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Research report

Chronic buspirone treatment normalizes open field behavior in olfactory bulbectomized rats: Assessment with a quantitative autoradiographic evaluation of the 5-HT_{1A} binding sites☆

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Abstract

The olfactory bulbectomized (OBX) rat model of depression has been widely used in studies on the behavioral and neurochemical aspects of human depression. The objective of the present investigation was to assess open field (OF) activity and the brain regional 5-HT_{1A} receptor densities of the sham operated (SHX) and OBX rats treated with saline (SHX-SAL, OBX-SAL), and either 10 mg/(kg day) (SHX-B10, OBX-B10) or 20 mg/(kg day) (SHX-B20, OBX-B20) of buspirone for 14 days, delivered by a subcutaneous osmotic minipump. Adult Sprague–Dawley rats were used for this experiment. The surgery was performed on the first day of the experiment and the rats were randomly assigned to either the SHX or OBX groups. The results of the OF tests were organized in eight groups. Following 14 days of treatment and the final OF tests, the rats were sacrificed and the brains were used for 5-HT_{1A} receptor autoradiography using [^{3}H]8-OH-DPAT. The data showed that the OF activities, 14 days following surgery, in the OBX rats were significantly elevated when compared to the SHX rats. In the OBX rats, only the 14-day treatment with 20 mg/(kg day) of buspirone normalized the elevated OF activity, the same dose shown previously to be needed for the normalization of the regional 5-HT synthesis. A significant reduction in the number of 5-HT_{1A} receptor sites was found in most brain regions in the OBX rats when compared to the SHX rats. Data also show that the regional density of the 5-HT_{1A} receptors in OBX-SAL treated rats is lower than that of the SHX-SAL rats. The 14-day treatment with either 10 or 20 mg/(kg day) of buspirone reduced the 5-HT_{1A} receptors in most brain regions of the SHX rats, without an obvious dose-dependent effect of the buspirone. The comparison between the OBX-B20 and control (SHX-B20) rats suggests that the buspirone treatment resulted in a regional balance in the 5-HT_{1A} sites. A dose dependent reduction in the density of 5-HT_{1A} sites was observed in the sham rats, but the buspirone treatment had very little effect on the density of the 5-HT_{1A} receptors in the OBX rats. From these observations, we conclude that the antidepressant effects of buspirone in the OBX rat model of depression are likely mediated through the fine tuning of the regional imbalance of 5-HT_{1A} receptors with even increases of about 20% in some limbic regions. The data suggest that the neurochemical effects of antidepressants should be studied in animal models of depression rather than in normal rats.

Keywords: Olfactory bulbectomy; Buspirone; Open field; 5-HT_{1A} receptor; Autoradiography

1. Introduction

Buspirone was originally developed as an antipsychotic drug, showing antagonistic effects on the presynaptic D2 receptors with anxiolytic and antidepressant properties [39,45]. Buspirone is a partial agonist on the 5-HT_{1A} receptor [20]. This means that with high extracellular availability of serotonin, buspirone would exert antagonistic action on 5-HT_{1A} receptors, while with low serotonin availability, it would act as an agonist [54]. One should keep in mind that buspirone has a pharmacologically

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active metabolite, α2-adrenergic antagonist [13], which could contribute to a chronic treatment.

Serotonin (5HT) is a neurotransmitter that mediates a wide range of physiological functions, including sleep, feeding, aggression, sexual and parental behavior [28]. Numerous studies have implicated the impaired function of the 5-HT system in the pathogenesis of depression [1,18,37,62]. The olfactory bulbectomized (OBX) rat model of depression has been widely used in studies on behavioral and neurochemical aspects of human depression. This model is one of the rare models in which stable alterations in normal brain functions are associated with behavior and neurochemical changes and those neurochemical changes are normalized by chronic, and not acute, antidepressant treatments [60]. Among many neurochemical alterations found in the OBX rats is the alteration (non-uniform elevation) of 5-HT synthesis [32,79,80], resulting in elevated levels of 5-HT in the brain tissue [46], as well as the alteration of many other neurochemical, immune and neuroendocrine parameters (reviews [38,70]). Olfactory bulbectomy results in dysfunctional changes in many brain regions (*e.g.*, piriform cortex, amygdala; [15,40]) as a consequence of disrupted neuronal connections between the bulbs and other brain regions, despite the fact that olfactory bulbs consist of only 4% of the total brain mass in rats [14]. The behavioral changes following olfactory bulbectomy in rats have been widely reported (see [38,70]). These behaviors are quantifiable, replicable and reversed by chronic, but not acute, administration of therapeutically active antidepressants, including SSRIs [38].

The observed hyperactivity is not related to the loss of smell, as peripherally induced anosomia by zinc sulfate does not affect open field behavior [68]. The possible reason for the hyperactivity of the OBX rat may be due to difficulties in adaptation and risk assessment, or a decrease in competing behavior activity [70,77]. There have been many behavior studies performed in which the effect of antidepressants on behavioral changes were evaluated in the OBX rats, but there are very few studies in which the behavioral changes were correlated with brain neurochemical changes.

5-HT_{1A} receptors are located on the soma and dendrites of the 5HT neurons in the raphe nuclei (somatodendritic autoreceptors) [72,78]. In addition, these sites are also postsynaptic in the projection areas of serotonergic neurons (postsynaptic heteroreceptors). The highest densities of 5-HT_{1A} receptors in the brain are in the limbic brain areas, notably the hippocampus, lateral septum, cortical areas, and also the mesencephalic raphe nuclei (both the dorsal and median raphe nuclei) [5,73]. Electrophysiological and microdyalisis studies have shown that the stimulation of 5-HT_{1A} somatodendritic autoreceptors attenuates the firing of the 5-HT neurons [7,73], as well as the release of 5-HT in the synapses [66]. Prolonged stimulation of these receptors leads to their desensitization [7,26], and desensitization is mediated by G-protein uncoupling from the receptors [43], which reduces the binding capacity. Firing of raphe 5-HT neurons is, in part, regulated by the α-1A adrenergic heteroreceptors and this action is suggested to be stimulatory [63]. The adrenergic influence on the firing rate is more pronounced in the dorsal raphe, rather than the median raphe, areas [36]. The functionally important i2 loop in the α-1A adrenergic receptors has a role only in the coupling of receptors with G-protein, while 5-HT_{1A} i2 is involved in both coupling and the activation of the G-protein [75].

Changes in several parameters of serotonergic neurotransmission in affective disorders have been reported (*e.g.*, 5-HT synthesis [62] and 5-HT_{1A} receptors [23,51,64]). A general hypothesis of the alteration in 5-HT receptor function in subjects with depressive symptoms has been associated with the down-regulation of 5-HT_{1A} receptors [9], and the possible involvement of other 5-HT receptors (*e.g.*, 5HT2 [74]). Many clinical and preclinical studies have reported the down-regulation of 5-HT_{1A} and 5-HT2 sites with antidepressants (*e.g.*, [16,74]). Because of this, the functionality of 5-HT_{1A} sites has been linked to the depressive state [3,24] as well as the processes underlying emotion [33]. The functionality of 5-HT_{1A} receptors is changed by the action of antidepressants [31]. Several clinical studies have shown that interactions through 5-HT_{1A} receptors are important in successful treatments of depressive symptoms [11], and that an addition of a 5-HT_{1A} antagonist (*e.g.*, pindolol) or partial agonist (*e.g.*, buspirone) results in the accelerated action of SSRIs [4,11,16,35]. However, the treatment of depression with buspirone is somewhat controversial. For example, Schwezer et al. [65] reported that buspirone is effective in the treatment of major depression, while Blier [10] concluded that buspirone used for the treatment of depression was not successful because the doses used were not optimal. 5-HT_{1A} agonists have been shown to have antidepressant activity in many animal models of depression [45,70].

The involvement of 5-HT_{1A} receptors in behavior and processes underlying emotion have been established in a variety of animal models with mechanisms which are species dependent (reviewed [33]). The alteration in the 5-HT_{1A} receptors by antidepressants has been shown in laboratory animals [17,57], but in human PET studies the binding potential (Bmx/KD ratio) was decreased in the cell bodies (mainly pre-synaptic sites) without any change in the terminal (post-synaptic sites) regions [52,64].

We previously reported that in normal rats a single dose (10 mg/kg, i.p.) of buspirone induces a significant decrease of 5-HT synthesis throughout the rat brain, but that chronic treatment delivered by minipump did not produce a significant effect on 5-HT synthesis [55]. This suggests a desensitization of 5-HT_{1A} receptors in the normal rat brain. Watanabe et al. [79] showed a widespread but not uniform increase of regional 5-HT synthesis throughout the rat brain following olfactory bulbectomy. This elevation in 5-HT synthesis was restored to the levels found in the sham-operated rats (normal levels) by a 14-day treatment with 10 mg/(kg day) of citalopram [32] as well as a 20 mg/(kg day) treatment, as opposed to a 10 mg/(kg day) treatment, of buspirone [80]. This suggests that the chronic treatment of 20 mg/(kg day) of buspirone normalizes the brain 5-HT synthesis rate in the OBX rat, while a chronic treatment of 10 mg/(kg day) of buspirone desensitizes the 5-HT_{1A} receptors in the intact and sham operated rats. Because buspirone showed a dose dependent influence on regional 5-HT synthesis, which is the neurochemical parameter altered in some brain regions of depressed individuals [62] and produced a normalization at a higher dose in a rat study [80], it was thought that relationships