Microdialysis Approach to Study Serotonin Outflow in Mice Following Selective Serotonin Reuptake Inhibitors and Substance P (Neurokinin 1) Receptor Antagonist Administration: A Review

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Abstract: Classical antidepressant drugs such as Selective Serotonin Reuptake Inhibitors (SSRIs) display several disadvantages, e.g., the onset of action (2 to 3 weeks) to start clinical benefits is too long, and a significant proportion of patients do not respond to this monotherapy. Several strategies have been proposed to overcome these problems, notably the use of potentiating agents, which combined with SSRIs, augment or accelerate their established antidepressant activity. Recent clinical trials proposed that compounds with dual action on both central serotonin (5-HT) and noradrenaline (NA) systems would have a faster action than SSRIs alone. Preclinical electrophysiological and neurochemical studies demonstrated that the putative new class of antidepressants, substance P (neurokinin 1) NK1 receptor antagonists, enhance brain monoaminergic neurotransmissions by reducing the sensitivity of 5-HT1A autoreceptors in the Dorsal Raphe Nucleus, and possibly α2 autoreceptors in the Locus Coeruleus. However, in several clinical studies, a similar delay of therapeutic effects has been reported with NK1 receptor antagonists and SSRIs. Recently intracerebral in vivo microdialysis studies were performed to examine the effects of genetic or pharmacological blockade of Substance P (SP)/NK1 neurotransmission on SSRIs-induced increases in extracellular 5-HT levels in awake, freely moving mice. New evidences suggest that the combination of a NK1 receptor antagonist with a SSRI should benefit depressed patients. This review describes our current knowledge of the role of SP and its preferred NK1 receptors mainly in the modulation of brain serotonergic activity.

Key Words: Microdialysis, NK1 receptors, Selective Serotonin Reuptake Inhibitors, Substance P.

INTRODUCTION

Currently Available Standard Antidepressant Drugs and their Limits

To date, drugs approved for the treatment of major depressive disorders are believed to act on central monoaminergic systems, i.e., mainly on serotonin (5-hydroxytryptamine, 5-HT) and noradrenaline (NA) synaptic transmissions. Selective Serotonin Reuptake Inhibitors (SSRIs: paroxetine, fluoxetine, citalopram, escitalopram), Norepinephrine Reuptake Inhibitors (NRIs: reboxetine) and mixed 5-HT/NA reuptake inhibitors (SNRIs: venlafaxine which also achieves remission in depressed patients [1]) are among the most common antidepressant drugs prescribed so far. They exert their therapeutic effects by increasing availability of these neurotransmitters in synapses in various brain areas. Although SSRIs and NRIs are effective in treating most depressive episodes, a significant rate of depressed patients show only partial or no response to the treatment and some adverse effects were reported after their long-term administration as gain weight and sexual dysfunction [2-4]. In addition, the therapeutic efficacy of SSRIs and NRIs is blunted by their long delay, 6 to 12 weeks of treatment are required to achieve optimal clinical benefits in depressed patients [5]. Thus, psychopharmacological researches focus on strategies which might improve the therapeutic efficacy of these traditional antidepressant drugs. These researches are built on the assumption that an improvement of serotonergic and/or noradrenergic neurotransmission would predict a lower treatment-resistant rate and/or an earlier onset of action of antidepressant drugs.

Strategies Used to Enhance Antidepressant-Like Efficacy of SSRIs

Numerous preclinical studies have highlighted the role of presynaptic 5-HT1A and α2 autoreceptors in limiting the antidepressant action of SSRIs and NRIs, respectively. Autoreceptors are known to exert an inhibitory feedback control that regulates neurotransmission, i.e., the firing rate of neurons, the synthesis and release of a neurotransmitter. For the brain serotonergic system, autoreceptors are located either on cell bodies (somatodendritic, 5-HT1A sub-type) in the raphe nuclei or on terminals of serotonergic axonal projections from midbrain raphe nuclei (5-HT1B sub-type).

By using intracerebral in vivo microdialysis, it was described that hypofunction of somatodendritic 5-HT1A autoreceptors in the Dorsal Raphe Nucleus (DRN) induced by selective 5-HT1A receptor antagonists enhances the ability of SSRIs to increase extracellular 5-HT levels at serotonergic nerve terminals (frontal cortex, hippocampus) [6-8]. In hu-