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Differential effects of NMDA receptor antagonists at lower and higher doses on basal gamma band oscillation power in rat cortical electroencephalograms

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ABSTRACT

Schizophrenic patients have been shown to exhibit abnormal cortical gamma band oscillation (GBO), which is thought to be related to the symptoms of schizophrenia, including cognitive impairment. Recently, non-competitive NMDA receptor (NMDAr) antagonists such as MK-801 and ketamine have been reported to increase the basal GBO power in rat cortical electroencephalograms. However, the mechanisms underlying the increase in basal GBO power induced by non-competitive NMDAr antagonists remain unclear. In the present study, we characterized the non-competitive NMDAr antagonists-increased GBO (30–80 Hz) power. MK-801 (0.05–0.2 mg/kg) increased the GBO power, exhibiting an inverted U-shape dose–response curve; at higher doses (0.3–1 mg/kg), the increase in GBO was reversed. The GBO power was closely correlated with the high-frequency oscillation (130–180 Hz) power following MK-801 administration, while the GBO power was inversely correlated with the increase in delta oscillation (0.5–4 Hz) power at higher doses. PCP (1.25–10 mg/kg) and ketamine (2.5–30 mg/kg) also exhibited the inverted U-shape dose-responses for the basal GBO power similar to MK-801. Interestingly, memantine (10–30 mg/kg) dose-dependently and potently increased the GBO power without remarkably affecting the other frequency band. In contrast, other psychotomimetics, such as methamphetamine (1–10 mg/kg) and DOI (0.5–2 mg/kg), did not induce noticeable changes in the basal GBO power even at doses that induce abnormal behaviors, indicating that the increase in GBO power induced by NMDAr antagonists is not necessarily attributed to psychotomimetic effects. In conclusion, the basal GBO power increase in response to non-competitive NMDAr antagonists may reflect the cortical hyperglutamatergic state through GABAergic disinhibition.

1. Introduction

Abnormalities in the cortical gamma band oscillation (GBO), which is an essential mechanism for cortical information transmission and processing, have been observed in psychiatric disorders including schizophrenia (Sz) (Başar and Güntekin, 2008; Uhlhaas and Singer, 2010; Woo et al., 2010). An abnormal GBO is thought to be related to symptoms in Sz, including cognitive dysfunction (Uhlhaas and Singer, 2010; McNally et al., 2013). Thus, cortical GBO power has attracted attention as a translational biomarker in Sz (Gandal et al., 2012).

Subanesthetic doses of non-competitive *N*-methyl-D-aspartate receptor (NMDAr) antagonists, such as phencyclidine (PCP) and ketamine, produce schizophrenic symptoms in healthy humans (Javitt and Zukin, 1991; Krystal et al., 1994; Newcomer et al., 1999) and laboratory animals (Moghaddam and Jackson, 2003; Adell et al., 2012) and profoundly exacerbate pre-existing symptoms in Sz patients (Lahti et al., 1995). Recently, non-competitive NMDAr antagonists have been reported to enhance the basal (spontaneous) GBO power of cortical electroencephalogram (EEG) recordings and local field potential (LFP) recording from several brain areas

Abbreviations: GBO, gamma band oscillation; HFO, high frequency oscillation; DBO, delta band oscillation; NMDAr, *N*-methyl-D-aspartic acid receptor; Sz, schizophrenia; EEG, electroencephalogram; MK-801, (5*S*,10*R*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate; ketamine, 2-(2-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride; PCP, phencyclidine hydrochloride; memantine, 3,5-dimethyl-1-adamantanamine hydrochloride; METH, methamphetamine hydrochloride; DOI, (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride; PFC, prefrontal cortex; Glu, glutamate; GABA, gamma-amino butyric acid; FS/PV-IN, fast-spiking parvalbumin-containing GABA interneurons; PN, pyramidal neurons; AUC, area under the curve; ANOVA, analysis of variance.

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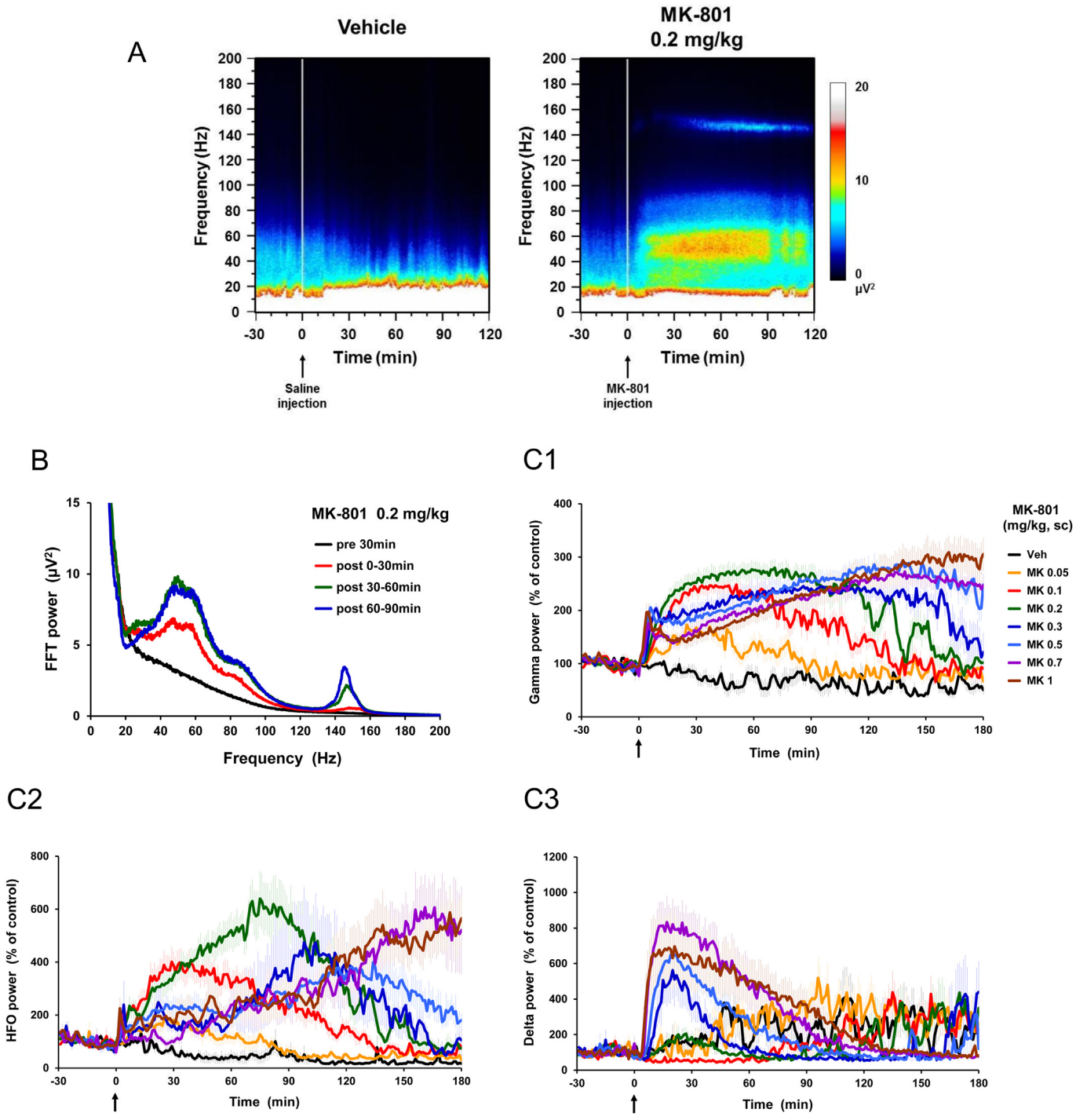

Fig. 1. Effect of MK-801 on basal EEG power recorded from rat prefrontal cortex. (A) Heatmap colors for time courses of changes in basal EEG power. The left and right panels show the average power in the vehicle-treated group ($n = 6$) and the MK-801 (0.2 mg/kg)-treated group ($n = 6$), respectively. The white lines (0 min) indicate the period of drug injections. (B) Averaged power spectrum (30-min bin) for the MK-801 (0.2 mg/kg)-treated group ($n = 6$). (C) Time courses for changes in GBO power (30–80 Hz; C1), HFO power (130–180 Hz; C2), and DBO power (0.5–4 Hz; C3) in cortical EEG before and after the administration of the vehicle or MK-801 (0.05–1 mg/kg). The arrows indicate the timing of the vehicle or MK-801 administration (0 min). The EEG power are shown as the corrected values normalized with the mean value before drug administration. (D) AUC values for 60 min after the administration of the vehicle or MK-801 in transitions of GBO power (D1), HFO power (D2), and DBO power (D3). The data represent the mean ± SEM obtained from 6 to 10 animals per group. The asterisks indicate the statistical significance compared to the vehicle ($^{*}P < 0.05$, $^{***}P < 0.001$) or the maximal effective dose at 0.2 mg/kg in GBO and HFO power ($^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$). (E) Correlations between GBO and HFO power in the MK-801 (0.05–1 mg/kg)-treated groups ($n = 62$; E1) and between GBO and DBO power in the MK-801 (0.2–1 mg/kg)-treated groups ($n = 42$; E2) during 0–60 min post-dosing.

including the prefrontal cortex (PFC) in freely moving rats (Pinault, 2008; Hakami et al., 2009; Nicolás et al., 2011; Kulikova et al., 2012). Likewise, the aberrant GBO increases have also been observed in ketamine-challenge studies in healthy humans (Hong et al., 2010; Sanacora et al., 2013). Therefore, the reduced function of NMDAr may be involved in the aberrant GBO increase, as well as schizophrenic symptoms.

Abnormal GBO is thought to be attributable to a disturbance in parvalbumin (PV)-containing gamma-amino acid (GABA) interneurons (Gonzalez-Burgos et al., 2010; Gonzalez-Burgos and