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BRAIN RESEARCH

Research Report

Repeated treatment with *N*-methyl-D-aspartate antagonists in neonatal, but not adult, rats causes long-term deficits of radial-arm maze learning

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ABSTRACT

Brain glutamatergic system is involved in synaptic plasticity as a base for learning and neural development. This study investigated the effects of neonatal and adult chronic antagonism of *N*-methyl-D-aspartate (NMDA) receptors, a subtype of glutamate receptors, on learning and/or memory. Rats were trained in the radial-maze learning, which is known as a measure of spatial working memory capacities, in adulthood after neonatal or adult repeated treatment of MK-801 (dizocilpine; 5-methyl-10,11-dihydro-5H-dibenzo[*a*,*d*]-cyclohepten-5,10-imine), a non-competitive antagonist, or neonatal repeated treatment of CGS 19755 (*cis*-4-phosphonomethyl-2-piperadine carboxilic acid), a competitive antagonist. Neonatal repeated treatment of MK-801 or CGS 19755 markedly impaired the radial-arm maze learning. In addition, the treatment altered activities differently in the radial-maze and in the open-field. On the other hand, adult repeated treatment with MK-801 affected neither the radial-maze learning nor activities. Results suggest that chronic blockade of NMDA receptors in a neonatal stage may produce long-lasting deteriorative effects on spatial working memory in adulthood.

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1. Introduction

N-methyl-D-aspartate (NMDA) receptors, a subtype of ionotropic glutamate receptors, have been implicated in numeral neural processes. For example, NMDA receptors are involved in long-term potentiation (LTP), which is believed as a physiological base for learning and/or memory (Abraham and Mason, 1988; Harris et al., 1984; Morris, 1989; Morris et al., 1986; Stringer et al., 1983). In fact, many studies have shown that NMDA antagonists induce learning and/or memory impairment (Kawabe et al., 1998a,b; Morris, 1989; Morris et al., 1986; Yoshihara and Ichitani, 2004).

In addition, it has been suggested that the repeated treatment of these antagonists such as phencyclidine (PCP) and MK-801 (dizocilpine; 5-methyl-10,11-dihydro-5H-dibenzo [*a*,*d*]-cyclohepten-5,10-imine) during an early developmental stage causes long-term alterations of anatomical, neurochemical, neurophysiological, and behavioral properties in rats

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Abbreviations: ANOVA, analysis of variance; AP5, 2-amino-5-phosphonopentanoic acid; CGS 19755, *cis*-4-phosphonomethyl-2-piperadine carboxilic acid; i.p., intraperitoneally; LTP, long-term potentiation; MK-801, 5-methyl-10,11-dihydro-5H-dibenzo[*a*,*d*]-cyclohepten-5,10-imine; NMDA, *N*-methyl-D-aspartate; PCP, phencyclidine; PND, postnatal day(s); SAL, saline

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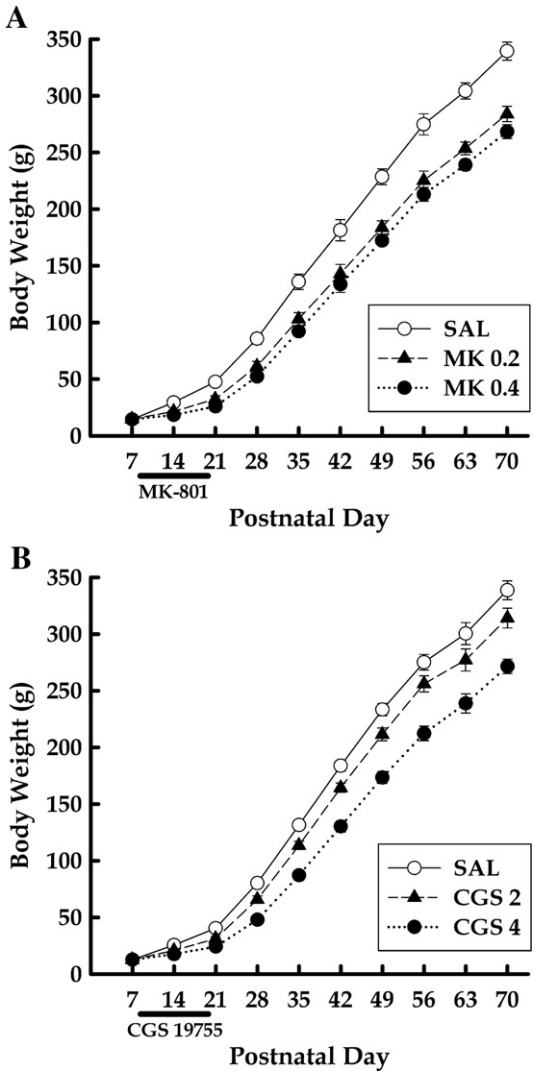

Fig. 1 – The time courses of mean body weight in rats neonatally treated with MK-801 (panel A) or CGS 19755 (panel B). Drugs were treated twice daily on postnatal days 7–20. Body weights in postnatal day 7 were measured immediately before the first drug treatment. Vertical bars indicate the S.E.M.

(Facchinetti et al., 1993, 1994; Gorter and de Bruin, 1992; Gorter et al., 1991a,b; 1992a,b; Griesbach and Amsel, 1998; Latysheva and Rayevsky, 2003; Nemeth et al., 2002; O'Donoghue et al., 1993; Sircar, 2003; Sircar and Soliman, 2003; Sircar et al., 1994; Stefani and Moghaddam, 2005; Virgili et al., 1994). For example, it was reported that neonatal repeated treatment of PCP increased NMDA-receptor bindings in the hippocampus and frontal cortex in adulthood (Sircar, 2003). It was also found that neonatal repeated MK-801 increased sensitivity to a competitive NMDA antagonist AP5 (2-amino-5-phosphonopentanoic acid) on the hippocampal electrophysiological responses in adulthood (Gorter et al., 1992b). These results suggest that neonatal repeated treatment of NMDA antagonists caused upregulation of hippocampal NMDA receptors in adulthood. In addition, it was found that neonatal repeated treatment with MK-801 or PCP caused an impairment in the spatial, but not cue, navigation task performance in the Morris water maze (Gorter and de Bruin, 1992; Nemeth et al., 2002; Sircar, 2003). This selective deficit in spatial learning agrees with the findings in rats with hippocampal lesions (Morris et al., 1982) or in those under the treatment of an NMDA antagonist in adulthood (Morris, 1989; Morris et al., 1986), thus the deficit might be, at least partly, due to dysfunction of hippocampal NMDA receptors induced by neonatal NMDA antagonism.

Although working memory is known as a memory type which is impaired by hippocampal lesions (Olton and Papas, 1979), by acute treatment of NMDA antagonists (Kawabe et al., 1998a,b), and in patients with some kinds of mental disorders (Castner et al., 2004; Goldman-Rakic, 1994; Hill, 2004; Pennington and Ozonoff, 1996), effects of neonatal or adult repeated treatment of NMDA antagonists on working memory in rats have not been well known yet. The purpose of the present study was to investigate the effects of these repeated treatments on working memory in rats. For this purpose, we designed to comparatively examine the effects of neonatal and adult repeated treatments of NMDA antagonists on the radial-arm maze learning, which is known as one of the measures of spatial working memory, and is highly sensitive to hippocampal damages (Olton and Papas, 1979) and NMDA receptor blockade (Kawabe et al., 1998a,b; Yoshihara and Ichitani, 2004). In neonatal treatment, we used both non-competitive and competitive antagonists, MK-801 and CGS 19755 (*cis*-4-phosphonomethyl-2-piperadine carboxilic acid), respectively.

2. Results

2.1. *Experiment 1: effects of neonatal repeated treatment of a non-competitive NMDA antagonist, MK-801*

Fig. 1A shows the time-course of mean body weight in each drug condition. MK-801-treated rats began to show a markedly slower increase of body weight immediately after the beginning of the treatment. There were significant main effects among drug groups [$F(2, 24)=19.02$, $p<.01$] and postnatal days [$F(9, 216)=2805.63$, $p<.01$], and a significant drug×postnatal day interaction [$F(18, 216)=13.72$, $p<.01$]. It was also revealed that MK-801 0.2 and 0.4 mg/kg groups had smaller body weight

Table 1 – Effects of neonatal and adult repeated treatment of NMDA antagonists on days to learning criterion in the radial-maze task (mean ± S.E.M.)

	Drug treatment	Days to criterion
Experiment 1 (neonatal)	SAL	8.7 ± 1.2
	MK-801 0.2 mg/kg	15.2 ± 1.5*
	MK-801 0.4 mg/kg	20.0 ± 0.0**
Experiment 2 (neonatal)	SAL	8.8 ± 1.0
	CGS 19755 2 mg/kg	10.7 ± 1.5
	CGS 19755 4 mg/kg	19.2 ± 0.5**
Experiment 3 (adult)	SAL	11.5 ± 1.2
	MK-801 0.2 mg/kg	11.3 ± 1.5
	MK-801 0.4 mg/kg	9.3 ± 1.7

* $p<.05$, ** $p<.01$ vs. SAL, a Kruskal–Wallis test followed by a Mann–Whitney test with significant levels modified by Ryan's method (Experiment 1), or an ANOVA followed by a Newman–Keuls test (Experiment 2).

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