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Short communication

Central administration of IGF-I and BDNF leads to long-lasting antidepressant-like effects

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Abstract

Drug development research has identified neurotrophic factors as a downstream target of chronic antidepressant treatments. In order to study their antidepressant-like effects, two neurotrophic factors, brain-derived neurotrophic factor and insulin-like growth factor I, were examined in the rat modified forced swimming test after a single icv administration. Both neurotrophins produced antidepressant-like behavioral effects in the modified rat forced swimming test, reducing immobility and increasing swimming. In contrast to currently used antidepressants, which produce acute effects in the forced swimming test, the effects of the neurotrophins were unusually long lasting and persisted at least 6 days after the treatment. Neither neurotrophic factor had an effect on locomotor activity. The results support a role for neurotrophic factors mediating the behavioral effects of antidepressant drugs.

Theme: Disorders of the nervous system
Topic: Neuropsychiatric disorders

Keywords: Antidepressant; Neurotrophin; Insulin-like growth factor I

The development of novel antidepressant treatments is driven by the limited efficacy and delayed onset of clinical effects for currently established antidepressants [15]. Neurotrophic factors, also known as neurotrophins, and their receptors may be candidates for novel antidepressant treatments. Neurotrophins are a family of protein growth factors that are involved in the development, plasticity, and survival of neurons during development [2,5,22]. In other roles, short-term cell signaling by neurotrophic factors appears to mediate cellular plasticity associated with learning and memory. Longer term effects of neurotrophins include increasing cell proliferation and neurogenesis in the adult animal [7]. Recently, studies have proposed that hippocampal cell proliferation and neurogenesis may be an important neural correlate of the onset and treatment of depression [11,21]. Therefore, neurotrophic factors may be implicated in depression or in the mechanism of antidepressant drugs.

Insulin-like growth factor-I (IGF-I) is an endogenous peptide with mixed effects on neural cell signaling and neurotrophic responses. Although IGF-I is present in highest amounts early in development, detectable levels are present throughout the lifespan, most prominently in the hippocampus and olfactory bulb [10]. IGF-I binds to a tyrosine kinase receptor (IGF-IR), which is structurally similar to the insulin receptor [13]. The largest source of IGF-I is from the liver, although the peptide is also produced centrally in the brain [27]. Repeated systemic or central (icv) administration of IGF-I has been shown to increase neurogenesis in the dentate gyrus of the hippocampus [1]. IGF-I also plays a

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role in the ability of exercise to increase neurogenesis. Specifically, exercise-induced increase in neurogenesis is mediated by IGF-I since blockade of IGF-I entry into the brain prevents exercise-induced increases in neurogenesis [28]. In addition, a recent report has shown that chronic administration of the antidepressants venlafaxine and fluoxetine increased the protein levels of IGF-I in the hippocampus [12]. Despite the relationship between neurogenesis, antidepressants, and IGF-I, there have yet to be any studies examining the possible antidepressant-like effects of IGF-I.

Another neurotrophic factor proposed to play a significant role in mood disorders such as depression is brain-derived neurotrophic factor (BDNF) [9]. BDNF is an endogenous polypeptide that has a high affinity for the tyrosine kinase receptor B (TrkB). Downstream from TrkB, BDNF activates the MAP-kinase pathway and leads to phosphorylation of cyclic-amp response element binding protein. Due to its short-term effects on cell signaling, BDNF has been implicated in models of learning and memory and long-term potentiation [29]. When administered chronically in adult rats, BDNF has been shown to increase neurogenesis in several brain regions [18,32].

A role for BDNF in depression is supported due to its effects on neurogenesis and because chronic administration of antidepressants or electroconvulsive shock treatment increases BDNF mRNA expression in the rat hippocampus [16], whereas chronic exposure to stress decreases BDNF mRNA expression in the rat hippocampus [30]. These findings point to the possibility that BDNF could participate in the clinical effects of antidepressant drugs. Studies utilizing behavioral models of depression have added further evidence for a role of BDNF in mood disorders. However, a variety of tissue sites, doses, delivery methods, and pretreatment times have been used. For example, chronic administration of BDNF (12–24 μl/day for 6–7 days) into the midbrain area was shown to produce antidepressant-like effects in the rat forced swimming test (specifically, a reduction of immobility) and in the learned helplessness paradigm [25]. As shown by another laboratory, acute administration of smaller doses of BDNF (0.25 and 1.0 μg) into the hippocampus also produced antidepressant-like effects in these paradigms, when rats were tested 3 days after the infusion [23]. However, administration of BDNF into the ventral tegmental area produced the opposite effect in the rat forced swimming test (specifically, an increase in immobility), when the rats were tested 7 days after the infusion [8]. The latter study raises questions about the overall role of BDNF and whether the effects of BDNF vary in different brain regions.

The current study examined the effects of central administration of IGF-I and BDNF in a well-established model of antidepressant activity: the rat forced swim test (FST) [19,20]. The FST has been shown to have high predictive validity for antidepressant activity [3,4]. Moreover, the modified version of the FST used here increases the ability of this test to differentiate between serotonergic and noradrenergic mediation of antidepressants [6,14]. Specifically, serotonergic compounds increase swimming behavior, while noradrenergic compounds increase climbing behavior. The overall effects of the neurotrophins were tested by giving varied doses by acute icv infusion, and animals were tested at different times following administration.

Male Sprague–Dawley rats (approximately 300 g on arrival; $N = 36$) were implanted with unilateral guide cannulae via stereotaxic surgery under pentobarbital anesthesia (coordinates: A/P: −1.0; M/L: +/− 1.3; D/V: −4.5 [17]). After 1 week of recovery, rats were exposed to the forced swim test. First, the rats were exposed to the forced swimming for 15 min (30 cm of water, 22–25 °C). On the following day, the rats received an icv infusion of either aCSF, IGF-I (0.1 or 1.0 μg), or BDNF (0.1 or 1.0 μg). Both IGF-I and BDNF were purchased from Bachem Bioscience Inc. (King of Prussia, PA). All infusions were given in 2 μl of solution over a period of 2 min. Then, 3, 6, and 12 days after the infusion, the rats were re-exposed to the forced swimming test for 5 min. The sessions were videotaped and scored for the frequency of swimming, climbing, and immobility (as previously described in [6]). In a second group of rats ($N = 20$), locomotor activity was measured 3 days after an icv infusion of either aCSF (2.0 μl), IGF-I (1.0 μg), or BDNF (1.0 μg). The rats were placed in an open field for 30 min, and their total distance traveled (cm) was recorded by an automated video tracking system (PanLabs; San Diego, Ca). At the end of the experiment, the rats were sacrificed and the correct placement of the guide cannulae was verified. Data for one animal were removed from analysis due to misplaced guide cannula.

The results for the IGF-I infusion are shown in Fig. 1 (see figure legend for statistics). Post hoc tests determined that infusion of the higher dose of IGF-I (1.0 μg) produced a significant decrease in immobility for days 3 and 6 after the infusion ($P < 0.05$) compared to the aCSF group. This was accompanied by a significant increase in swimming for days 3 and 6 after the infusion ($P < 0.05$) compared to the aCSF group, but no change in climbing behavior. The lower dose of IGF-I produced no significant behavioral effect on any of the test days.

The effects of BDNF infusion on the FST are shown in Fig. 2; they were similar to those of IGF-I (see figure legend for statistics). Post hoc tests determined that infusion of the higher dose of BDNF (1.0 μg) led to a significant decrease in immobility for days 3 and 6 after the infusion ($P < 0.05$) compared to the aCSF group. There was also a significant increase in swimming for days 3 and 6 after the infusion ($P < 0.05$) compared to the aCSF group, but no change in climbing. The lower dose of BDNF produced no significant behavioral effect on any day.

The results of the current experiment show that there was no significant change in immobility over the four test sessions for the vehicle group. Although most experiments using the FST do not use a repeated testing method, the