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Involvement of the neurotrophin and cannabinoid systems in the mechanisms of action of neurokinin receptor antagonists

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Abstract

The anxiolytic- and antidepressant-like effects of the neurokinin (NK) receptor antagonists have been shown in behavioral studies. According to the involvement of neurotrophin signaling in the mechanisms of action of psychotropic agents, we aimed to investigate whether the selective NK_1, NK_2, or NK_3 receptor antagonists (GR-205171, SR48968, and SR142801, respectively) affect nerve growth factor (NGF) contents in the brain regions involved in the modulation of emotions. To gain a mechanistical insight into the process by which the NK antagonists regulate brain NGF levels, we evaluated the role of the cannabinoid system which is linked to depression and/or antidepressant effects and appears to interact with neurotrophin signaling. According to the results, single injection of the NK receptor antagonists (3, 5, and 10 mg/kg, i.p.) into gerbils did not alter NGF or endocannabinoid (eCB) levels quantified by Bio-Rad protein assay and isotope-dilution liquid chromatography/mass spectrometry, respectively. Three-week administration of 10 mg/kg NK antagonists significantly elevated both NGF and eCB levels in brain-region specific fashion. Pre-application of the CB_1 receptor neutral antagonist AM4113 (5.6 mg/kg) prevented the elevation of NGF or eCB induced by the NK antagonists. AM4113 showed no effect by itself. We conclude that the cannabinoid system is implicated in the mechanisms of action of NK receptor antagonists including the upregulation of brain NGF levels.

1. Introduction

In recent years, the previously dominating interest relating the effects of psychotropic medications on neurotransmitters has

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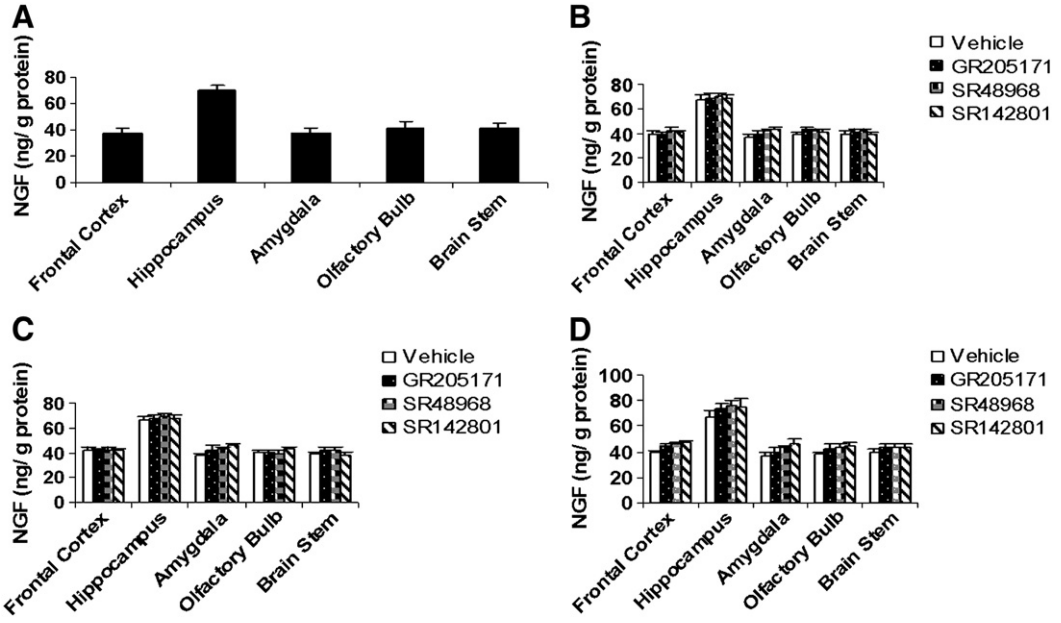

Figure 1 Brain regional levels of NGF at baseline and following acute administration of 3 mg/kg NK receptor antagonists. NGF levels did not differ from those of baseline values and vehicle-treated control groups ($p > 0.05$). A: Baseline levels of NGF, B: NGF levels 24 h after the treatment, C: NGF levels 48 h after the treatment, D: NGF levels 72 h after the treatment. NGF levels are expressed as ng of NGF per g of protein in the resuspended NGF homogenate. Data are expressed as mean ± SEM of n = 5/group.

shifted towards the effects of these agents on intraneuronal signal transduction and neurotrophins (Manji et al., 2000). There is ample evidence that neurotrophins exert numerous neuroprotective effects under pathological conditions which might be important in particular for neurodegenerative and psychiatric diseases (Shaltiel et al., 2007; Schulte-Herbrüggen et al., 2008). In general, the neurotrophic hypothesis of depression proposes that the etiology of depression and/or the action of antidepressant drugs are due, in part, to the regulation of central neurotrophin signaling. Several lines of evidence suggest that neurotrophic factors act as mediators of antidepressant responses. This has led to the investigation of the effects of psychotropic agents on neurotrophin signaling (Dias et al., 2003; Vinay et al., 2004). In recent years, the potential anxiolytic- and antidepressant-like effects of compounds that target the neurokinin (NK) receptors, a class of G protein-coupled receptors which are found in the central nervous system and peripheral tissues, have attracted a growing interest. In this sense, several selective and CNS-penetrating NK receptor antagonists which demonstrate efficacy in the treatment of emesis, anxiety, and depression have been synthesized (Dableh et al., 2005; Griebel et al., 2001; Salomé et al., 2006; Varty et al., 2002; Varty et al., 2003; Zocchi et al., 2003). As compared to the NK_1 antagonists, there are limited data suggesting that the NK_2 or NK_3 receptor antagonists may possess antidepressant and/or anxiolytic properties, meanwhile, the existing data are promising (Ebner et al., 2009; Ribeiro et al., 1999; Rizzo et al., 2003; Steinberg et al., 2001; Stratton et al., 1993). NK_1, NK_2, and NK_3 receptors have been identified in both rodents and humans (Bensaid et al., 2001; Pennefather et al., 2004). The localization of the NK receptors in the cortex, hippocampus, amygdala, and septum may be consistent with the anxiolytic- and antidepressant-like effects of the NK antagonists. Meanwhile, the precise mechanism/s by which these therapeutic effects are brought about are not yet known. We have recently shown that a wide range of psychotropic drugs including desipramine, fluoxetine, phenelzine, haloperidol, and clozapine elevate brain regional levels of NGF (Hassanzadeh and Hassanzadeh, 2010), however, the underlying mechanism(s) have remained elusive. In recent years, the endocannabinoid system (eCBs) and its regulatory functions in both the central and peripheral nervous systems have attracted attention. According to the reports, the eCBs is engaged in a plethora of physiological functions including the emotional disturbances (Bambico et al., 2009; Viveros et al., 2005, 2007). This ubiquitous signaling system appears to be involved in the pathophysiology and/or treatment of depression; as deficiency in the eCB signaling is associated with a behavioral phenotype similar to the symptom profile of severe depression (Hill and Gorzalka, 2005; Serra and Fratta, 2007). Furthermore, CB_1 cannabinoid receptors and the enzymes involved in the synthesis and degradation of the eCB ligands are located in the brain regions crucial for emotionality and stress regulation (Vinod and Hungund, 2006; Witkin et al., 2005). Meanwhile, the neurobiological mechanism(s) linking the eCBs with the pathophysiology of mood disorders and antidepressant action remain somewhat controversial. There are several previous reports indicating the interaction between the endocannabinoids and neurotrophins as well as the signaling interaction between the CB_1 and tyrosine kinase receptors (Angelucci et al., 2008; Aso et al., 2008; Calatozzolo et al., 2007; Williams et al., 2003). This background prompted us to design a study evaluating the involvement of the neurotrophin and eCB systems in the mechanisms of action of the selective NK antagonists. We selected gerbils because the structure and pharmacology of the NK receptors in gerbils resemble those of humans. In particular, gerbils have been suggested to be more suitable species than mice or rats for investigating the anxiolytic- or antidepressant-like effects of NK_1 antagonists (Varty et al., 2002). Furthermore, the selective NK_3 receptor antagonist osanetant has higher affinity for