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BRAIN RESEARCH

Research Report

Exacerbated mechanical allodynia in rats with depression-like behavior

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ARTICLE INFO

Article history:
Accepted 8 January 2008
Available online 26 January 2008

Keywords:
Allodynia
Melatonin
Depression
Anterior cingular cortex
Neuropathic pain
Nerve injury
WKY rat

ABSTRACT

Although a clinical connection between pain and depression has long been recognized, how these two conditions interact remains unclear. Here we report that both mechanical allodynia and depression-like behavior were significantly exacerbated after peripheral nerve injury in Wistar-Kyoto (WKY) rats, a genetic variation of Wistar rats with demonstrable depression-like behavior. Administration of melatonin into the anterior cingular cortex contralateral to peripheral nerve injury prevented the exacerbation of mechanical allodynia with a concurrent improvement of depression-like behavior in WKY rats. Moreover, there was a lower plasma melatonin concentration and a lower melatonin receptor expression in the anterior cingular cortex in WKY rats than in Wistar rats. These results suggest that there exists a reciprocal relationship between mechanical allodynia and depression-like behavior and the melatoninergic system in the anterior cingular cortex might play an important role in the interaction between pain and depression.

1. Introduction

An apparent clinical relationship between pain and depression has long been recognized. Several epidemiological studies demonstrate that pain and depression frequently co-exist in up to 70% of chronic pain cases (Arnow et al., 2006; Bair et al., 2003; Magni et al., 1985; Von Knorring et al., 1983). Depression has been shown to result in decreased pain threshold and increased analgesic requirement (Jackson and Onge, 2003). It is estimated that the occurrence of depression in patients with chronic pain is higher, ranging from 30% to 54%, than that (about 17%) in the general population (Sullivan et al., 1992; Banks and Kerns, 1996; Ferrer-Garcia et al., 2006). Similarly, the presence of a depressive disorder significantly increases the risk of developing chronic pain (Leino and Magni, 1993; Magni et al., 1993, 1994). Patients with a previous history of clinical depression are at least twice more likely to develop a chronic pain condition than patients without depression (Von Korff and Simon, 1996). While antidepressants affect mood changes in chronic pain patients, they do not always improve outcome measures of clinical pain (Littlejohn, Guymer, 2006; Carter, 2002). In this regard, several studies have suggested that the effect of antidepressants on chronic pain may not be related to their anti-depression property (Atkinson et al., 1998; Collins et al., 2000; Max et al., 1987, 1992; Mico et al., 2006; Sharav et al., 1987). To date, the relationship between pain and depression remains unclear.

A subset of Wistar-Kyoto (WKY) rats, a genetic variation of the Wistar strain (Okamoto and Aoli, 1963; Porsolt et al., 1977,

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0006-8993/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2008.01.038

1978a,b), as well as Flinders sensitive line (FSL) rats (Overstreet et al., 2005), has been used as preclinical models of depression. In comparison with normal Wistar rats, WKY rats demonstrate hormonal, behavioral, and physiological changes that resemble those found in patients with clinical depression. For instance, WKY rats are hypersensitive to stress secondary to the disrupted hypothalamic–pituitary–adrenal and hypothalamic–pituitary–thyroid axes. Moreover, WKY rats exhibit an overall decreased activity, few exploratory behaviors, hypolocomotion, and a high level of behavioral immobility in the forced swimming test (Pare, 1993, 1994, 1996; Armario et al., 1995). Pharmacologically, desipramine (a tricyclic antidepressant) acutely reverses depression-like behavior such as a prolonged duration of immobility in the forced swimming test in WKY rats (Porsolt et al., 1978a,b; Lopez-Rubalcava, Lucki, 2000; De La Garza, Mahoney, 2004).

Previous studies have suggested that common biological pathways and neurotransmitters including serotonin and norepinephrine may be involved in the mechanisms of pain and depression (Schatzberg, 2004; Fishbain et al., 1997) and that certain brain regions such as the anterior cingular cortex (ACC) play a critical role in the integration of mood and nociception (Johansen et al., 2001; Gao et al., 2004; LaGraize et al., 2004; Frankland and Teixeira, 2005). In addition, melatonin (5-methoxy-*N*-acetyltryptamine), a pineal neurohormone and a derivative of serotonin, may be critically involved in the regulation of both mood and pain (Sugden, 1983; El-Shenawy et al., 2002). It has been shown that melatonin receptor type 1(MT1)-knockout mice displayed depression-like behavior with altered sensory responses and attention deficits (Weil et al., 2006). Moreover, melatonin has been shown to produce antinociception and enhance morphine analgesia mediated through spinal MT receptors (Tu et al., 2004; Li et al., 2005). These data suggest that the central melatoninergic system might play an important role in the mechanism of interactions between pain and depression and ACC could be a forebrain region of interest in this process.

Using a preclinical model of combined depression-like behavior and nociceptive behavior (mechanical allodynia) induced by chronic constriction nerve injury (CCI) in WKY rats, we sought to 1) compare the degree of mechanical allodynia after CCI between WKY and Wistar rats and 2) examine the effect of melatonin on both mechanical allodynia and depression-like behavior by its direct administration into ACC.

2. Results

2.1. *Exacerbation of depression-like behavior in WKY rats following CCI*

The baseline immobility score in the forced swimming test (duration of immobility in seconds during a 5-min period) was nearly three times higher in WKY rats than in Wistar rats (Figs. 1A, B, $n=6$, $P<0.01$). CCI significantly increased the immobility score in the forced swimming test in both WKY and Wistar rats when examined on day 3 after CCI (Figs. 1A, B, each $P<0.05$). This increased immobility score reached a plateau on postoperative day 3 in Wistar rats and there were no differences in the immobility score between Wistar-CCI and Wistar-sham

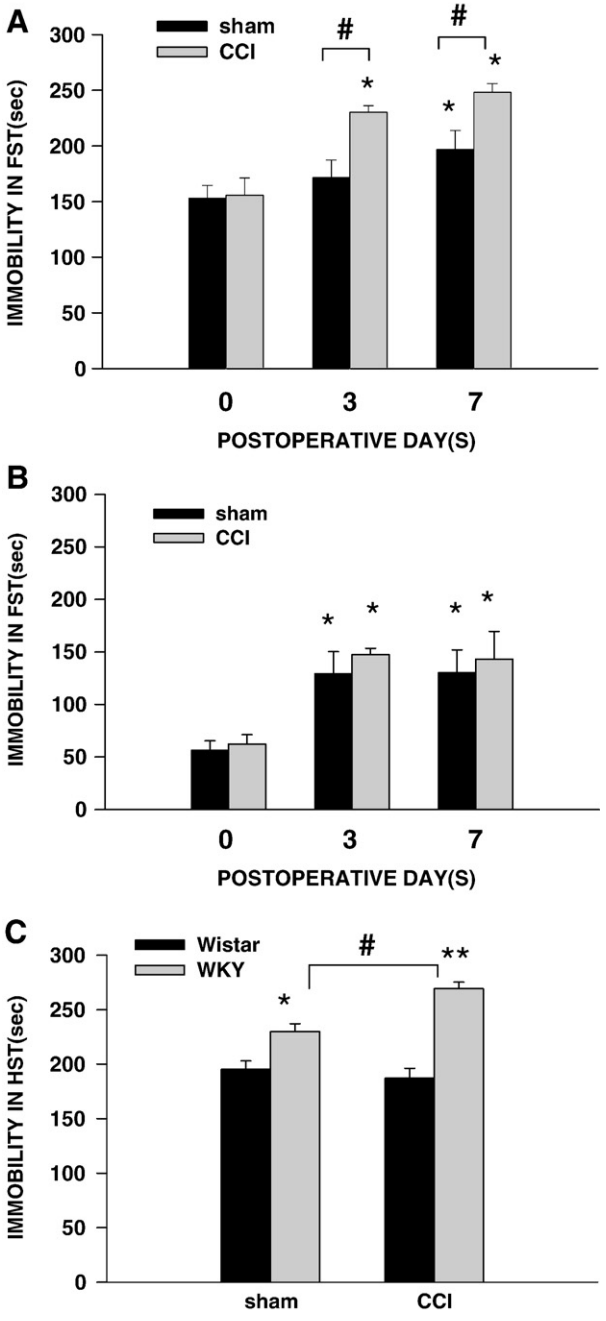

Fig. 1 – Exacerbation of depression-like behavior after CCI. A, B: There were differences in the baseline immobility time in the forced swimming test between WKY (A) and Wistar rats (B). The duration of immobility was increased after CCI in both WKY (A) and Wistar (B) rats. However, the duration of immobility remained significantly higher in WKY rats with CCI than WKY rats with sham operation. C: The immobility time in the horizontal suspension test was longer in WKY rats than Wistar rats with CCI or sham operation, when examined on postoperative day 7. * $P<0.05$, as compared to the baseline of each corresponding group. # $P<0.05$ as compared with sham rats of each group.