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BRAIN RESEARCH

Research Report

The antidepressant agomelatine inhibits stress-mediated changes in amino acid efflux in the rat hippocampus and amygdala

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ABSTRACT

Agomelatine is a potent melatonergic (MT1 and MT2) receptor agonist and $5HT_{2C}$ antagonist that is an effective antidepressant in animal models of depression and in patients suffering from depression. Our recent studies revealed that acute restraint stress increases extracellular levels of glutamate and GABA and that these increases in amino acid efflux are inhibited by some but not all antidepressants. In view of the increasing evidence supporting a role of amino acids in the pathology of depression, the current study examined whether acute stress-mediated changes in glutamate and GABA neurotransmission are modulated by agomelatine. In agreement with our previous work, acute stress increases extracellular glutamate levels in the basolateral nucleus of the amygdala (BLA). Similarly, acute stress increases glutamate efflux in the central nucleus of the amygdala (CeA). In the hippocampus, acute stress increases glutamate efflux and elicits an oscillatory pattern of GABA efflux. Agomelatine administration (40 mg/kg ip) prior to acute stress inhibited stress-mediated increases in glutamate efflux in the hippocampus, BLA and CeA. These results demonstrate that acute agomelatine administration effectively inhibits acute stress-mediated changes in extracellular glutamate in the rat hippocampus and amygdala. While acute stress did not modulate GABA efflux in these regions, agomelatine treatment induced an overall reduction of GABA levels in the hippocampus. These data suggest that agomelatine modulates amino acid efflux in limbic structures implicated in major depressive disorder.

1. Introduction

Acute stress modulates the functional activities of limbic brain regions such as the hippocampus and amygdala, including behavioral processes such as learning consolidation and retrieval (Joels and Baram, 2009; McEwen and Gianaros, 2011). Underlying these behavioral responses, acute stress is known to facilitate amygdalar long term potentiation (LTP) (Vouimba et

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al., 2004) while inhibiting hippocampal LTP (Shakesby et al., 2002). A variety of neurotransmitter systems may contribute to these acute stress-mediated adaptations, including the glutamatergic system (Reagan et al., 2008). For example, pharmacological analyses have implicated NR2B-containing NMDA receptors in acute stress mediated electrophysiological changes (Wang et al., 2006) and more recent studies have demonstrated that acute stress differentially regulates the phosphorylation state of GluA1 and GluA2 AMPA receptor subunits in the hippocampus and amygdala (Caudal et al., 2010). Neurochemical studies have also determined that acute stress regulates extracellular levels of glutamate in these limbic regions. For example, in vivo microdialysis studies by Yamamoto and colleagues determined that acute restraint stress increases extracellular levels of glutamate in the rat hippocampus (Lowy et al., 1993). Studies by Moghaddam revealed that acute restraint stress and acute swim stress increased extracellular glutamate levels in the rat hippocampus, stress-induced changes that were inhibited by the voltage-gated Na^+-channel blocker tetrodotoxin (TTX) (Moghaddam, 1993). Noise stress also increases glutamate levels in the rat amygdala in a TTX-dependent manner (Singewald et al., 2000). More recently, we have demonstrated that acute stress increases extracellular levels of glutamate in the basolateral nucleus of the amygdala (BLA) and the central nucleus of the amygdala (CeA) in a TTX-dependent manner (Reznikov et al., 2007). Studies that have examined GABA neurochemistry have identified region-specific and stressor-specific responses to acute stress in the rat amygdala. For example, extracellular levels of GABA in the rat hippocampus are differentially affected by different types of acute stress (de Groote and Linthorst, 2007), while noise stress fails to increase GABA efflux in the rat amygdala (Singewald et al., 2000). Our recent studies indicate that acute restraint stress elicits an oscillatory pattern of GABA efflux in the rat BLA, acute stress effects that were inhibited by TTX (Reznikov et al., 2009).

Collectively, these studies demonstrate that acute stress modulates GABAergic and glutamatergic tones in the hippocampus and amygdala, which may thereby participate in stress-induced plasticity changes in these limbic regions. Given the putative role of stress in neuropsychiatric conditions like depressive illness, it is surprising that relatively few studies have examined the ability of antidepressants to modulate acute stress effects on amino acid efflux in the hippocampus and amygdala. Agomelatine is a potent melatonin (MT1 and MT2) receptor agonist (Audinot et al., 2003) and $5HT_{2C}$ antagonist (Millan et al., 2003) that possesses antidepressant effects in various animal models of depression (Barden et al., 2005; Bertaina-Anglade et al., 2006; Bourin et al., 2004; Papp et al., 2003) and anxiety (Millan et al., 2005; Papp et al., 2006). Moreover, an antidepressant effect of agomelatine

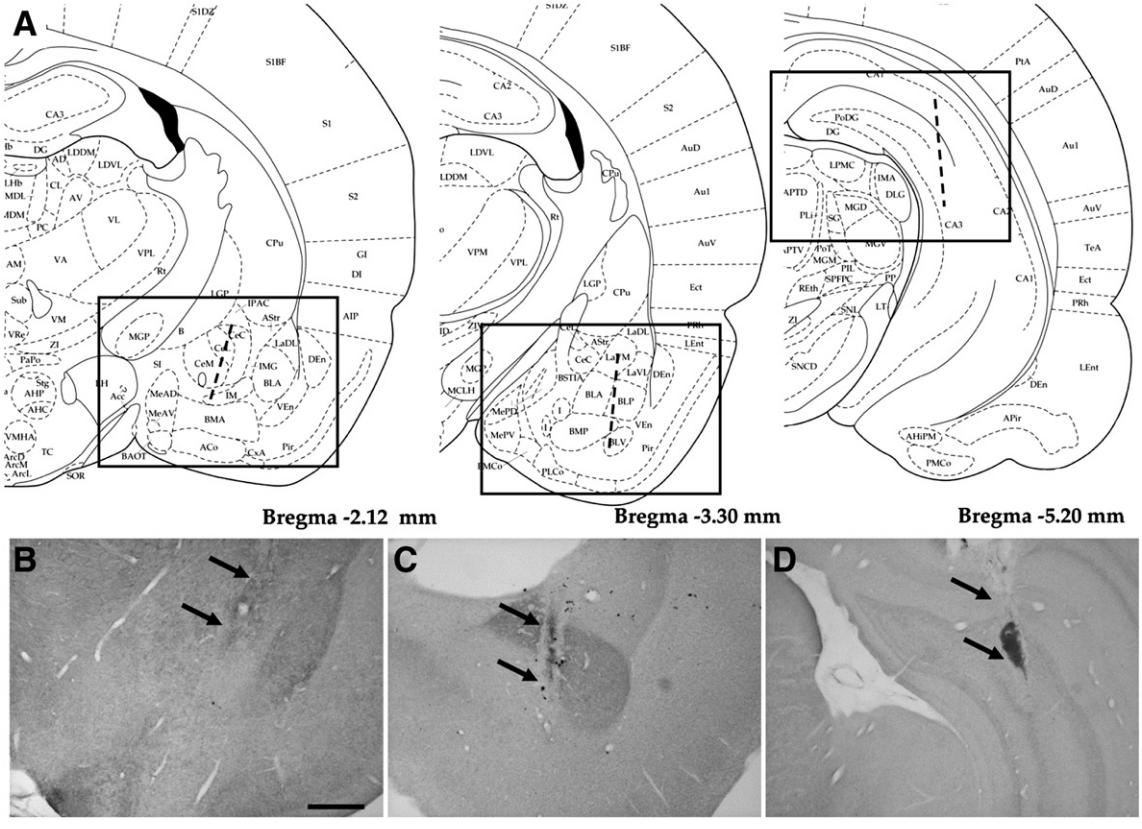

Fig. 1 – A. Schematic representation of microdialysis probe placements for (L–R) CeA, BLA and hippocampus. The boxed area and dashed lines indicate the approximate regions and probe tracts, respectively, which are represented below. B–D. Photomicrographs of acetylcholinesterase-stained sections indicating probe tracts (arrows) for CeA (B), BLA (C) and hippocampus (D). Scale bar in (B) represents approximately 1 mm for all photomicrographs.
Figures in panel A are adapted from Paxinos and Watson (1998).