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Research Report

Effects of an NMDA-receptor antagonist MK-801 on an MMN-like response recorded in anesthetized rats

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ABSTRACT

In the human brain, auditory sensory memory has been extensively studied using a well-defined component of event-related potential named the mismatch negativity (MMN). The MMN is generated in the auditory and frontal cortices in response to deviant stimuli. In monkeys, cortical *N*-methyl-D-aspartate (NMDA) receptors have a central role in the generation of the MMN. MMN-like responses have also been recorded in other animals, including rats. The present study aimed at determining whether the MMN-like response in rats depends on an intact NMDA-receptor system. We recorded auditory evoked responses during an oddball paradigm epidurally in anesthetized rats that had received intraperitoneal injections of saline or an NMDA-receptor antagonist MK-801. An MMN-like response was recorded in the oddball paradigm in saline-treated rats. Further, this response was dose-dependently blocked by MK-801. These results suggest that the MMN-like response in rats depends on an intact NMDA-receptor system.

1. Introduction

An infrequent change in the sequence of standard auditory stimuli in an oddball paradigm elicits an auditory event-related potential (ERP) component in humans termed the mismatch negativity (MMN) (Näätänen et al., 1978, 2007). MMN is presumed to reflect the existence of a memory trace of the frequent standard stimulus at the moment of the presentation of an infrequent, deviant, stimulus (Näätänen, 1990, Näätänen et al., 1978). The MMN is considered an automatic and "pre-attentive" phenomenon (Näätänen, 1990, Näätänen et al., 1993); it can be recorded in the absence of subject's attention to auditory stimuli (Alho et al., 1992, Näätänen, 1991) and even in unconscious coma patients (Kane et al., 1993). ERPs resembling MMN (MMN-like ERPs) have also been recorded in various non-human animal species including primates (Javitt et al., 1994,

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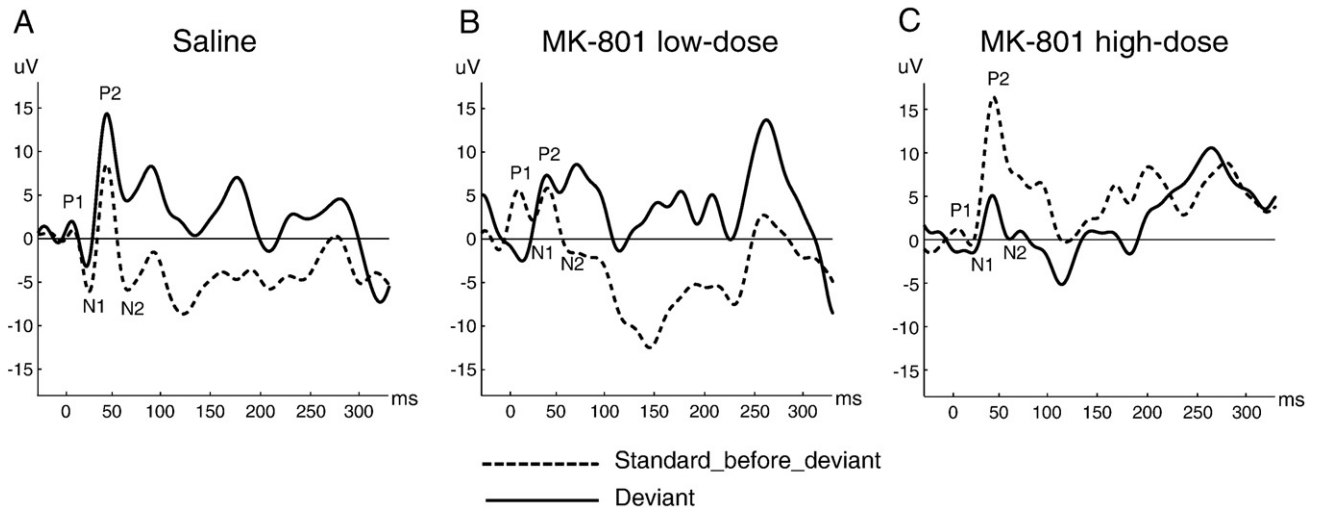

Fig. 1 – Evoked responses to the Standard_before_deviant and Deviant tones recorded in the oddball paradigm in the saline (A), MK-801 low-dose (B) and MK-801 high-dose (C) conditions. The 0-ms time point indicates the start of the stimulus.

1996), rabbits (Ruusuvirta et al., 1996), cats (Csépe et al., 1989, 1994), guinea pigs (Kraus et al., 1994) and rats (Ruusuvirta et al., 1998). The results obtained in rats have not been consistent, however. Lazar and Metherate (2003) found no MMN-like ERPs in epidural recordings above the auditory cortex during an oddball paradigm in rats anesthetized with intraperitoneal injections of urethane and xylazine. In contrast, Ruusuvirta et al. (1998) found such ERPs between 63 and 196 ms from stimulus onset in recordings above the auditory cortex in urethane-anesthetized rats.

In the central nervous system, glutamate is the main excitatory neurotransmitter (Dingledine et al., 1999, Sheng, 2001). One type of ionotropic glutamate receptors is the *N*-methyl-D-aspartate (NMDA) receptor. The NMDA receptors seem to play a central role in the generation of the MMN. In unanesthetized monkeys, intracortical injections of NMDA-receptor antagonists (phencyclidine, MK-801) dose-dependently blocked the generation of MMN recorded intracortically in the primary auditory cortex (Javitt et al., 1996).

Research elucidating neural mechanisms underlying MMN and, further, the role of the NMDA receptors in the generation of MMN can yield information that is potentially of high clinical relevance, especially in the field of schizophrenia research. Namely, schizophrenia patients have reduced MMN responses (Javitt et al., 1993, 1995; Shelley et al., 1991), and evidence of possible genetic markers for schizophrenia suggests that the disease is related to dysfunction in genes involved in signal transduction in NMDA receptors (Brzustowicz et al., 2004). The combination of these two lines of evidence with a possibility to measure MMN in rats may therefore pave the way for a new era of clinical research on the disease enabled by the use of animal models, including genetic ones, in related explorations.

The present study aimed at determining whether rats under pentobarbital-sodium anesthesia show MMN-like ERPs and, further, if they do whether these ERPs can be blocked by a high-affinity uncompetitive NMDA-receptor antagonist MK-801. This drug blocks the NMDA receptor by binding within the ionofore of the channel independently of glutamate concentration (Rogawski and Wenk, 2003). The experimental design included animals treated with saline, a low-dose of MK-801, or a high-dose of MK-801.

Table 1 – The mean (±SEM) latencies (ms) and amplitudes (μV) of the P1, N1, P2 and N2 components of the ERPs to the Standard_before_deviant (StbD) and Deviant (Dev) tones in the saline, MK-801 low-dose and MK-801 high-dose conditions

	Saline		MK-801 low-dose		MK-801 high-dose	
	StbD	Dev	StbD	Dev	StbD	Dev
P1						
Latency	8.5 (1.4)	7.0 (1.3)	12.3 (2.0)	16.5 (3.1)	12.0 (2.8)	14.2 (2.7)
Amplitude	3.2 (1.1)	2.8 (2.2)	8.4 (3.7)	4.0 (1.4)	4.8 (3.7)	4.4 (2.1)
N1						
Latency	22.3 (2.2)	20.2 (2.5)	33.5 (4.2)	28.7 (5.0)	24.0 (2.4)	27.1 (4.7)
Amplitude	−9.5 (3.1)	−8.2 (3.2)	−5.1 (3.1)	−9.2 (3.6)	−4.1 (3.8)	−10.0 (2.9)
P2						
Latency	40.5 (2.7)	40.6 (2.7)	51.2 (4.7)	52.1 (5.6)	42.7 (1.8)	46.0 (4.4)
Amplitude	13.8 (4.1)	19.6 (5.4)	11.2 (5.7)	12.4 (4.6)	18.6 (4.7)	8.2 (4.9)
N2						
Latency	59.9 (2.9)	58.7 (2.8)	76.0 (5.5)	73.8 (6.9)	65.2 (3.4)	64.1 (5.0)
Amplitude	−8.3 (5.0)	0.1 (3.3)	−8.8 (4.0)	−1.7 (5.0)	0.4 (4.7)	−2.1 (5.7)