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Research Report

Non-peptide oxytocin receptor ligands and hamster circadian wheel running rhythms

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ABSTRACT

The synchronization of circadian rhythms in sleep, endocrine and metabolic functions with the environmental light cycle is essential for health, and dysfunction of this synchrony is thought to play a part in the development of many neurological disorders. There is a demonstrable need to develop new therapeutics for the treatment of neurological disorders such as depression and schizophrenia, and oxytocin is currently being investigated for this purpose. There are no published reports describing activity of oxytocin receptor ligands on mammalian circadian rhythms and that, then, is the purpose of this study. Non-peptide oxytocin receptor ligands that cross the blood brain barrier were systemically injected in hamsters to determine their ability to modulate light-induced phase advances and delays of circadian wheel running rhythms. The oxytocin receptor agonist WAY267464 (10 mg/kg) inhibited light induced phase advances of wheel running rhythms by 55%, but had no effect on light-induced phase delays. In contrast, the oxytocin receptor antagonist WAY162720 (10 mg/kg) inhibited light-induced phase delays by nearly 75%, but had no effect on light-induced phase advances. Additionally, WAY162720 was able to antagonize the inhibitory effects of WAY267464 on light-induced phase advances. These results are consistent for a role of oxytocin in the phase-delaying effects of light on circadian activity rhythms early in the night. Therefore, oxytocin may prove to be useful in developing therapeutics for the treatment of mood disorders with a concomitant dysfunction in circadian rhythms. Investigators should also be cognizant that oxytocin ligands may negatively affect circadian rhythms during clinical trials for other conditions.

1. Introduction

Oxytocin (OT) is being investigated for the possible treatment of severe neurological diseases such as autism (Hollander et al., 2007), anxiety (Ring et al., 2006), postpartum depression (Kim et al., in press) and schizophrenia (MacDonald and Feifel, 2012), and it has well known social and behavioral effects in animals, including the Syrian hamster (Albers and Bamshad, 1998; Guzman et al., 2014). There is also evidence that dysfunction in circadian rhythms, manifest as disruptive sleep/wake cycles, are also symptomatic in some cases of autism (Glickman, 2010; Tordjman et al., 2013). Other mood disorders such as anxiety and depression have more established linkages to the circadian timing system

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(Hickie et al., 2013; Partonen, 2012). Several recent reviews have made the case for more research efforts in developing oxytocin as a possible treatment for pathological states of mood (Manning et al., 2012; MacDonald and Feifel, 2013) and, therefore, when considering the linkage mentioned above between circadian rhythms and these pathologies, it is of timely interest to investigate the activity of oxytocin on circadian rhythms in mammals.

Mammalian circadian rhythms are generated by clock cells located within the suprachiasmatic nucleus (SCN) at the ventral base of the hypothalamus (Ralph et al., 1990). Retinal projections synchronize the timing of the circadian pacemaker with that of the light:dark cycle and the circadian pacemaker in turn synchronizes peripheral pacemakers located throughout the body that control numerous physiological processes (Levi and Schibler, 2006; Liu et al., 2007). In nature, sunlight advances the circadian rhythms of mammals at dawn, and will delay the rhythms at dusk; therefore the clock is reset twice each day as the seasons change. The Syrian hamster is one of the standard mammalian models used to study circadian rhythms due to the incredible timed precision of the wheel running activity in this species. In particular, the hamster is well suited to examine how drugs influence the ability of light to phase advance and phase delay the circadian rhythms in wheel running activity at times reflecting dawn and dusk, respectively.

There is some indirect evidence that OT receptors are located within the SCN of rodents, primarily the presence of mRNA for the OT receptor in the rat SCN (Vaccari et al., 1998; Young et al., 1997). However, there is significant evidence for OT neurons in the paraventricular nucleus of many mammalian species (Dzirbikova et al., 2011; Morin and Blanchard, 1993; Ni et al., 2014; Whitman and Albers, 1998) and there is a reciprocal connection between the SCN and this nucleus (Krout et al., 2002). Therefore, the probable presence of OT receptors in the SCN and the close association of OT neurons in other areas of the hypothalamus provide a further rationale for examining the role of OT in circadian rhythms.

Most OT receptor agonists and antagonists developed to date are peptides, which limits their suitability for the treatment of CNS diseases (Manning et al., 2012). Recently, two non-peptide ligands for the OT receptor have become available, the agonist WAY267464 (Ring et al., 2010), and the antagonist WAY162720 (Ring et al., 2006). Both of these compounds will cross the blood brain barrier, and thus presented the opportunity herein to test each for any ability to modulate light induced phase advances and delays of the circadian wheel running rhythms in hamsters.

2. Results

2.1. *Effects of the oxytocin receptor agonist WAY267464 on light-induced phase advances and delays of hamster circadian activity rhythms*

WAY267464 inhibited light-induced phase advances by approximately 55% at a dose of 10 mg/kg (ANOVA $F_{3,21}=6.634$, $P=0.002$; Fig. 1). A light pulse at CT 19 following vehicle injection elicited a phase advance of 1.52 ± 0.1 h, and the same light pulse following a systemic injection of 10 mg/kg WAY267464 elicited a phase advance of 0.69 ± 0.1 h (Fig. 1).

In contrast, WAY267464 tested at the same dosage range as above (0.1–10 mg/kg) had no effect on phase delays elicited by light pulses at CT 14 (Table 1).

2.2. *Effects of the oxytocin receptor antagonist WAY162720 on light-induced phase advances and delays of hamster circadian activity rhythms*

The oxytocin receptor antagonist WAY162720 had no effect on light-induced phase advances when tested at doses from 0.1 to 10 mg/kg (Table 1).

However, WAY162720 dose dependently inhibited light-induced phase delays by approximately 75% at the highest dose of 10 mg/kg (ANOVA $F_{3,21}=7.131$, $P=0.002$; Fig. 2). A ten minute light pulse at CT 14 preceded by vehicle injections elicited a phase delay of hamster wheel running rhythms of 0.75 ± 0.05 h, and that delay was reduced to 0.18 ± 0.1 h following injections of 10 mg/kg WAY162720 (Fig. 2).

2.3. *WAY162720 antagonizes the inhibitory effects of WAY267454 on light-induced phase advances of hamster circadian activity rhythms – evidence for OT receptor specificity of these compounds in the hamster*

WAY267464 (10 mg/kg) inhibited light-induced phase advances of hamster wheel running rhythms by approximately 30%, and this effect was completely antagonized by concomitant injection of 10 mg/kg WAY162720 (ANOVA $F_{3,21}=5.718$, $P=0.005$; Fig. 3). Light pulses at CT 19 preceded by vehicle injections advanced wheel running rhythms by 1.58 ± 0.06 h, and this effect was reduced to 1.14 ± 0.06 h following injections of 10 mg/kg WAY267464, but to only 1.47 ± 0.11 h when 10 mg/kg WAY162720 was injected along with 10 mg/kg WAY267464 (Fig. 3).

3. Discussion

3.1. *Summary of key findings*

Systemic injections of the OT receptor agonist WAY267464 significantly inhibited light-induced phase advances, but not delays of wheel running rhythms at a dose of 10 mg/kg (Fig. 1, Table 1). In contrast, the OT receptor antagonist WAY162720 inhibited light-induced phase delays, but not advances of wheel running rhythms at the same dose (Fig. 2, Table 1). WAY162720 also antagonized the inhibitory effect of WAY267464 on light-induced phase advances, providing further evidence for OT receptor specificity of these compounds (Fig. 3). The effective dose of both WAY267464 (10 mg/kg) and WAY162720 (1–10 mg/kg) in this study are equivalent to the doses used in mice to study anxiolytic activity with the four-plate test (Ring et al., 2006, 2010). Therefore, these results indicate a role for oxytocin in the pathway whereby light entrains the circadian pacemaker in hamsters, or in the case of the agonist WAY267464, in a separate system that can modulate the effects of light on the pacemaker.