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Research Report

Acute activation of CB1 cannabinoid receptors transiently decreases PSA-NCAM expression in the dentate gyrus of the rat hippocampus

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ABSTRACT

Recent evidence indicates that the polysialylated neural cell adhesion molecule (PSA-NCAM) is involved in hippocampal plasticity. On the other hand, CB1 receptor activation is known to disturb some hippocampal processes involving plastic changes, such as learning and memory. Therefore, the present study investigated the effect of HU-210, a CB1 receptor agonist, on the expression of PSA-NCAM protein in the dentate gyrus (DG) and CA3 region of the rat hippocampus. It was found that at a dose of 0.1 mg/kg i.p. of HU-210, the number of PSA-NCAM immunoreactive (IR) cells in the DG declined in a time-dependent manner. The decrease in PSA-NCAM expression was observed at 1 and 2 days (ca. 21% and 30%, respectively), but not after 4 h and 4 days following HU-210 administration. However, HU-210 treatment did not change the length density of PSA-NCAM immunopositive processes in CA3 mossy fibers at all the time points measured. The effect observed in the DG on day 2 was blocked by AM-251 (1 mg/kg, i.p.), a CB1 receptor antagonist, given 30 min before HU-210. Neither the number of Ki-67 (IR) cells (a marker of proliferation) nor the number of doublecortin-IR cells (a marker of immature neurons) was affected by HU-210 (0.1 mg/kg, i.p.) treatment at any of the time points. An analysis of co-localization of CB1 receptor protein with PSA-NCAM protein revealed that both proteins were not present in the same population of neurons in the subgranular layer of the DG. The observed changes in PSA-NCAM expression were not related to the reduction of proliferation or differentiation of newly born cells, but were possible due to alternations in the synaptic activity in the DG. However, such alteration in the PSA-NCAM expression may change the timing of the functional maturation of newly born neurons. Moreover, the above finding suggests that acute activation of CB1 receptors may result in the stiffening of the hippocampal structure and susceptibility to plastic changes and may lead to functional impairment governed by alterations in the hippocampal structure.

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Abbreviations: BrDU, 5-bromo-2'deoxyuridine; CCK, cholecystokinin; DCX, doublecortin; DG, dentate gyrus; DSI, depolarization-induced suppression of inhibition; LTP, long-term potentation; LTD, long-term depression; PSA-NCAM, polysialic acid-neural cell adhesion molecule; PV, parvalbumin; THC, Δ9-tetrahydrocannabinol

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1. Introduction

Neuronal plasticity is an important mechanism by which the brain adapts its function to environmental changes. Plastic changes occur not only at the synaptic level, but are also manifested as alterations in the neuronal or brain structure. In functional terms, plastic changes play, among others, an important role in learning and memory, adaptation to stress or addiction.

Recent studies indicate that neural cell adhesion molecules (NCAM) may be an important modulator of neural plastic changes observed in synaptic rearrangements, remodeling of the neuronal shape and generation of long-term potentation and depression (LTP and LTD) (Kiss et al., 2001). The attachment of negatively charged sialic acid residues with a large hydrated volume [specifically polysialic acid (PSA)] to an extracellular domain of NCAM proteins attenuates the adhesive properties of neurons and enables the rearrangement of cell–cell and extracellular matrix-to-cell contacts (Rutishauser and Landmesser, 1996). PSA-NCAM has been shown to regulate cell migration, neurite outgrowth, and axonal fasciculation in the developing central nervous system (Zhang et al., 1992). Its expression is not only limited to the period of brain development (Seki and Arai, 1991a), but is also observed in discrete brain areas that maintain the ability to undergo structural and functional changes in adulthood (Miragall et al., 1988; Theodosis et al., 1994; Nacher et al., 2002b). The mature hippocampus is a structure in which a prominent expression of PSA-NCAM has been constitutively observed (Seki and Arai, 1991b, 1999) and has been associated with the changes in the activity-dependent synaptic plasticity of the adult brain (Seki and Rutishauser, 1998; Cremer et al., 2000; Dityatev et al., 2004) and with the maturation and differentiation of newly born neurons in the dentate gyrus (DG) of the hippocampus (Seki and Arai, 1993). In accordance with these roles, PSA-NCAM expression has been described in newly generated neurons in the granular layer of the DG, in mossy fibers, granule neuron axons, in both the hilus and the CA3 subfield (Seki and Arai, 1991b, 1993, 1999), and also in non-granule neurons (interneurons) (Nacher et al., 2002a). A functional analysis indicates that the PSA-NCAM molecule plays an important role in the hippocampus-dependent learning and memory formation (Fox et al., 1995; Becker et al., 1996; Sandi et al., 2003; Florian et al., 2006). Furthermore, electrophysiological studies show that PSA-NCAM is involved in inducing LTP or LTD in various regions of the hippocampus (Muller et al., 1996; Becker et al., 1996; Schmidt-Hieber et al., 2004). Thus, alterations in the hippocampal expression of PSA-NCAM are mandatory for the structural remodeling of synaptic connections associated with long-term memory and maturation of newly generated neurons.

Current findings indicate that the endocannabinoid system that acts through CB1 receptors is also able to modulate synaptic plasticity in the brain (Chevaleyre et al., 2006). Autoradiographic, immunohistochemical and in situ hybridization studies show that the distribution of CB1 receptor in the brain is heterogenous (Herkenham et al., 1991; Mailleux and Vanderhaeghen, 1992; Moldrich and Wenger, 2000). The highest expression of this receptor type is observed in the cerebral cortex, hippocampus, lateral caudate-putamen, substantia nigra pars reticulata, cerebellum, globus pallidus, cerebellum, olfactory bulb and amygdala. CB1 receptors are expressed on the cell bodies and the nerve terminals of neurons, especially in the subpopulation of inhibitory interneurons, and such distribution seems to be conserved across different regions (Katona et al., 1999, 2001). It is known that CB1 receptors are capable of changing synaptic plasticity in the hippocampus (Davies et al., 2002). Electrophysiological studies have shown that activation of CB1 receptors attenuates LTP and LTD (Misner and Sullivan, 1999; Bohme et al., 2000; Mato et al., 2004). Moreover, they also play a major role in the modulation of synaptic transmission by a phenomenon called depolarization-induced suppression of inhibition (DSI) (Ohno-Shosaku et al., 2001; Wilson and Nicoll, 2001). Besides synaptic changes, CB1 receptor activation may also influence hippocampal plasticity by affecting neurogenesis in the DG of the hippocampus (Rueda et al., 2002; Jin et al., 2004; Jiang et al., 2005; Aguado et al., 2005, 2006). Furthermore, it has been found that even acute activation of hippocampal CB1 receptors evokes cognitive deficits, such as impairment of memory or learning (Lichtman et al., 1995) and plays a pivotal role in the regulation of emotional states associated with stress and anxiety (Viveros et al., 2005), i.e. effects also based on the remodeling of the hippocampal structure (Kiss et al., 2001).

Although recent findings indicate that both cannabinoids and the PSA-NCAM molecule may influence various forms of hippocampal plasticity, there is no evidence on whether the PSA-NCAM protein is engaged in CB1 receptor-driven hippocampal plasticity. Therefore, using immunohistochemistry, we investigated the effect of the CB1 receptor agonist HU-210, on the expression of PSA-NCAM in the DG of the rat hippocampus. In this region, the PSA-NCAM molecule is expressed by immature neurons and plays an important role in the migration and maturation of newly born neurons, but is also engaged in the process of learning and encoding new spatial memory by its ability to rearrange cell–cell synaptic contacts (Song et al., 2005). Since the PSA-NCAM protein controls synaptic plasticity and is a marker of immature neurons, it seemed important to determine whether the CB1 receptor agonist had any effects on the rate of proliferation and neuronal differentiation of newborn cells. For this reason, we determined the impact of HU-210 on the expression of Ki-67, a marker of proliferation (Kee et al., 2002) and doublecortin (DCX), a microtubule-associated phosphoprotein (Rao and Shetty, 2004), which is also a marker enabling visualization of newly born, immature neurons. Additionally, we determined the effect of HU-210 treatment on the length density of PSA-NCAM-positive mossy fiber axons in the CA3 subfield of the hippocampus. Finally, in order to find an anatomical substrate for such an interaction, we investigated whether PSA-NCAM protein was localized in the same population of neurons as were CB1 receptors.

2. Results

2.1. *The effect of HU-210 treatment on PSA-NCAM expression in the dentate gyrus*

An immunohistochemical study showed that PSA-NCAM-immunoreactive (IR) cells are preferentially located in the