8-OH-DPAT regulates the amplitude and the phase of LH surge in ovariectomized steroid-primed rats

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Precise interactions between ovarian steroids and neurotransmitters are required for the secretion of phasic LH surge. Previous data suggested the existence of an interactive stimulatory effect of progesterone (P) and serotonin (5-HT) on LH release. In the present work the effects of 8-OH-DPAT, a selective 5-HT₁₆ agonist, on phasic LH secretion were tested in ovariectomized rats implanted for 6 days with a pellet of 17 β estradiol (OVX-E₂) and in OVX-E₂ treated with progesterone (OVX-E₂-P). Intraperitoneal injection of 8-OH-DPAT at 11.00 h in the morning of the expected LH surge had no effect on circadian plasma levels of progesterone (P) and serotonin (5-HT). Previous data suggested the existence of an interactive stimulatory effect of P and 8-OH-DPAT on phasic LH release. SDZ 216-525, a specific 5-HT₁₆ antagonist administered 60 min before 8-OH-DPAT, inhibited the stimulatory effect of the 5-HT₁₆ agonist on the amplitude of LH surge. The present data suggest that progesterone is required for the regulation of phasic LH release by 5-HT₁₆ agonists and that under this hormonal condition the activation of 5-HT₁₆ receptors induces a phase advance and an increase in LH surge.

Keywords: phasic LH release; 8-OH-DPAT; progesterone; phase shift; rat

Introduction

The effects of gonadal steroids on gonadotropin release are believed to be exerted at the level of the hypothalamus via altering the activity of a number of neurotransmitters. Considerable evidence suggest that serotonin (5-HT) plays an integral role in the generation of phasic LH release (for a review see Vitale & Chiocchio, 1993). Ovarian steroids have been shown to alter 5-HT synthesis, turnover, release and binding sites (Cone et al., 1981; Héry et al., 1982; Biegon & McEwen, 1982; Cone et al., 1983; Johnson & Crowley, 1986) suggesting that the influence of gonadal steroids on LH release might be at least, partially mediated by a modulation of the serotonergic transmission.

In brain areas involved in the control of LH secretion, serotonergic neurotransmission is modulated by progesterone (P) (Walker & Wilson, 1983; James et al., 1989). Furthermore, P and 5-HT are believed to stimulate LH release in an interactive way. Joint administration of P and 5-hydroxytryptophan, the precursor of 5-HT, increased LH secretion, whereas anti 5-HT drugs blunted the facilitatory action of P on LH release (Johnson & Crowley, 1986). This may result from an interactive stimulatory effect of P and 5-HT on LHRH neurons, since we recently reported that P potentiated the increase in LHRH release induced by a 5-HT₁₆ receptor agonist in fetal hypothalamic cells in culture (Héry et al., 1995).

The following experiments were performed in order to determine whether P could interact with a 5-HT₁₆ receptor agonist, 8-OH-DPAT (8-Hydroxy-2-(di-n-propylamino) tetralin) (Middlemiss & Fozard, 1983), to stimulate phasic LH release in vivo.

Results

Effects of 8-OH-DPAT on phasic LH release

In OVX-E₂ rats which received no further treatment, plasma LH levels showed high amplitude daily fluctuations, with maximal levels at 19.00 h (Figure 1A). Under these hormonal conditions, 8-OH-DPAT modified neither the kinetic, nor the amplitude of LH surge (Figure 1A).

The amplitude of LH surge was greater in OVX-E₂-P rats, than in OVX-E₂ (F₁,₇₅ = 14.05 Figure 1B). Although the onset of LH surge was early in OVX-E₂-P, the highest levels of LH were found at 19.00 h in OVX-E₂-P and OVX-E₂ rats (Figure 1B). A single injection of 8-OH-DPAT at 11.00 h increased the amplitude of LH surge in OVX-E₂-P (F₁,₁₅₂ = 18.969), with maximal levels at 17.00 h (Figure 1B). 8-OH-DPAT became unable to increase the magnitude of the LH surge when RU 38486 a progesterone antagonist, was administered together with P at 09.00 h in OVX-E₂-P rats. (F₁,₇₄ = 38.731, Figure 1B).

Effect of SDZ-216525 on phasic LH release in OVX-E₂-P rats

In OVX-E₂-P rats, administration of a 5-HT₁₆ receptor antagonist (SDZ 216-525, 1 mg/kg) at 10.00 h in the morning of the expected LH surge delayed the onset of the phasic LH surge and decreased its magnitude (Figure 2A). A one way analysis of variance showed that the LH surge measured in the group of OVX-E₂-P rats treated with SDZ 216-525 was not significantly different from that measured in OVX-E₂ rats. (F₁₄ = 1.354 Figure 2A compared to Figure 1A). Administration of SDZ 216-525 1 h before 8-OH-DPAT injection in OVX-E₂-P rats dramatically reduced the magnitude of LH surge (F₁,₇₁ = 29.38), without altering the time of peak (Figure 2B).

Effect of 8-OH-DPAT on hypothalamic LH-RH contents in OVX-E₂-P rats

The administration of 8-OH-DPAT at 11.00 h in OVX-E₂-P rats significantly decreased hypothalamic levels of LHRH 30 min later (1.85 ± 0.06 compared to 2.45 ± 0.12 ng/hypothalamus).

Discussion

The present results show that a single injection of 8-OH-DPAT in the morning of the expected LH surge induces a phase advance in the phasic surge of LH and an increase in its amplitude in OVX steroid primed rats. A pretreatment of OVX-E₂ animals with P is required to observe these 5-HT₁₆ receptor agonist effects.

The involvement of 5-HT in LH release has long been investigated with several techniques but contradictory results
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Figure 1 (A) Effect of 8-OH-DPAT on phasic LH release in ovariectomized estradiol (E2) treated rats. 8-OH-DPAT was injected at 11:00 h. (B) Effect of 8-OH-DPAT + RU 38486 (RU) in ovariectomized estradiol, progesterone (P) treated rats. P or P + RU 38486 were injected at 9:00 h, 8-OH-DPAT was injected at 11:00 h. Each point represents the mean ± SEM of 8 to 15 rats (corresponding to 2 or 3 experiments).

Figure 2 (A) Effect of SDZ 216-525 on phasic LH release in ovariectomized estradiol progesterone (P) treated rats. P and SDZ 216-525 were injected at 9:00 h and 10:00 h respectively. (B) Effect of SDZ 216-525 on 8-OH-DPAT effect in ovariectomized estradiol progesterone (P) treated rats. SDZ 216-525 and 8-OH-DPAT were injected at 10:00 h and 11:00 h respectively. Each point represents the mean ± SEM of 8 to 15 rats (corresponding to 2 or 3 experiments).

were obtained (Vitale & Chiocchio, 1993). These discrepancies could be explained by the differential effects of 5-HT on specific receptor subtypes involved in LHRH and LH release mechanisms and by differences in the hormonal status of the animals used in each study. Nevertheless there is general consensus about the fact that pharmacological manipulations of the serotonergic transmission indicate a facilitatory role of 5-HT on preovulatory LH surge, although the 5-HT receptor subtypes involved in this regulation have not been established yet.

An inhibition of the preovulatory LH surge by ketanserin or ritanserin was recently reported and showed the involvement of 5-HT1 receptors in the 5-HT-induced stimulation of phasic LH release (Tanaka et al., 1993; Dow et al., 1994). Nevertheless Dow et al. (1994) emphasized the fact that these drugs inhibit both phasic and basal LH release, and that 5-HT1 receptor antagonists also block at adrenoreceptors antagonist properties. To our knowledge, the effects of 5-HT1 receptor agonists on the regulation of LH release have been only reported in studies analysing the short term effect of 8-OH-DPAT (Johnson & Sanders, 1987; Aguilar et al., 1993). These studies reported an increase in LH secretion 15 to 30 min after the systemic injection of 8-OH-DPAT in prepubertal female rats or in OVX-E2 primed rats, whereas LH release is decreased in OVX rats.

The positive effect of 8-OH-DPAT on phasic triggering of LH release, reported here, in OVX-E2-P rats, appears to be specifically mediated by 5-HT1A receptors activation since the effect of 8-OH-DPAT was inhibited by the specific 5-HT1A antagonist SDZ 216-525 (Schoeffter et al., 1993). It is well admitted that 5-HT1A receptors may function as auto (Sotelo et al., 1990) as well as heteroreceptors (Verge et al., 1986; Frankfurt et al., 1993) being located in both cases on neuronal cell bodies and dendrites. The present effect of 8-OH-DPAT is unlikely to be induced by activation of 5-HT1A somatodendritic autoreceptors since similar effects were observed by others using non specific 5-HT agonists whose affinities for autoreceptors are very low (Chen et al., 1981; Lenahan et al., 1986).

We recently reported a stimulatory effect of 8-OH-DPAT on LHRH release from fetal hypothalamic cells (Héry et al., 1995). It is therefore reasonable to hypothesize that the decrease in hypothalamic LHRH content observed 30 min following 8-OH-DPAT administration is associated with an increased release of the neurohormone, and that the increase in LH release could result at least partially from an action of 8-OH-DPAT in the hypothalamus.

Under our experimental conditions the presence of P was required in order to observe the stimulatory effect of 8-OH-DPAT on LH release in OVX-E2 rats. Indeed, 8-OH-DPAT treatment alone had no effect in OVX-E2 rats and we showed that the 8-OH-DPAT induced stimulation of LH release in OVX-E2-P animals was inhibited by a pretreatment with the potent antiprogestin RU 38486. This is not the...