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High frequency stimulation of the anterior vermis modulates behavioural response to chronic stress: involvement of the prefrontal cortex and dorsal raphe?

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ABSTRACT

Some evidence suggests that the cerebellum modulates affect via connectivities with mood-regulating cortico-limbic structures, such as the prefrontal cortex and monoamine nuclei. In rats exposed to chronic unpredictable stress (CUS), we examined the neuro-behavioural effects of high frequency stimulation and surgical ablation/disconnection of the cerebellar vermis. CUS reduced sucrose preference, increased novelty-induced feeding suppression and passive coping. These depressive-like behaviours were associated with decreased cerebellar *zif268* expression, indicating possible cerebellar involvement in stress pathology. These were paralleled by decreased vermal Purkinje simple and complex spiking activity and raphe serotonergic activity. Protracted (24-h) vermal stimulation reversed these behavioural deficits through serotonin-mediated mechanisms since this effect was abrogated by the serotonin-depleting agent pCPA. Vermal stimulation and disconnection lesion also enhanced serotonergic activity, but did not modify prefrontocortical pyramidal firing. This effect was likely mediated by 5-HT_{1A} receptors (5-HT_{1A}R). Indeed, acute vermal stimulation mimicked the effect of the 5-HT_{1A}R agonist 8-OH-DPAT in inhibiting serotonergic activity, which was prevented by pre-treatment with the 5-HT_{1A}R antagonist WAY100,635. These results demonstrate vermal involvement in depressive-type behaviour via its modulatory action on serotonergic neurons. They further suggest that vermal and mPFC stimulation may bestow therapeutic benefits via parallel pathways.

1. Introduction

The cerebellum has been conventionally attributed with motor function. Although, in recent years, the limbic cerebellar vermis (CBv) has been recognized to be involved in some cognitive and affective processes, and as a region of interest in neuropsychiatric disorders (Rapoport et al., 2000; Konarski et al., 2005; Schutter and van Honk, 2005). The complexity of cerebellar function may owe to an enormous density of neurons, hence to a phenomenal processing power that is capable of integrating a vast array of information. The CBv - fastigial nuclear complex and the flocculonodular lobes, which constitute the limbic cerebellum (Berntson and Torello, 1982), send polysynaptic projections via the fastigial nucleus to several limbic structures, primarily to the prefrontal cortex (PFC), but also to midbrain nuclei (Rapoport et al., 2000; Habas et al., 2009; Stoodley and Schmahmann, 2010). The PFC is a central hub in the limbic network that is engaged in executive, self-referential, mood-regulating and stress-adaptive functions (Bambico and Belzung, 2013). The existence of a massive closed-loop cortico-cerebellar circuit is thought to bestow the CBv an ideal position to influence emotion and mood-related function, as well as cognitive processes (Strick et al., 2009). It is thus not surprising that CBv abnormalities are associated with a cognitive-affective syndrome consisting of blunted affect, irritability, and social disinhibition, with cognitive deficits (Riva and Giorgi, 2000).

Depression is a common, debilitating psychiatric disorder that involves multiple molecular and neuroanatomical substrates. Its precise pathophysiology remains elusive, but impairments in both glutamatergic and serotonin (5-HT) signaling in the PFC and the hippocampus

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are widely acknowledged as contributing factors (Bambico and Belzung, 2013). Many antidepressants enhance 5-HT neurotransmission, potentially modifying the function of pre- and/or postsynaptic 5-HT receptors. Among them, the 5-HT_{1A}R has been linked to the therapeutic effects of 5-HT-acting agents, such as selective serotonin reuptake inhibitors (SSRIs). 5-HT_{1A}R is expressed on somatodendritic domains of 5-HT-containing neurons of the dorsal raphe (DR) where they negatively regulate the activity of 5-HT neurons. Chronic SSRI alleviates symptoms via their capacity to attenuate 5-HT_{1A} autoreceptor function by rapid internalization (Riad et al., 2004; Riad et al., 2008) or slow desensitization (Bambico and Belzung, 2013). Recently, glutamatergic transmission in the PFC has also been implicated in rapid antidepressant action through synaptogenic mechanisms (Bambico and Belzung, 2013).

The cortico-cerebellar circuit may be implicated in depressive disorders, and both the cerebellum and the PFC display significant atrophy and volume reduction among unmedicated patients. Imaging studies show profound alteration in structural integrity (diminished) and regional blood flow or metabolic activity (increase or decrease) in the CBv in unipolar and bipolar depression (Lippmann et al., 1982; Dolan et al., 1992; Loeber et al., 1999; Kruger et al., 2003; Fujimoto et al., 2008; Lin et al., 2012; Su et al., 2014) that appear to relate to symptom severity and response to treatment (Davies et al., 2003; Loeber et al., 1999). This cerebellar involvement seems to parallel changes in the PFC, with inhibition of its dorsomedial/dorsolateral subregion and activation in its ventromedial and cingulate subregions detected among depressed individuals. These changes are likewise reversed by antidepressant treatment (Price and Drevets, 2010).

Deep brain stimulation (DBS) is a somatic/surgical antidepressant approach that delivers high frequency, low-power electrical current into select limbic regions. Targeting the medial prefrontal cortex (mPFC), specifically the subgenual cortex, has been shown effective in ameliorating depressive symptoms in patients and in animal models (Hamani et al., 2010b). Its basic design has been used as far back as in the eighties, and earlier trials of pacemaker-type stimulation of the vermis has been shown to mitigate refractory symptoms in depressives, schizophrenic and anxious patients (Riklan et al., 1977). The precise mechanism underlying the therapeutic activity of DBS is still unclear. Some evidence underscores a functional deactivation or disconnection lesion effect (Grill et al., 2004; McIntyre et al., 2004; Kern and Kumar, 2007; Birdno and Grill, 2008; Deniau et al., 2010). This notion appears to be consistent with some behavioural effects seen in classical vermal lesion experiments (Supple et al., 1987; Supple et al., 1988; Bobee et al., 2000; Sacchetti et al., 2002).

There is a paucity of current research that explore the therapeutic potential of targeting the limbic CBv for psychiatric and neurological disorders. There is a need to better understand neural mechanisms that underlie the behavioural impact of CBv activity in relation to affective states, such as its influence on 5-HT and PFC glutamatergic neurotransmission. We therefore tested whether DBS-like stimulation of the CBv (CBv-Stim) can induce antidepressant-like effects in a chronic stress-based animal model. We employed DBS because of its significant potency in refractory depression (Mayberg et al., 2005; Kern and Kumar, 2007), and its utility as an experimental tool in understanding neural pathophysiology in depression. Using in vivo electrophysiology, we examined whether the effects of CBv-Stim and CBv ablation are mediated by 5-HT or by glutamatergic activity in the mPFC. We hypothesized that chronic stress and depression are associated with decreased inhibitory cerebellar-mPFC coupling that could be mitigated by high frequency DBS-like stimulation (Alalade et al., 2011).

2. Methods & materials

2.1. General time line

The schedule of experimental procedures is represented in a chronogram shown in Fig. 1. All animals underwent sucrose exposure and discrimination training; thereafter they were exposed to 5 weeks of chronic unpredictable stress (CUS). Afterwards, some animals were subjected to CBv electrophysiology in order to assess the effect of CUS on Purkinje cell firing activity (Fig. 1A, 1st branch, cohort 1), or were immediately sacrificed for ex vivo brain analysis (Fig. 1A, 2nd branch, cohort 2). The rest of CUS and CTR animals were surgically implanted with DBS electrodes into the CBv or mPFC (Fig. 1A, 3rd branch, cohort 3). Behavioural tests commenced after 4 days of post-surgical recovery and were completed on the 5th - 6th day post-surgery. Electrophysiological recordings were carried out on the 6th - 8th day. A second group of non-CUS animals were used for additional behavioural and acute electrophysiological experiments as needed (Fig. 1A, 4th branch, cohort 4). All behavioural tests described were conducted between 9:00 and 19:30. Rats were subjected to a serial testing procedure (modified after Bambico et al., 2010 and Walf and Frye, 2007). Behavioural records were encoded and analyzed using an automated tracking system (Videotrack system, View Point Life Sciences, Montreal, Quebec, Canada) or by visual inspection by an analyst blind to the experimental groupings.

2.2. Maintenance and preparation of animals

Experiments were carried out on male, adult Wistar rats (Charles Rivers, Ste. Constant, Quebec, Canada) weighing ~300 g. They were housed in pairs or trios in standard polycarbonate cages and maintained under standard conditions (12:12 light-dark cycle, lights on at 07:30; temperature at 20 ± 2 °C; 50–60% relative humidity, and ad libitum access to food and water, unless otherwise prescribed by procedures. Methods were undertaken in compliance to the ethical guidelines mandated by the local institutional animal care committee, the Canadian Institutes of Health Research and the Canadian Council on Animal Care.

2.3. Drugs

The selective serotonin reuptake inhibitor, citalopram hydrobromide was intraperitoneally administered at a dose of 10 mg/kg for an injection volume of 1.0 ml/kg. The serotonin synthesis inhibitor para-chlorophenylalanine (pCPA) was administered 72 and 48 h before testing, each at a dose of 350 mg/kg, intraperitoneally for a 1.0 ml/kg volume. The 5-HT_{1A}R agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) was intravenously administered at a cumulative dose of 5 μg/kg (3, 1 and 1 μg/kg) for a total injection volume of 0.3 ml. The 5-HT_{1A}R antagonist *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl)cyclohexanecarboxamide trihydrochloride (WAY100,635) was intravenously administered at 100 μg/kg for an injection volume of 0.1 ml. The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor agonist quisqualic acid was prepared to obtain a concentration of 1.5 mM in 400 mM NaCl (pH 8.0). Equithesine and chloral hydrate was used as anesthetics in surgical procedures and in electrophysiological experiments, respectively. All doses chosen were based on effective doses demonstrated previously (Bambico et al., 2007; Bambico et al., 2009; McLaughlin et al., 2012). Drugs were dissolved in 0.9% physiological saline. The pH of vehicles and solutions used in the experiments was adjusted to 7.2. All drugs were purchased from Sigma-Aldrich Canada, Ltd., except for citalopram, which was kindly provided by Lundbeck (Copenhagen, Denmark).

2.4. Sucrose discrimination training and sucrose preference test (SPT)

The behavioural experiment employed to test anhedonia-like response was based on CUS-induced reduction of sucrose preference employed by Moreau et al. (1992) and Bambico et al. (2009). Three days after arrival in the facility, all animals had free access for 4 days to tap water and 1% sucrose solution (w/v). Consumption was recorded