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Research Report

Peptidic delta opioid receptor agonists produce antidepressant-like effects in the forced swim test and regulate BDNF mRNA expression in rats

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ABSTRACT

Systemically active, nonpeptidic delta opioid receptor agonists have been shown to produce antidepressant and anxiolytic effects in animal models in rodents. In addition, delta agonists have been shown to increase expression of brain-derived neurotrophic factor (BDNF) mRNA, an effect of some antidepressants, which may be important for the clinical efficacy of antidepressant drugs. The present study examined whether a variety of peptidic delta agonists, DPDPE, JOM-13, a systemically active derivative of DPDPE, deltorphin II, and H-Dmt-Tic-NH-CH_2-Bid could produce convulsions and antidepressant-like effects in the forced swim test. In addition, some of these compounds were examined for their influence on BDNF mRNA expression. All four agonists dose-dependently decreased immobility in the forced swim test, indicating an antidepressant-like effect. Only JOM-13 produced convulsions at doses required for antidepressant-like effects. In addition, DPDPE increased BDNF mRNA expression, as measured by in situ hybridization, in the frontal cortex. The antidepressant-like effect of the agonists in the forced swim test and the increase in BDNF mRNA expression produced by DPDPE were blocked by the delta antagonist naltrindole. Therefore, activation of the delta receptor by centrally administered peptidic agonists and intravenously administered JOM-13 produces behavioral antidepressant-like effects without producing convulsions, and some peptidic agonists can increase BDNF mRNA expression, however, not as consistently as the systemically active nonpeptidic agonists.

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1. Introduction

Delta opioid receptor agonists are known to produce many behavioral effects in rodents, including antinociception, increased locomotor activity, convulsions, and antidepressant-like effects (Fraser et al., 2000a,b; Broom et al., 2002a,b,c; Comer et al., 1993; Hong et al., 1998). In addition, the nonpeptidic delta agonist (+)BW373U86 has been shown to increase brain-derived neurotrophic factor (BDNF) mRNA expression in several brain regions in the rat (Torregrossa et al., 2004, 2005). Increased expression and activity of BDNF have been implicated in the mechanism of action of antidepressant drugs (Duman, 2004).

The potential use of delta agonists as analgesics and antidepressants has led to the development of many different compounds that activate the delta opioid receptor. The earliest selective delta agonists were peptides, including [Tyr-D-Pen-Gly-Phe-D-Pen] (DPDPE) and [Tyr-D-Ala-Phe-Glu-Val-Val-Gly-NH_2] (deltorphin II). The poor bioavailability of peptidic compounds led to the development of systemically active, nonpeptidic delta agonists, including BW373U86 and SNC80. Most behavioral and physiological effects of delta agonists have been demonstrated to occur with both the peptidic and nonpeptidic agonists; however, there are a few exceptions. The nonpeptidic delta agonists produce convulsions in mice (Comer et al., 1993; Hong et al., 1998; Broom et al., 2002a), rats (Broom et al., 2002c), and nonhuman primates (Dykstra et al., 1993; Pakarinen et al., 1995; Negus et al., 1994). On the other hand, peptidic agonists have not been reported to produce convulsions in any species; however, they do produce wet dog shakes, unstable movement, and epileptic discharges as measured by electroencephalogram (EEG) (Haffmans and Dzoljic, 1983). These findings suggest that activation of the delta receptor by both peptidic and nonpeptidic agonists can lead to EEG changes, but only the nonpeptides produce overt convulsions.

Both peptidic and nonpeptidic agonists have been shown to produce antinociception (Fraser et al., 2000a) and increases in locomotor activity (Fraser et al., 2000b). In contrast, antidepressant-like effects and increased BDNF mRNA expression have only been demonstrated with nonpeptidic agonists (Broom et al., 2002b; Saitoh et al., 2004; Torregrossa et al., 2004). However, there is evidence that peptidic agonists may produce antidepressant-like effects from studies showing that the enkephalinase inhibitor RB101 produces antidepressant-like effects in the learned helplessness and forced swim tests (Tejedor-Real et al., 1998; Baamonde et al., 1992; Jutkiewicz et al., 2005a,b). This effect can be blocked by the selective delta antagonist naltrindole, suggesting that endogenous opioid peptides such as met-enkephalin and leu-enkephalin can produce antidepressant-like effects by activating the delta opioid receptor. However, 32 mg/kg RB101 administered intravenously did not increase BDNF mRNA expression in the frontal cortex or hippocampus (Jutkiewicz et al., submitted for publication), indicating that there may be differences in the effects produced by the endogenous peptides and nonpeptidic agonists at the delta receptor.

Therefore, the aim of the present study was to determine if the peptidic agonists DPDPE, deltorphin II, Tyr-c[D-Cys-Phe-D-Pen]OH (JOM-13), and the pseudo-peptide H-Dmt-Tic-NH-CH_2-Bid could produce antidepressant-like effects in a modified rat forced swim test, an assay used to predict the antidepressant potential of novel compounds. In addition, we determined the ability of some of the agonists to increase BDNF mRNA expression in the frontal cortex and hippocampus by in situ hybridization. We also determined whether these effects were mediated by the delta receptor by administering the selective delta antagonist naltrindole.

2. Results

2.1. Forced swim test studies

DPDPE dose-dependently decreased immobility in the forced swim test, indicating an antidepressant-like effect

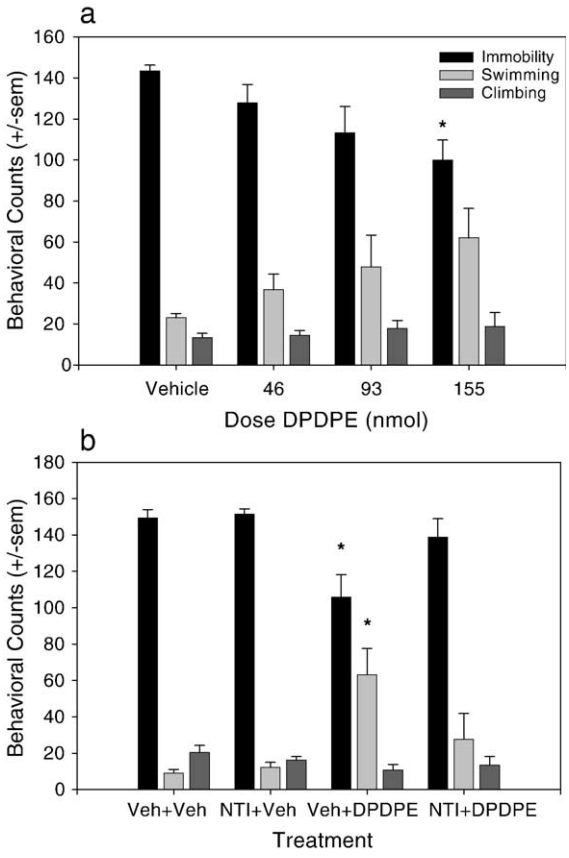

Fig. 1 – Antidepressant-like effects of DPDPE in the forced swim test. (a) Effect of increasing doses of DPDPE given i.c.v. on immobility, swimming, and climbing behaviors when given 30 min before the forced swim test. DPDPE dose-dependently and significantly decreased immobility indicating an antidepressant-like effect (n = 8 for vehicle and n = 6 for each dose of DPDPE). (b) Effect of 10 mg/kg naltrindole (NTI) given 30 min before 155 nmol DPDPE on behaviors in the forced swim test. NTI blocked the antidepressant-like effect of DPDPE (n = 5 per group, except Veh + DPDPE, n = 6). Data are expressed as the mean ± standard errors of the mean (SEM), and statistical differences are determined by comparison to the vehicle-treated control. *$P < 0.05$.