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Research Report

Desipramine attenuates forced swim test-induced behavioral and neurochemical alterations in mice: An *in vivo* ^{1}H-MRS study at 9.4 T

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ABSTRACT

The forced swim test (FST) is a behavioral paradigm that is predicative of antidepressant activity in rodents. The objective of this study was to examine the effects of desipramine (DMI) pretreatment on behavioral and regional neurochemical responses in the left dorsolateral prefrontal cortex (DLPFC) and hippocampus of mice exposed to the FST using proton magnetic resonance spectroscopy (^{1}H-MRS). An ultra short echo stimulated echo acquisition (STEAM) localization sequence (TR/TM/TE = 5000/20/2.2 ms) was used to measure *in vivo* proton spectra from the left DLPFC (voxel volume: 7 μl) and hippocampus (6 μl) of C57BL/6 mice at 9.4 T and acquired proton spectra post-processed offline with LCModel. The FST induced significant increase of glutamate (Glu) and myo-inositol (mIns) concentrations in the left DLPFC and hippocampus, respectively. In addition, creatine + phosphocreatine (Cr + PCr) concentrations in the left DLPFC were significantly decreased as compared to control. The metabolic alterations induced by the FST were reverted to level similar to control by acute DMI administration. Our results suggest that glutamatergic activity and glial cell dysfunction may contribute to the pathophysiological mechanisms underlying depression and that modulation of synaptic neurotransmitter concentrations represents a potential target for antidepressant drug development.

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Abbreviations: FST, forced swimming test; DMI, desipramine; 1H-MRS, proton magnetic resonance spectroscopy; DLPFC, dorsolateral prefrontal cortex; TCA, tricyclic antidepressants; 5-HT, serotonin; NE, norepinephrine; PI-cycle, phosphatidylinositol cycle; IP1, inositol monophosphatase; STEAM, stimulated echo acquisition; VOI, volume of interest; RARE, rapid acquisition with a relaxation enhancement; FASTMAP, fast automatic shimming technique by mapping the projections; VAPOR, variable power RF pulses with optimized relaxation delays; Glu, glutamate; mIns, myo-inositol; Cr, creatine; PCr, phosphocreatine; Ala, alanine; Asp, aspartate; GABA, γ-aminobutyric acid; Glc, glucose; Gln, glutamine; GPC, glycerophosphorylcholine; PCho, phosphorylcholine; Lac, lactate; Scy, scyllo-inositol; NAA, N-acetylaspartate; NAAG, N-acetylaspartylglutamate; Tau, taurine; CRLB, Cramer–Rao lower boundary

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1. Introduction

Tricyclic antidepressants (TCA) are the most frequently used drugs for the treatment of depression. They block the presynaptic reuptake of serotonin (5-HT) and/or norepinephrine (NE) and, thereby, increase the amount of neurotransmitters available at the synapse (U'Prichard et al., 1978). Desipramine (DMI) is the one of TCA that has been studied extensively in behavioral models of depression in rodent (Antonio et al., 1988; Detke et al., 1995, 1997; Detke and Lucki, 1996).

The forced swimming test (FST) is a behavioral model developed to predict the efficacy of antidepressant drugs and is sensitive to compounds acting on the 5-HT and/or NE system (Porsolt et al., 1977). The test is based on the observation that the animal, after an initial struggling phase, develops an immobile posture when immersed in cold water without the possibility of escape. Immobility in the FST was originally considered as a model of depression (Porsolt et al., 1977) and is thought to reflect either a failure of persistence in escape-directed behavior (i.e. behavioral despair). Unlike the rat FST model, in mice, one exposure is sufficient to generate a stable immobility readout that can be changed by acute pretreatment with antidepressant agents (Petit-Demouliere et al., 2005). The mechanism of the effects, which still remains unclear, may reflect changes occurring in neurotransmitter receptors and receptor-mediated signal transduction systems.

Until recently, research has focused on the ability of antidepressant drugs to increase escape motivated behavior in the FST paradigm, with little examination of the neurochemical consequences of swim stress or the neurochemical basis of antidepressant-induced behavioral changes that occur in this test. *In vivo* magnetic resonance spectroscopy (^{1}H-MRS), which has become a versatile tool in medicine and pharmacological research, is a unique method for non-invasive quantification of brain metabolites. Recent technical and methodological developments in high field and in spectra analysis have dramatically increased the neurochemical information content achievable from *in vivo* ^{1}H NMR spectra (Pfeuffer et al., 1999; Tkáč et al., 2004).

In this study, we investigated the effects of DMI pretreatment on *in vivo* neurochemical responses in mice that were exposed to FST (see Fig. 1) using ^{1}H-MRS. Two brain regions (left dorsolateral prefrontal cortex (DLPFC) and left hippocampus) that are important areas of neuroanatomical circuits of depression and in modulating cognitive brain function were selected to determine region-specific therapeutic responses. The DMI, one of the TCA, was chosen to monitor therapeutic responses since the selective 5-HT reuptake inhibitors (SSRIs) such as fluoxetine have a weak effect on the immobility time of mouse FST, while the DMI apparently can induce anti-immobility effects (Detke et al., 1995; Sanchez and Meier, 1997; Yamada and Sugimoto, 2002).

2. Results

2.1. Behavioral test

The single IP administration of DMI with dose of 10 mg/kg to mice 45 min prior to the FST led to a significant decrease in the mean count for immobility (20.4%) compared to the saline+FST group ($t=2.79$; d.f.=18; $P=0.012$). The climbing and swimming behaviors were not modified significantly by treatment with DMI. The effects of treatment with DMI on the behavioral responses are illustrated in Fig. 2.

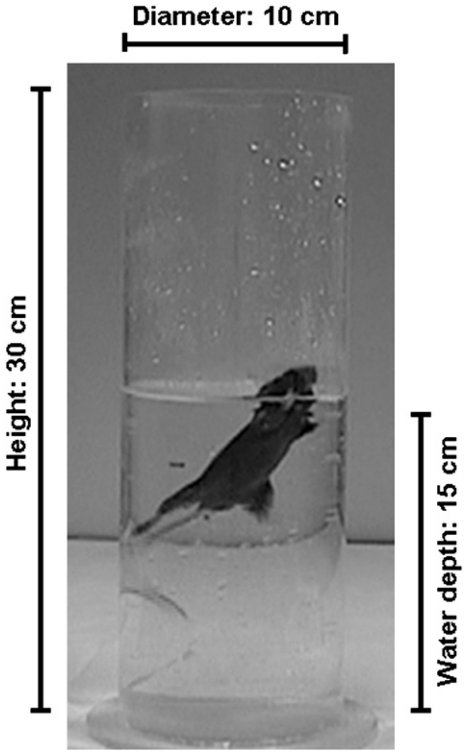

Fig. 1 – A mouse shows active behavior in an inescapable cylinder during the FST procedure. The tests were performed for 6 min prior to MRI/MRS acquisitions. All swimming sessions were recorded from the front view.

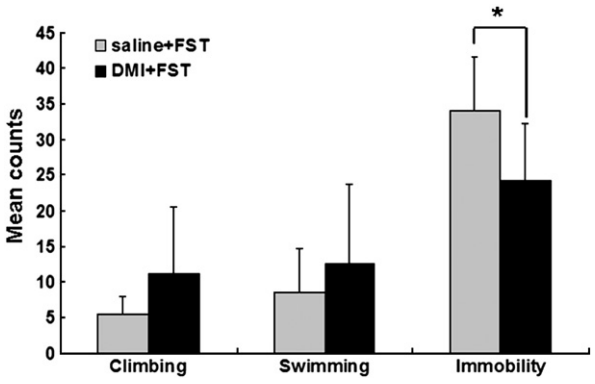

Fig. 2 – Effects of acute DMI treatment (10 mg/kg, IP) on the behavioral responses of C57BL/6 mice subjected to the FST (mice treated with saline, $n=10$; mice treated with DMI, $n=10$). The predominant behavior is scored every 5 s during the last 4 min of the test by a blinded scorer. Data are expressed as mean counts. Significance level (independent *t*-test): $^*P<0.05$.