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Comparison of the V1b antagonist, SSR149415, and the CRF1 antagonist, CP-154,526, in rodent models of anxiety and depression

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Abstract

Vasopressin and corticotropin releasing factor (CRF) are both critical regulators of an animal's stress response and have been linked to anxiety and depression. As such, antagonists of the CRF1 and V1b receptor subtypes are being developed as potential treatments for affective disorders. The two most characterized V1b and CRF1 antagonists are SSR149415 and CP-154,526, respectively, and the present studies were designed to compare these two compounds in acute animal models of affective disorders. We employed five anxiety models: Separation-induced pup vocalizations (guinea pig and rat), elevated plus-maze (EPM), conditioned lick suppression (CLS), and marble burying (mouse); as well as three depression models: forced swim test (FST; mouse and rat) and tail suspension test (TST; mouse). SSR149415 (1–30 mg/kg) was active in the vocalization, EPM and CLS models, but inactive in marble burying. CP-154,526 (1–30 mg/kg) was active in vocalization models, but inactive in EPM, CLS, and marble burying. SSR149415 was inactive in all depression models; CP-154,526 was active in rat FST but inactive in mouse models. This work demonstrates the different profiles of V1b and CRF1 receptor antagonists and supports both approaches in the treatment of affective disorders.

Keywords: Vasopressin; V1b receptor; Corticotropin-releasing factor; CRF-1 receptor; HPA axis; Anxiety; Depression; Behavior; Rat; Mouse; Guinea pig

1. Introduction

The hypothalamic–pituitary–adrenal (HPA) axis regulates an animal's response to stress. Two key regulators of the HPA axis, vasopressin and corticotrophin-releasing factor (CRF) are released during stressful events and bind to receptors in the pituitary. There they synergistically trigger the release of adrenocorticotropin hormone (ACTH), which is circulated in the bloodstream to the adrenal glands. The stress hormone corticosterone (cortisol in primates) is released by the adrenal glands and binds to receptors in the pituitary, limbic structures and the hypothalamus. Sustained elevation of HPA activity is considered a causal factor in human affective disorders (Dinan, 1994; Gold et al., 1988). Dampening HPA axis activity has been hypothesized to be a potential avenue for the treatment of affective disorders (Holsboer, 1999).

There is strong evidence from human studies for a link between affective disorders and vasopressin and CRF. For example, high numbers of both vasopressin- (Purba et al., 1996) and CRF-expressing (Raadsheer et al., 1994) neurons have been reported in post mortem analyses of depressed patients as compared to controls. Also, relative to healthy controls, depressed patients have elevated concentrations of both vasopressin in plasma (Van Londen et al., 1997) and CRF in cerebrospinal fluid (CSF) (Nemeroff et al., 1984). Bremmer et al. (1997) reported that patients suffering from post-traumatic stress disorder have elevated levels of CRF in their CSF. Finally, antidepressant treatment has been shown to lower CSF concentrations of CRF in depressed patients (Nemeroff et al., 1991).

More recently, there has been increasing evidence to support central, non-HPA effects of both vasopressin and CRF.

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Neuroanatomically, vasopressin (Hernando et al., 1998) and CRF receptors (Primus et al., 1997) are localized in brain regions associated with anxiety and depression. Using in vivo studies, Appenrodt et al. (1998) demonstrated that central administration of vasopressin induced anxiety-like behavior, and this effect is intact in hypophysectomized animals (Appenrodt and Schwarzberg, 2000). Similarly, there is clear evidence of a central role for CRF in anxiety (see Zorrilla and Koob, 2004). For example, rodents that receive central administration of CRF (Dunn and Berridge, 1990) have been reported to have a high anxiety-like profile. Collectively, these studies suggest an important role of central receptors in mediating the effects of vasopressin and CRF.

In terms of endogenous receptors, four G-protein-coupled receptors are known to bind vasopressin: V1a, V1b, V2, and oxytocin; while two distinct subtypes of the CRF receptor have been identified: CRF1 and CRF2. Of these, the CRF1 and V1b receptor subtypes have been most thoroughly investigated and data from both pharmacological and non-pharmacological studies support the involvement of both receptors in anxiety-like and depression-like behaviors in rodents. For example, chronic stress is known to increase depression and stunt hippocampal neurogenesis, but this effect is blocked with chronic administration of either a V1b or a CRF1 antagonist (Alonso et al., 2004). As well, CRF1 knockouts have reduced anxiety relative to controls (Heinrichs et al., 1997; Smith et al., 1998). Pharmacologically, antagonism of either CRF1 or V1b receptors has been investigated pre-clinically and clinically for possible utility in treating affective disorders.

Preclinical studies also support the hypothesis that centrally located receptors mediate the anxiolytic-like and antidepressant-like effects of V1b and CRF1 receptor antagonists. Salomé et al. (2006) have demonstrated that central administration of a V1b antagonist can reduce anxiety-like and depression-like behavior. Additionally, Okuyama et al. (1999) have demonstrated that the anxiolytic-like effects of a variety of CRF1 antagonists are seen at doses lower than those required to blunt stress-induced elevations in ACTH. Jointly, these data point to a clear contribution of central receptors in the efficacy of both V1b and CRF1 receptor antagonists.

The two most extensively investigated V1b and CRF1 receptor antagonists are SSR149415 and CP-154,526, respectively. SSR149415 is potent at both the human and rat V1b receptors (Griffante et al., 2005) and in the rat, SSR149415 is highly selective over the V1a, V2 and oxytocin receptor subtypes (Griebel et al., 2002b). In terms of efficacy, SSR149415 has been shown to increase licks in a punished lick assay and time spent in the open arms of an elevated plus-maze (EPM) in rats (Griebel et al., 2002a). In the forced swim model (FST) of depression, SSR149415 significantly decreases the time rats spend immobile (Griebel et al., 2002a; Overstreet and Griebel, 2005). For a review of the effects of SSR149415 in animal models of anxiety-like behavior see Griebel et al. (2005). CP-154,526 is selective at the CRF1 receptor subtype with an affinity of 5.7 nM (rat) and has good brain penetration (Schulz et al., 1996). CP-154,526 has also been widely characterized across numerous animal models of anxiety. For example, it increases the amount of time that rats spend in the open arms of the EPM (Griebel et al., 1998; Lundkvist et al., 1996) and reduces separation-induced vocalizations in rat pups (Kehne et al., 2000). Antalarmin, a structurally similar CRF1 antagonist, lowers separation-induced calls in guinea pig pups (Griebel et al., 2002b). Results have varied in punished licking conflict tests. Griebel et al. (1998) tested CP-154,526 up to 20 mg/kg and reported no effect; Millan et al. (2001) on the other hand reported a significant increase in punished licking (at 80 mg/kg). In depression models, Overstreet et al. (2004) reported that CP-154,526 decreased immobility in the FST using Flinders Sensitive Line rats and Griebel et al. (1998) reported a similar effect using CD rats. For a review of the effects of CP-154,526 in animal models of anxiety and depression see Seymour et al. (2003).

The data collected to date for SSR149415 and CP-154,526 are from a variety of labs using different conditions and methods to assess compounds. Here, we directly compare these two compounds in animal models of anxiety and depression. Rat and guinea pig pup separation-induced vocalizations, rat EPM, rat conditioned lick suppression (CLS) and mouse marble burying were used as models of anxiety. Rat and mouse FST and a mouse tail suspension test were used as models of depression. The aim of these studies was to compare the profiles of these two novel approaches for the treatment of anxiety and depression.

2. Methods

2.1. Animals

Male CD rats were used in the EPM, FST (weighing 180–280 g) and the CLS assay (500–800 g). For the rat pup USV assay, male and female CD rats (7–10 days old weighing 25–30 g) were used. Male and female Hartley Guinea pig pups aged 5–21 days old were used for the guinea pig pup vocalization studies. Male CD1 mice (25 g) were used in the marble burying, forced swim and tail suspension tests. All animals were obtained from Charles River Laboratories and were naïve at the time of the study, except the CLS animals, which were pre-conditioned prior to testing. The animals were group housed for all studies except the CLS for which the animals were single housed. All studies were conducted during the light phase of a 12 h light cycle (lights on 7 a.m., lights off 7 p.m.). Food and water were available *ad libitum*; CLS rats were restricted to 1 h of water each day to ensure motivation to lick for a 0.2% saccharin solution. Animal care and testing procedures were conducted in conformity with the Schering-Plough Institutional Animal Care and Use Committee, and in compliance with the NIH "Guide to the Care and Use of Laboratory Animals" and the Animal Welfare Act.

2.2. Drugs

SSR149415, synthesized by the Chemical Research at the Schering-Plough Research Institute, was suspended in 0.4% Tween 80. CP-154,526 (Synchem Inc.) was dissolved in 1% 2-