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Sumatriptan Mediated Growth Hormone Responses Do Not Alter Throughout the Menstrual Cycle

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The objective of this study was to determine the effects of oral sumatriptan on growth hormone (GH) release throughout the menstrual cycle in healthy female volunteers. A placebo-controlled cross-over design was employed. Subjects were tested a total of six times over two consecutive menstrual cycles; twice in the early follicular phase, twice in midcycle and twice in the late luteal phase. Oral sumatriptan (100 mg) and placebo were administered on alternate visits. Twelve healthy female volunteers aged between 18–40 years with regular menses and not taking oral contraceptives were recruited. Baseline blood samples at 0 min were taken for GH, oestrogen and progesterone estimation. GH was measured at +60, +90, +120 and +180 min following administration of oral sumatriptan 100 mg or matched placebo. GH, progesterone and oestrogen were measured by radioimmunoassay. At each phase of the menstrual cycle serum GH levels peaked at 60–90 min following administration of oral sumatriptan compared to placebo which showed no response. Analysing GH response to sumatriptan and placebo over time for the three phases of the menstrual cycle (three-way ANOVA) demonstrates that the GH response to sumatriptan did not alter.

KEY WORDS—growth hormone; sumatriptan; menstrual cycle; 5HT; sex steroids

INTRODUCTION

There is evidence that the sensitivity of certain neurotransmitters receptors alters in response to gonadal steroids (Yatham *et al.*, 1989; Dinan *et al.*, 1990; O'Keane *et al.*, 1991). Growth hormone (GH) responses to pyridostigmine (O'Keane and Dinan, 1992), clonidine (Matussek *et al.*, 1984), tryptophan (Bancroft *et al.*, 1991), GHRH (Lan *et al.*, 1987) and arginine (Merimee and Fineberg, 1971) are all increased in women during high oestrogen phases of the menstrual cycle. It has also been noted that oestrogen may augment exercise-induced increased growth hormone release (Franz and Rabkin, 1965). Furthermore, it has been shown that the pulsatile release throughout the menstrual cycle of growth hormone is enhanced by E2 via an amplitude-modulated effect on the endogenous GH pulse and possibly by progesterone (Devesa *et al.*, 1991).

Serotonin is among the many neurotransmitters that participate in the hypothalamic control of pituitary secretion. The diversity of neuroendocrine responses to various 5HT challenge agents suggest that different 5HT subtypes may modulate different responses (Meltzer and Nash, 1988). In man administration of intravenous but not oral L-tryptophan (LTP) and 5-hydroxytryptophan (5HTP) results in a consistent elevation in plasma growth and prolactin hormone (Handwerger *et al.*, 1975; Lancranfan *et al.*, 1977; Meltzer *et al.*, 1982; Westenberg *et al.*, 1982; Charney *et al.*, 1982; Maschat *et al.*, 1983; Cowen *et al.*, 1985). Increases in PRL, cortisol and GH have been demonstrated following both oral and intravenous administration of *m*-chlorophenylpiperazine (m-CPP), which binds to 5HT1a, 5HT1c and 5HT1d receptors as well as 5HT2 receptors (Charney *et al.*, 1987; Murphy *et al.*, 1989). The neuroendocrine effects of 5HT1a agonists have been well documented, for example buspirone stimulates the secretion of PRL, cortisol and GH in normal volunteers.

Sumatriptan is a novel 5HT1 agonist which has been introduced for the treatment of migraine (SSISG, 1991). Sumatriptan displays a high affinity for both 5HT1b and 5HT1d receptor subtypes and is approximately five times less potent at 5HT1a receptors (Peroutka, 1993). Furthermore, sumatriptan is essentially inactive at other 5HT, dopaminergic or cholinergic receptors (Feniuk *et al.*, 1991).

The 5HT1d side has been described in the bovine caudate by Heuring and Peroutka (1987). These

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sites are present in the brain of most mammalian species including man and are particularly enriched in the basal ganglia and the substantia nigra (Herrick-Davis and Titaler, 1988; Waeber *et al.*, 1988; Peroutka *et al.*, 1989).

Sumatriptan penetrates the CNS to a limited extent (Dallas, 1989). A number of recent studies have shown that subcutaneous sumatriptan causes a short-lived rise in serum growth hormone levels in healthy volunteers (Franceschini *et al.*, 1994; Herdman *et al.*, 1994). A 5HT1d-mediated effect of sumatriptan on GH release was proposed. We have previously demonstrated that the neuroendocrine responses to less selective 5HT probes vary considerably throughout the menstrual cycle (O'Keane and Dinan, 1992). If GH responses to sumatriptan alter throughout the menstrual cycle this may indicate changes in 5HT1d receptor sensitivity. The present study was undertaken to determine the effects of oral sumatriptan on GH release throughout the menstrual cycle in healthy female volunteers.

METHODS

Eleven female volunteers aged between 18–40 years with regular menses and not taking oral contraceptives took part in the investigation which was approved by the local ethics committee. All subjects gave informed consent and were physically healthy, on no medication and had a negative pregnancy test. Each subject was tested a total of six times over two consecutive menstrual cycles, twice in the early follicular phase (day 2–4), when sex steroids are low, twice in midcycle (day 12–14) when oestradiol (E2) levels are relatively high and twice in late luteal phase (day 23–25) when progesterone levels are relatively high. Active drug (100 mg sumatriptan) and placebo were administered alternately. Volunteers, but not testers, were blind to treatment and successive participants were first tested with either placebo or active drug.

Volunteers fasted from midnight the night before and presented at 8.00 h in the morning. They relaxed for 30 min following insertion of a cannula in a forearm vein. The cannula was heparinized to keep the vein patent. A baseline sample of blood was taken by vacuum extraction at 0 min for GH, oestrogen and progesterone. Volunteers were then administered either sumatriptan 100 mg or matched placebo orally at 0 min. Subsequent blood samples were extracted for GH at +60, +90, +120 and +180 min. Subjects remained supine and awake throughout the procedure.

Hormonal assays

GH levels were analysed using a method whereby the test serum competes with radiolabelled human GH for sites on human GH antiserum (Raite, 1983). This assay has a sensitivity of 0·45 mU/l, an intrassay precision of 1·6 per cent and an interassay precision of 2·3 per cent at about 10 mU/l. Plasma E2 levels were measured by radioimmunoassay using a commercial kit (Diagnostic Products Corporation). This assay has a sensitivity of 5·6 pmol/l and intrassay and interassay variations of 2·7 per cent and 3·5 per cent respectively at a concentration of 376 pmol/l. Progesterone levels were assayed using a commercial kit 'Coat a Count Progesterone' (Diagnostic Products Corporation). The progesterone assay has a sensitivity of 0·16 nmol/l and inter- and intraassay variations of 7·5 per cent and 6·6 per cent respectively at 9·0 nmol/l.

Statistical analysis

Data was analysed using the computerized statistical program Statgraphics (Statistical Graphics Corporation, 1993). Endocrine responses over time to active drug and placebo were compared by three-way Analysis of Variance (ANOVA). Tukey comparisons were used where appropriate, as was the Pearson product–moment correlation coefficient.

RESULTS

Growth hormone

The baseline GH concentrations (mean ± SEM) for follicular, ovulatory and luteal phases were 1·3 ± 0·2 mU/l, 0·75 ± 0.15 mU/l, and 1·16 ± 0.28 mU/l. In all cases GH peaked at 60–90 min following administration of sumatriptan compared to placebo which showed no response. Measuring GH response as the maximum level post-sumatriptan administration relative to baseline, GH responses (mean ± SEM) were as follows: follicular phase, 4·33 ± 1·35 mU/l, midcycle 5·86 ± 1·34 mU/l and late luteal phase 6·32 ± 2·13 mU/l (see Figure 1). No GH response to placebo was noted. Analysing GH responses to sumatriptan and placebo over time for the three

phases of the menstrual cycle, a three-way ANOVA yields a drug by cycle phase by time interaction which is not significant (follicular versus midcycle, $p = 0{\cdot}45$; follicular versus luteal, $p = 0{\cdot}37$; luteal versus midcycle, $p = 0{\cdot}48$). The response to sumatriptan does not alter significantly throughout the menstrual cycle.

Oestrogen and progesterone

Plasma concentrations (mean ± SEM pmol/l) of E2 vary throughout the menstrual cycle, in the early follicular phase 203 ± 67·8 pmol/l, at midcycle 471 ± 70 pmol/l and in luteal phase 351·48 pmol/l. The concentrations of progesterone (mean ± SEM nmol/l) were in early follicular phase 3·2 ± 0·0 nmol/l, in midcycle 4·9 ± 1·9 nmol/l and in luteal phase 17·94 ± 3·26 nmol/l. There was no significant correlation between plasma GH and oestrogen ($r = 0{\cdot}12$, $df = 35$, p = n.s.).

DISCUSSION

The results of this study indicate that oral sumatriptan increases serum growth hormone levels in female subjects and this response does not vary significantly throughout the menstrual cycle. The elevation lasts less than 3 h following acute administration. This is to our knowledge the first such report as previous studies have used a subcutaneous route of administration.

It is well established that neuroendocrine responses to challenge drugs in females can vary significantly depending on their menstrual status. It has been shown that PRL responses may fluctuate with oestrogen levels over the course of the menstrual cycle, the 5HT1a agonist, buspirone induced a PRL response which is highest premenstrually (Yatham *et al.*, 1989; Dinan *et al.*, 1990). O'Keane *et al.* (1991) demonstrated that the PRL responses to d-fenfluramine (a 5HT releasing agent) were maximal premenstrually. Recent studies investigating the effect of the menstrual cycle on the GH response to various challenge agents have given varying results. O'Keane and Dinan (1992) found that the GH responses to pyridostigmine, a cholinesterase inhibitor, was maximal in the late luteal phase. Histamine induced a GH response to TRH/GnRH in women during the luteal phase with high oestrogen levels, whereas no responses were found in early follicular phase with low oestrogen levels (Knigge *et al.*, 1990). Increased GH responses during ovulation compared to menstruation were found with clonidine (Holst *et al.*, 1989), an opiate agonist (Hoehe, 1988) and arginine (Knigge *et al.*, 1990). Other

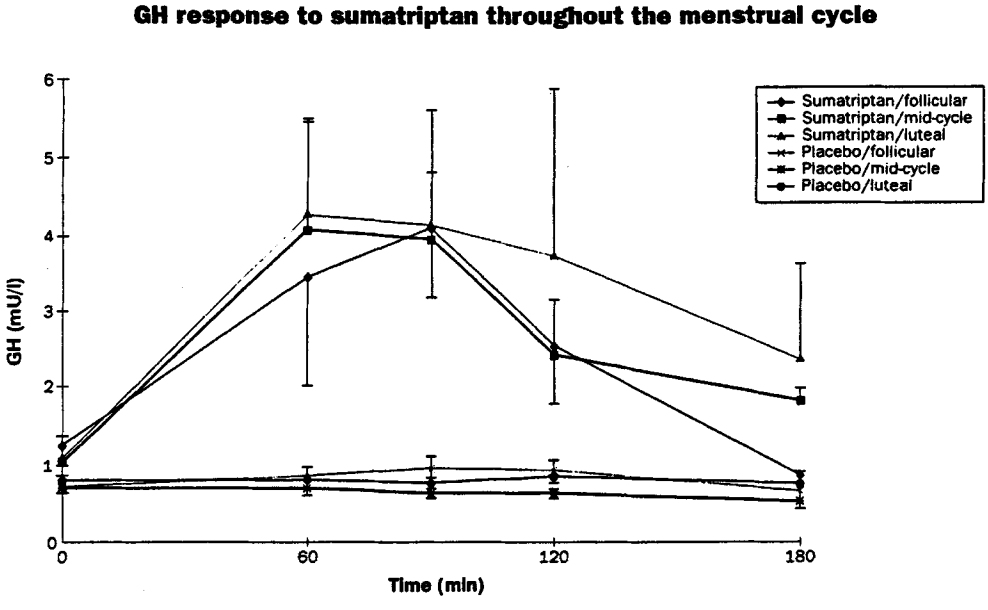

Figure 1. Plasma growth hormone responses to sumatriptan and placebo in the early follicular phase, midcycle and luteal phase of the menstrual cycle. In each case sumatriptan was administered at time 0. Results are expressed as mean ± SEM

studies have found no change across the menstrual cycle in GH responses to LTP (Bancroft *et al.*, 1991), GH releasing peptide 6 (Pevala *et al.*, 1993), desipramine hydrochloride (Saxena *et al.*, 1974), or hp GRF-40 (human pancreatic tumour GH releasing factor) (Evans *et al.*, 1984).

Our results show that there was a sumatriptan-induced GH response, but there was no correlation between serum GH and plasma E2 levels, and the magnitude of the response did not alter significantly throughout the menstrual cycle. Using the GH response to sumatriptan as a measure of 5HT1d receptor sensitivity, these results suggest that sex steroids do not alter the sensitivity of that receptor.

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