, exposure to a single session of cold water swim stress may represent a nonpharmacological model for altering NMDA receptor-gated neurotransmission in the intact mouse (Deutsch et al., 1997c). In the IECS paradigm, the BALBc mouse, a genetically inbred strain, was more sensitive to the behavioral effects of MK-801 and stress-induced alterations of endogenous NMDA receptor-mediated neurotransmission, than the outbred strain of NIH Swiss mouse. Stress-induced alterations of NMDA receptor-gated neurotransmission may be more sensitively reflected in changes in MK-801's ability to antagonize electrically precipitated seizures, compared with MK-801's ability to elicit popping behavior, in mice. Importantly, the BALBc inbred strain of mouse may possess advantages in preclinical screening paradigms designed to assess NMDA receptor agonist interventions for disorders such as schizophrenia. Furthermore, stressed BALBc mice may be preferred for this purpose in the IECS paradigm, whereas nonstressed BALBc mice may serve as the preferred mouse subject in the MK-801-elicited popping paradigm.

The homologous human genes responsible for behavioral sensitivity to MK-801, a high-affinity analogue of PCP that binds to the same hydrophobic channel domain of the NMDA receptor-associated ionophore, in the mouse may mediate the psychotomimetic properties of PCP and psychosis-proneness. Theoretically, these homologous mouse genes are amenable to identification and precise chromosomal localization, and their quantitative contributions to behavioral sensitivity to MK-801 measured (QTL). Ultimately, these QTL studies may contribute to an improved understanding of the complex genetics and treatment of schizophrenia.

In summary, although there are alternative animal models available for studying NRH in intact animals as a way to explore avenues for the treatment of schizophrenia that do not rely on dopamine blockade, the results are not simple and straightforward. Given the complex, multifaceted nature of this illness, it may not be surprising that different behavioral paradigms give different results, as in the case of 7-nitroindazole's opposite effects on MK-801 in the IECS and popping paradigms. The complexity of schizophrenia necessitates the application of multiple behavioral paradigms, and the examination of the complex interaction between behavioral history and genetics in these different paradigms. As this paper demonstrates, the optimal paradigm and conditions for studying alterations of NMDA receptor-mediated neurotransmission in an intact animal vary. Specifically, in this study, the stressed BALBc mouse in IECS and the nonstressed BALBc mouse in popping were shown to be optimal. Moreover, the data suggest that predictions of efficacy of NMDA receptor agonist interventions in schizophrenia will require thorough screening in a battery of behavioral paradigms under a variety of conditions.

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