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Research article

Antidepressant action via the nitric oxide system: A pilot study in an acute depressive model induced by arginin.

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HIGHLIGHTS

- iNOS expression in the brain is increased with arginine depressive rat model.
- Milnacipran elevates serum NO in this model.
- Fluoxetine raises brain eNOS expression in this model.
- Either milnacipran or mirtazapine do not change NOS expressions in this model.

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ABSTRACT

Nitric oxide (NO) may be a neurotransmitter related to major depressive disorder (MDD) because the selective neuronal NO synthase (NOS) inhibitor, 7-nitroindazole, induces dose-dependent antidepressant-like effects. However, its role in MDD is not yet known. The purpose of our study was to determine if antidepressants improve depression via the NO pathway using an acute depressive rat model induced by L-arginine (AR). Three types of antidepressants were examined, fluoxetine (FLX, 10 mg/kg), milnacipran (MIL, 30 mg/kg), and mirtazapine (MIR, 10 mg/kg), in a depressive model that used AR (750 mg/kg) pretreatment. mRNA expression levels of three NOS subtypes were analyzed by real-time PCR, as well as serum NO levels. Significant increases in iNOS mRNA expression levels were found in brain regions after AR treatment, although the eNOS gene tended to decrease with AR injection. After antidepressant treatment, there were no mRNA expression changes in either nNOS or iNOS. However, eNOS mRNA expression significantly increased with FLX (cerebellum, $P = 0.011$; hippocampus, $P = 0.011$; midbrain, $P = 0.011$; pons, $P = 0.013$; striatum, $P = 0.011$; and thalamus, $P < 0.001$). There was a statistically significant increase in serum NO levels with MIL treatment ($P = 0.011$). We conclude that changes in eNOS mRNA levels in the brain with FLX treatment, and amount of serum NO with MIL treatment may be related to antidepressant effects of both agents, but further experiments are needed to confirm involvement of the NO system in MDD.

1. Introduction

Major depressive disorder (MDD) is an important mental disorder, with a lifetime prevalence rate of 10–30% for women and 7–15% for men [1]. Changes in monoamine neurotransmitters in the brain, including norepinephrine, serotonin, and dopamine, are implicated in MDD pathogenesis [2]. Several studies on the nitric oxide (NO) system suggest that it may also be involved in MDD. NO levels in MDD patients have been found to be both increased [3] and decreased [4], potentially due to differing NO subtypes, different states, or different treatments received. In particular, MDD patients that attempt suicide are reported to have high plasma NO levels [5].

NO is synthesized from L-arginine (AR) by three NO synthase (NOS) isoforms: neuronal (nNOS), inducible (iNOS), and endothelial NOS (eNOS) [6]. The non-selective NOS inhibitor, L-N^G-nitroarginine methyl ester (L-NAME), and the selective neuronal NOS inhibitor, 7-nitroindazole, induce dose-dependent antidepressant-like effects in the forced swimming test [7–9]. Furthermore, hippocampal NOS expression is significantly increased in depressed patients [10]. Thus, we propose that antidepressants may exert an effect via the brain NO system. To our knowledge,

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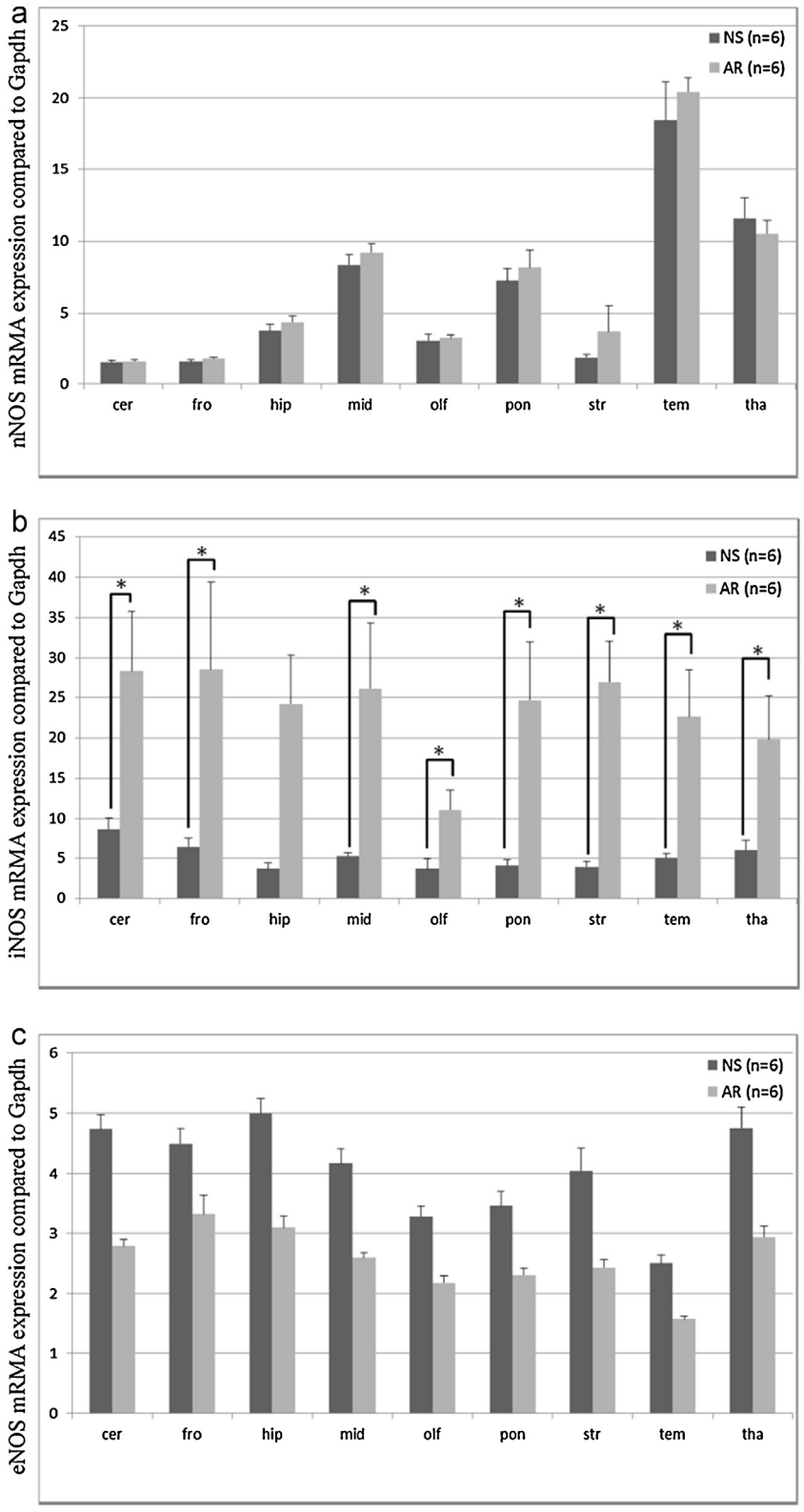

Fig. 1. mRNA expression of NOS subtypes. (A) nNOS, (B) iNOS, and (C) eNOS in brain tissue with or without AR treatment. Values are expressed as mean + S.E.M. ($n = 6$; $^*P < 0.05$). NS, normal saline; AR, L-arginine; NOS, nitric oxide synthase; nNOS, neuronal NOS; iNOS, inducible NOS; eNOS, endothelial NOS; cer, cerebellum; fro, frontal cortex; hip, hippocampus; mid, midbrain; olf, olfactory; str, striatum; tem, temporal cortex; tha, thalamus.

there are only a few reports investigating antidepressant mechanisms of the NO system. Here, we determine if antidepressants representing distinct drug categories, specifically, fluoxetine as a selective serotonin reuptake inhibitor (SSRI), milnacipran as a serotonin noradrenalin reuptake inhibitor (SNRI), and mirtazapine as a noradrenalin serotonin system antidepressant (NaSSA), also work as NO modulators in an acute depressive model induced by AR. Our findings will provide new information on MDD treatment options.