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The H_3 receptor protean agonist proxyfan enhances the expression of fear memory in the rat

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Abstract

Consolidation of fear memory requires neural changes to occur in the basolateral amygdala (BLA), including modulation of histaminergic neurotransmission. We previously demonstrated that local blockade or activation of histamine H_3 receptors in the BLA impaired or ameliorated, respectively, retention of fear memory. The histamine H_3 receptor is a G-protein-coupled receptor (GPCR) displaying high constitutive activity that regulates histamine neurons in the brain. Proxyfan is a high-affinity histamine H_3 receptor protean agonist exhibiting the full spectrum of pharmacological activities, from full agonist to full inverse agonist depending on the competition between constitutively active and quiescent H_3 receptors in a given tissue or brain region. Therefore, protean agonists are powerful tools to investigate receptor conformation and may be useful in designing specific compounds selective for the various receptor conformations. In the present study we examined the effect of post-training, systemic or intra-BLA injections of proxyfan on contextual fear memory. Rats receiving intra-BLA, bilateral injections of 1.66 ng proxyfan immediately after fear conditioning showed stronger memory for the context-footshock association, as demonstrated by longer freezing assessed at retention performed 72 hr later compared to controls. Comparable results were obtained when doses as low as 0.04 mg/kg of proxyfan were injected systemically. Hence, our results suggest that proxyfan behaves as an H_3 receptor agonist with a low level of constitutive activity of the H_3 receptor in the rat BLA.
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Keywords: Basolateral amygdala; Protean agonism; Contextual fear conditioning; Local administration; Systemic administration; Constitutive activity

1. Introduction

The therapeutic potential of H_3 receptor antagonist/inverse agonists for correcting cognitive deficits is raising great interest. There is convincing evidence that systemic administration of such compounds in experimental animals have procognitive effects in learning paradigms such as the five-choice, serial reaction time task (Ligneau et al., 1998), the object recognition test (Giovannini et al., 1999), the two-choice place recognition test (Orsetti et al., 2001), the five-trial inhibitory avoidance test (Fox et al., 2002a, 2003), the elevated-plus maze task (Onodera et al., 1998) and in social memory (Fox et al., 2003). However, when administered locally, into restricted brain regions H_3 ligands may have other effects on the expression of some forms of memory. For instance, post-training administrations of

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the H_3 receptor antagonists/inverse agonists thioperamide or clobenpropit into the basolateral amygdala impair memory for aversive events (Passani et al., 2001), whereas agonists such as R-α-methylhistamine improve the expression of fear memory after contextual fear conditioning (Cangioli et al., 2002). In the same learning paradigm, post-training injections into the dorsal hippocampus of R-α-methylhistamine improve memory consolidation (Giovannini et al., 2003). Almost invariably, the behavioural effects of histaminergic compounds have been studied following systemic or local administration into small brain regions, which are known to be crucial for the behavioural response under study. Both approaches have advantages and caveats: systemic treatments are clinically relevant, but histaminergic compounds are known to affect arousal, anxiety, perception (Brown et al., 2001), and stress (Westerink et al., 2002), therefore the mechanisms of action remain unexplored. On the other hand, local administrations of these compounds may reveal how the histaminergic system affects cognitive processing by modulating local neuronal circuitry, intracellular pathways and may explain potential unwanted, or side effects of the molecules under investigation. In the present study, we correlated the behavioural effects of systemic and intra-basolateral amygdala (BLA), post-training injections of proxyfan in the rat, on contextual fear memory. Aversive training tests such as contextual fear conditioning are used to assess emotional memory. They implicate the association between a neutral cue (the context, in this case) and a footshock. Re-exposure to the same environment will induce a measurable stereotyped behaviour. Furthermore, there is extensive evidence that crucial neural changes mediating emotional memory occur in the BLA (LeDoux, 2000). The interest in proxyfan stems from the recent discovery that the H_3 receptor shows a high degree of agonist-independent activity (Morisset et al., 2000), a phenomenon also referred to as constitutive activity, as demonstrated both in vivo (Morisset et al., 2000) and in vitro, in recombinant and native H_3 receptors (Rouleau et al., 2002). Several of the classical H_3 antagonists, such as thioperamide and ciproxifan, behave as potent inverse agonists, as they block the intracellular pathways associated with active H_3 receptors in transfected cells (Morisset et al., 2000; Rouleau et al., 2002). The high-affinity H_3-receptor ligand proxyfan (Ligneau et al., 2000; Morisset et al., 2001), on the other hand, is a "protean" agonist, which displays the full spectrum of pharmacological activities from full agonism to full inverse agonism (Gbahou et al., 2003). Little is known of the behavioural effects of proxyfan. In a dipsogenia test in mice proxyfan behaves as an antagonist/partial agonist (Fox et al., 2002b). Furthermore, proxyfan modulates the sleep-wake cycle in a different manner depending on the animal species (Gbahou et al., 2003), hence depending on the conformation of the receptors and their constitutive activity. The H_3 receptor is apparently one of the most highly constitutively active receptors so far detected, hence we used proxyfan to study its functional significance in a memory test that requires the activation of the amygdala, one of the brain regions with the highest density of H_3 receptor mRNA and binding sites in the rat (Pillot et al., 2002).

2. Materials and Methods

2.1. Animals

Male albino Wistar rats (average body weight 290 g) were used in all experiments. Rats were individually housed in a room with a natural light–dark cycle and constant temperature (20 ± 1 °C), and had free access to food and water throughout the experiments. Animals used in this study were cared for in accordance with the guidelines of the European Community recommendations (86/606/CEE) and were approved by the Animal Care Committee of the Università di Firenze.

2.2. Behavioural experiments

2.2.1. Apparatus

Contextual fear conditioning was induced in a basic Skinner box module (Modular Operant Cage, Coulbourn Instruments Inc., PA, USA) as in previous experiments (Cangioli et al., 2002; Passani et al., 2001). Box dimensions were 29 × 31 × 26 cm. The top and the two opposite sides were made of aluminium panels, the other two sides of transparent plastic and the floor of stainless steel rods connected to a shock delivery apparatus (Grid Floor Shocker, model E13-08, Coulbourn Instruments Inc. PA, USA). The number of the electric shocks and the inter-shock interval duration was predetermined by a stimulus programming device (Scatola di comando Arco 2340, Ugo Basile, Italy). The apparatus was placed in an acoustically insulated room kept at a constant temperature of 20 ± 1 °C. Illumination inside the room was 60 lux.

2.2.2. Contextual fear conditioning procedure

The rat was gently taken manually from the home cage, placed in a bucket and carried from the housing to the soundproof room, and then placed in the conditioning apparatus (contextual cue). The rat was left undisturbed for 3 min. and subsequently seven 1-s, 1-mA electric footshocks were administered at 30-s intervals. The rat was removed 2 min after the end of the stimulation, therefore spending a total time of 8 min inside the conditioning apparatus. The same conditioning

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