Emotional Disorders Induced by Hemoprssin and RVD-Hemopressin (a) Injection in Rats

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The endocannabinoid (eCB) system is strongly involved in psychiatric diseases such as anxiety, depression, bipolar disorder, schizophrenia and suicide (Rubino et al., 2015). Different studies have demonstrated a dysfunction of eCB signaling in patients with mood disorders (Hungund et al., 2004; Koethe et al., 2007; Hill et al., 2008) and preclinical data suggest that the direct or indirect stimulation of cannabinoid (CB) receptors exert anxiolytic and antidepressant actions (Zarrindast et al., 2010; Rutkowska and Jachimczuk 2004; Adamczyk et al., 2008; Moreira and Crippa, 2009). On the other hand, the eCB system modulates serotonin (5-HT), norepinephrine (NE) and dopamine (DA) neurotransmission (Fišar, 2012), which could represent an attractive and novel approach in the treatment of depression and other mood disorders. However, the failure of clinical trials involving endocannabinoid modulators has dampened the initial enthusiasms (Wyrofsky et al., 2015). Hemopressin (Hp), a hemoglobin α chain-derived peptide which plays an antagonist/inverse agonist role on CB1 receptors (Heimann et al., 2007; Gomes et al., 2009) points to a new pharmacological approach in the treatment of mood disorders. Recent studies have reported the anxiogenic effects of Hp, after central and peripheral administration in rats tested with the elevated plus maze (Fogaça et al., 2015). The authors suggested either a direct involvement of Transient Receptor Potential Vanilloid Type (TRPV1) channel or increased levels of anandamide, but excluding CB1 receptor activation (Fogaça et al., 2015). Recently, a N-terminally extended peptide of Hp, RVD-hemopressin(α) [RVD-hp(α)], also known as PEPCAN-12, was found to bind CB1 receptors as a negative allosteric modulator (Bauer et al., 2012; Han et al., 2014). The aim of our work was to investigate the possible behavioral effects of intraperitoneal (i.p) injection of Hp (0.05 mg/kg) and RVD-hp(α) (0.05 mg/kg), using a series of validated behavioural tests (locomotor activity/open field test, light-dark exploration test, forced swim test) in rats, (Leone et al., 2015). The behavioural data were also related to NE, DA and 5-HT, levels and to the gene expression of monoamine oxidase (MAO-B) and catechol-O-methyltransferase (COMT), evaluated by high performance liquid chromatography (HPLC) analysis and real-time reverse transcription polymerase chain reaction (RT-PCR), in rat prefrontal cortex.

In our experiment, we confirmed the anxiogenic effect of Hp, described by Fogaça (2015), and we also found a decrease of locomotor activity in the open field test and an increase of behavioural despair in the forced swim test. By contrast, we observed that an injection of RVD-hp(α) did not modify the locomotor activity, but induced a significant anxiolytic and antidepressant effect. In addition,. Hp administration decreased monoamines in prefrontal cortex and increased the enzymes involved in their catabolism, while RVD-hp(α) increased monoamine and decreased the enzymes in prefrontal cortex .The present study suggest that behavioral effects of Hp could be mediated by TRPV1 channel, as described by Fogaça (2015), while the anxiolytic and antidepressive effects of RVD-hp(α) depend on CB1 receptor activity.

In conclusion, in the present study we demonstrated behavioral activities by peripheral Hp and RVD-hp(α), also involving modulatory effects on monoaminergic signaling in the prefrontal cortex. These peptides could represent a new perspective in the development of anxiolytic and antidepressive drugs.

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