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BRAIN RESEARCH

Research Report

The effects of OB-induced depression on nociceptive behaviors induced by electrical stimulation of the dura mater surrounding the superior sagittal sinus

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ABSTRACT

A bi-directional relationship between depression and migraine has been widely reported in epidemiological and clinical studies, but the mechanisms of interaction between these disorders have not been fully examined using animal models. The aim of the present study was to investigate the effects of depression elicited by olfactory bulbectomy (OB) on trigeminovascular nociception in conscious rats. The nociception was induced by electrical stimulation of the dura mater surrounding the superior sagittal sinus (SSS); this procedure causes nociception similar to that experienced during vascular headaches such as migraine. We showed that nociceptive behaviors (grooming and head flicks) were significantly enhanced in OB rats as compared to sham-operation (Sham) rats and that these nociceptive behaviors were correlated with depressive-like behaviors. Systemic administration of the antidepressant amitriptyline (AMI) significantly alleviated nociceptive behaviors in both the OB rats and Sham rats. Plasma levels of substance P (SP), but not plasma calcitonin gene-related protein (CGRP), significantly increased in OB rats and plasma SP levels decreased to normal following AMI treatment. Furthermore, changes in plasma SP levels were associated with both depressive-like behaviors and nociceptive behaviors. In conclusion, our results indicate that OB-induced depression can exacerbate trigeminovascular nociception, which may be mediated by SP. Moreover, we demonstrate that inhibition of SP release may contribute to the antinociceptive effect of AMI.

1. Introduction

For more than a century, studies have reported an association between migraine and psychiatric disorders such as depression, anxiety, phobias and panic disorders (Frediani and Villani, 2007). In epidemiological studies, depressed patients have shown a more than three-fold risk for migraine compared to non-depressed patients; likewise, migraineurs have shown a more than three-fold risk of depression compared to non-migraine patients (Benzenhofer, 1994; Torelli and D'Amico, 2004). In addition, depression predicts first-onset migraine and migraine predicts first-onset depression (Breslau et al., 2000; Lewandowski and Palermo, 2009). This evidence suggests a bi-directional relationship between migraine and depression. Recent studies have shown that both diseases share common genetic risks and biochemical and environmental factors

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(Muller and Schwarz, 2007; Pietrobon, 2005; Schur et al., 2009). Moreover, several studies have found that patients with comorbid depression and migraine were more severely impaired by their disorders (Fasmer and Oedegaard, 2001; Oedegaard et al., 2005). Depressed patients with migraine have more depressive episodes and more irritability, anxiety and somatic symptoms than those without migraine (Hung et al., 2006a, 2006b; Oedegaard and Fasmer, 2005); migraineurs with depression have more headaches, longer headache duration (Hung et al., 2006b, 2008; Mitsikostas and Thomas, 1999) and more somatic discomfort (Maizels and Burchette, 2004; Mongini et al., 2004, 2006) compared to patients not suffering from depression. In contrast, one study reported the following conflicting finding: comorbid major depression did not influence the frequency of migraine attacks, headache duration and the progression of migraine-related disability (Breslau et al., 2003). The inconsistency in these findings may be due to differences in the characteristics of the subjects (i.e., age and gender), differences in assessment procedures, and whether subjects were taking antidepressants or other psychotropic drugs. Because of this conflicting evidence, the nature of the relationship between migraine and depression is not fully understood and needs to be further explored using animal models of depression and migraine.

To our knowledge, there is no published study on the association between depression and migraine in animal models. The olfactory bulbectomized (OB) rat model has been widely accepted as a classical animal model of agitated depression (Goyal et al., 2009; Rodriguez-Gaztelumendi et al., 2009; Wang et al., 2007). OB rats display a series of behavioral (e.g., anxious and excitation behaviors), physiological, neurochemical, endocrinological and immunological changes that resemble those observed in humans with major depression (Burke et al., 2010; Cryan and Holmes, 2005; Hellweg et al., 2007; Sato et al., 2010). These changes can be reversed by chronic, but not acute, treatment with various antidepressants including amitriptyline (AMI) (Jarosik et al., 2007; Mar et al., 2000; Sato et al., 2010; Song and Leonard, 2005). In addition, the electrical stimulation of trigeminal nerve-innerving tissues such as the dura mater (Kurosawa et al., 1995; Panteleev et al., 2005), the superior sagittal sinus (SSS) (Benjamin et al., 2004; Hoskin et al., 2001; Kaube et al., 1993; Storer et al., 2004), the dural arteries (Andreou et al., 2009; Gupta et al., 2006; Juhl et al., 2007), or the trigeminal ganglion (Clayton et al., 1997; McCall, 1997; Samsam et al., 2000), activates the trigeminovascular nociceptive pathway (Goadsby, 2002; Tepper et al., 2001) and has been widely used as an animal model of migraine. However, the nociceptive behaviors mimicking the headache experience of migraineurs cannot be observed in these animal models because in all of these studies, animals were stimulated while anaesthetized and were therefore not conscious. In our recent work, we have successfully established a new procedure for trigeminovascular nociception through stimulation of the dura mater surrounding the SSS in conscious rats and have observed nociceptive behaviors (Dong et al., 2010; Wang et al., 2010b). This new animal model for migraine can help us obtain a better assessment of nociceptive behaviors and improve our understanding of the mechanisms underlying migraine. Previous studies have shown that nociceptive behaviors induced by different kinds of stimuli were either reduced or enhanced in both the OB model (Wang et al., 2010a) and unpredictable chronic mild stress (UCMS) model of depression (Shi et al., 2010b). Until the present study, the effects of depression using the OB model on our migrane model, trigeminovascular nociception elicited by electrical stimulation of the dura mater surrounding the SSS, have not been examined.

Neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P (SP) have been linked to trigeminovascular nociceptive mechanisms via dural vasodilation and neurogenic inflammation (Fusayasu et al., 2007; Fusco et al., 2003; Williamson and Hargreaves, 2001). Most studies have found increased plasma CGRP levels in both migraineurs (Ashina et al., 2000; Fusayasu et al., 2007; Goadsby and Edvinsson, 1993) and nociceptive animal models (Buzzi et al., 1991; Ebersberger et al., 1999; Goadsby et al., 1988; Zagami et al., 1990); a conflicting report observed no change in plasma CGRP levels in migraineurs (Tvedskov et al., 2005). Similarly, conflicting data on the changes in plasma SP levels have been presented in both migraineurs and nociceptive animal models (Ebersberger et al., 1999; Goadsby and Edvinsson, 1993; Goadsby et al., 1988, 1990; Jang et al., 2011). The levels and roles of plasma SP and CGRP induced by electrical stimulation of the dura mater surrounding the SSS in OB rats have not been investigated.

The present study aimed to clarify the effects of depression, elicited by OB, on trigeminovascular nociception in rats (induced by electrical stimulation of the dura mater surrounding the SSS, which mimics migraine). We address the following issues: a) how OB-induced depression affects nociceptive behaviors such as grooming and head flicks; b) how the plasma levels of SP and CGRP are affected by these procedures; and c) whether the nociceptive behaviors and plasma levels of SP and CGRP could be restored by administering the antidepressant AMI.

2. Results

2.1. *Body weight changes and depressive-like behaviors elicited by OB*

On the day before surgery, there was no significant difference in the body weight of rats in the OB and sham-operation (Sham) group (232.8±1.5 g vs. 231.8±1.9 g, $P=0.544$). However, the rats in the OB group gained weight more slowly than rats in the Sham group. Fourteen days after surgery, there was a significant difference in body weight between the two groups (repeated measures data of ANOVA, $F(1,41)=103.2$, $P<0.001$), as shown in Fig. 1A. On the 14th day post surgery, the average body weight was 307.3 g in the OB group, lower than the average body weight of 339.6 g in the Sham group. Thus, there was a significant effect of OB on body weight.

On the 15th day after surgery, there were notably higher levels of the locomotor (travel distance) and rearing (number) behaviors in the open field test in the OB group compared with the Sham group (travel distance: 2572.8±124.0 cm vs. 1277.4±71.5 cm, $P<0.001$, see Fig. 1B; number of rearing behaviors: 18.9±1.3 vs. 9.1±0.6, $P<0.001$, see Fig. 1C). Moreover, rats in the OB group swam longer distances and spent more time exploring the platform than those in the Sham group (repeated measures data of ANOVA, swimming distance: