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Neuroendocrine effects of sumatriptan

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Abstract. The neuroendocrine effects of the 5-HT receptor agonist, sumatriptan (6 mg subcutaneously), were studied in 11 healthy male subjects using a placebo-controlled, cross-over design. Compared to placebo, sumatriptan significantly lowered levels of plasma prolactin but increased those of plasma growth hormone. There was no effect on plasma cortisol concentrations. The neuroendocrine effects of sumatriptan differ from those of previously described 5-HT-receptor agonists, and may be a consequence of selective activation of 5-HT_{1D} or 5-HT_{1B} receptors. However, the present data cannot exclude the possibility that the neuroendocrine changes reflect non-specific stress responses or changes in pituitary blood flow.

Key words: 5-HT receptor – Sumatriptan – Prolactin – Cortisol – Growth hormone

Sumatriptan is a 5-hydroxtryptamine (5-HT) receptor agonist recently introduced for the treatment of migraine headache (Dechant and Clissold 1991). Ligand binding studies in human and animal brain have shown that sumatriptan has a high affinity for the 5-HT_{1D} receptor subtype but may also interact with 5-HT_{1A} and 5-HT_{1B} receptors (Schoeffter and Hoyer 1989; Peroutka and McCarthy 1989; Oksenberg et al. 1992). Sumatriptan has a low affinity for other monoamine receptors (Peroutka and McCarthy 1989).

Drugs with agonist properties at 5-HT receptors produce characteristic changes in the secretion of anterior pituitary hormones (Cowen 1992). Recent neuroendocrine investigations have suggested that the secretion of particular hormones may be regulated by more than one 5-HT-receptor subtype. In the rat for example, increased release of corticotrophin (ACTH) can be produced by drugs with selective actions at 5-HT_{1A}, 5-HT_{1C} and 5-HT_2 receptors (Gilbert et al. 1988; King et al. 1989; Gartside et al. 1992). The reason for this apparent duplication of 5-HT regulation is not clear but it allows changes in the secretion of a single hormone to be used to determine the effect of different classes of 5-HT-receptor ligands.

Studies in vivo have suggested that sumatriptan penetrates the central nervous system only to a limited extent (Dallas et al. 1989; Sleight et al. 1990); a preliminary report, however, has indicated that it may increase plasma growth hormone (GH) levels in healthy volunteers (Rolandi et al. 1992). The present study was undertaken to confirm this finding and also to determine whether administration of sumatriptan would alter plasma concentrations of prolactin (PRL) and cortisol in healthy male subjects.

Materials and methods

Subjects and neuroendocrine testing. Twelve healthy male subjects (mean age 32.4 years, range 24–43 years) took part in the investigation which was approved by the local ethics committee. Subjects were tested twice, with an interval of 7–14 days between tests, receiving sumatriptan (6 mg subcutaneously) on one occasion and an equivalent volume of subcutaneous saline on the other. One subject developed an acute feverish illness shortly after his saline test and was found to have very high levels of cortisol and GH during the baseline sampling period. The data of this subject were therefore excluded from the analysis. Testing was carried out single-blind and the order of treatments was randomised. Subjects fasted after a light breakfast and came to the laboratory at 1200 hours at which time an indwelling venous cannula was inserted. After a 60-min rest period, three baseline venous samples were taken at 15-min intervals (− 30, − 15 and 0 min). Sumatriptan or saline (0.5 ml over 5 s) was then administered and further venous samples taken at 15-min intervals for the following 120 min.

Biochemical measurements. Plasma was separated by centrifugation and stored at − 30° C. The samples from any one subject were always assessed in the same assay procedure by a technician blind to the order of drug administration. Plasma concentrations of PRL and GH were determined by standard immunoradiometric assays (reagents provided by Netria, London, UK). Plasma cortisol was determined by a standard double-antibody radioimmunoassay (Bioclin, Cardiff, UK). Inter- and intra-assay coefficients of variation (CV) over the ranges encompassed by the standard curves were as follows: PRL, 2.4% and 4.8%; GH, 2.6% and 4.1%; cortisol, 4.3% and 5.8%. Because GH can suppress its own release (Cryer and Daughaday 1977), as is our usual practice we excluded the tests of subjects whose plasma GH levels at time 0 exceeded 10 mU/l.

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Statistical analysis. Hormonal responses were plotted against time and analysed with a two-way repeated measures analysis of variance (ANOVA). Differences between individual time points were assessed with Fisher's test of least significant difference.

Results

PRL responses

There was no significant difference in baseline plasma PRL concentrations (at time 0) between the sumatriptan and placebo days (mean ± SEM PRL on placebo day = 121 ± 14 mU/l; on sumatriptan day = 140 ± 21 mU/l; $P > 0.1$). Following sumatriptan administration, plasma PRL concentrations fell significantly compared to placebo (Fig. 1). The ANOVA on the change from baseline PRL values showed a significant main effect of test day ($F = 9.50$; $df = 1,10$; $P = 0.008$) and time ($F = 5.38$; $df = 7,70$; $P = 0.0002$) and a significant interaction between these measures ($F = 4.55$; $df = 7,70$; $P = 0.0003$). Post-hoc testing showed that plasma PRL levels following sumatriptan were significantly lower at all time points from + 30 min onwards (Fig. 1).

Cortisol responses

In contrast to the effect of sumatriptan on plasma PRL there was no change in plasma cortisol values compared to placebo injection (Fig. 2). The ANOVA showed no significant effect of test day ($F = 0.24$; $df = 1,10$; $P = 0.62$) or of time ($F = 1.8$; $df = 10,100$; $P = 0.069$) and there was no significant interaction between these measures ($F = 0.79$; $df = 10,100$; $P = 0.63$).

GH responses

The GH responses of three subjects were excluded because of high baseline levels of plasma GH in one or both tests. In the remaining eight subjects plasma GH was increased by sumatriptan. The ANOVA showed no significant effect of test day ($F = 3.5$; $df = 1,7$; $P = 0.084$) but there was a significant effect of time ($F = 3.4$; $df = 10,70$; $P = 0.001$) and a significant interaction between these measures ($F = 4.5$; $df = 10,70$; $P < 0.0001$). Post-hoc testing showed that sumatriptan significantly elevated plasma GH compared to placebo at all time points from + 30 min, with the exception of + 120 min (Fig. 3).

Subjective responses

Six subjects reported transient side effects following sumatriptan. There were four complaints of pain and tingling at the injection site and/or in the upper body; one subject

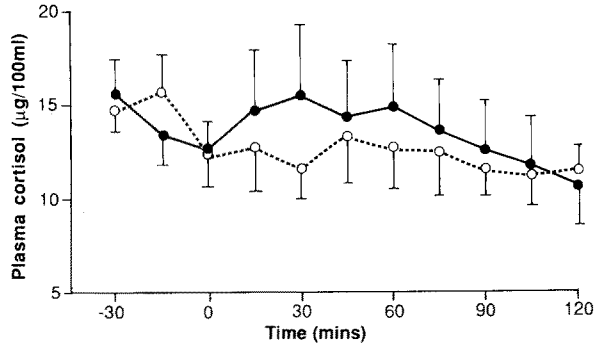

Fig. 2. Mean ± SEM plasma cortisol in 11 healthy male subjects who were tested on two occasions receiving sumatriptan (6 mg subcutaneously; *closed circles*) or placebo (*open circles*) at time 0. There is no significant difference in plasma cortisol levels following sumatriptan compared to placebo (ANOVA)

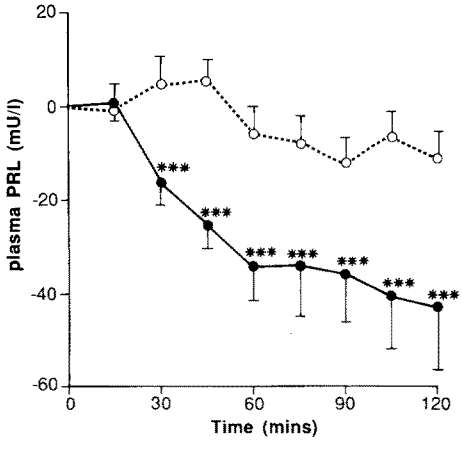

Fig. 1. Change from baseline (time 0 of plasma PRL (mean ± SEM) in 11 healthy male subjects who were tested on two occasions receiving sumatriptan (6 mg subcutaneously; *closed hcircles*) or placebo (*open circles*) administered at time 0. Plasma PRL levels following sumatriptan are significantly lower than those following placebo; *** $P < 0.001$ (ANOVA and Fisher's test of least significant difference)

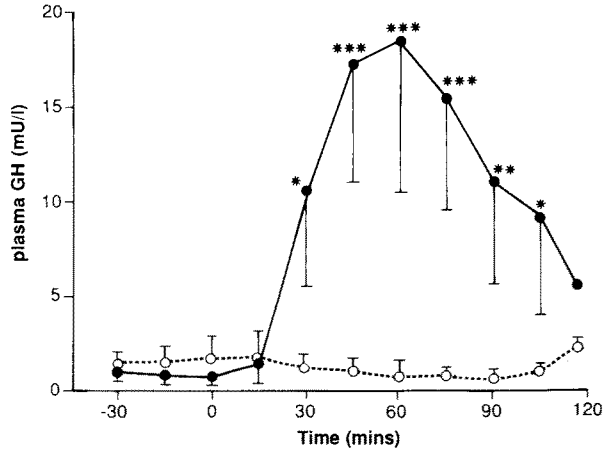

Fig. 3. Mean ± SEM plasma GH in eight healthy male subjects who were tested on two occasions receiving sumatriptan (6 mg subcutaneously; *closed circles*) or placebo (*open circles*) administered at time 0. Plasma GH levels following sumatriptan are significantly higher than those following placebo; *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$, (ANOVA and Fisher's test of least significant difference)

complained of headache and one of drowsiness. No subjects complained of adverse effects after placebo injection.

Discussion

Our results indicate that sumatriptan increases plasma GH levels but lowers the concentration of plasma PRL. In contrast, sumatriptan did not change plasma levels of cortisol. The increase in plasma GH we observed is consistent with the findings of Rolandi et al. (1992), who also found no change in plasma cortisol levels following subcutaneous sumatriptan. However, Eckland et al. (1992) did find a dose-related reduction in plasma cortisol following oral sumatriptan administration (50–200 mg).

Experimental studies in animals suggest that sumatriptan penetrates the blood-brain barrier poorly (Dallas et al. 1989; Sleight et al. 1990). This raises the possibility that the neuroendocrine effects we have seen following sumatriptan may be due to non-specific factors such as the stress of the injection or the short-lived adverse effects noted above. In addition, in animal studies sumatriptan constricts arteries in the cranial circulation (Connor and Feniuk 1992). A similar effect in humans could conceivably alter pituitary blood flow, and thereby indirectly influence pituitary hormone secretion. In fact, the neuroendocrine effects of sumatriptan were rather specific in that while plasma GH was increased, plasma PRL and cortisol were not, making stress-related hormone secretion unlikely. Similarly, the fact that plasma GH levels were increased by sumatriptan while plasma PRL levels fell seems to argue against a generalised change in pituitary blood flow as an explanation for altered hormone secretion.

5-HT neurones are believed to influence PRL and GH levels largely at hypothalamic level where they regulate the secretion of peptide releasing hormones which are then transported to the anterior pituitary gland to release the corresponding pituitary hormone (see Checkley 1980). In certain areas of the hypothalamus, the blood-brain barrier is relatively permeable (Checkley 1980), making it possible that sumatriptan could alter pituitary hormone secretion by an action at 5-HT-receptors in this brain region. Some studies suggest that 5-HT may also influence the release of certain hormones, such as corticotropin and GH, by a direct action at pituitary level (Montage and Calas 1988). Release of hormones by this mechanism would not require sumatriptan to penetrate the blood-brain barrier (Checkley 1980).

If sumatriptan is producing neuroendocrine changes by activation of 5-HT receptors, ligand-binding studies suggest that stimulation of 5-HT_{1D}, 5-HT_{1A} or 5-HT_{1B} receptors may be involved (Peroutka and McCarthy 1989; Schoeffter and Hoyer 1989; Oksenberg et al. 1992). The actions of 5-HT_{1A} receptor agonists on neuroendocrine function in humans have been fairly well characterised and include increases in plasma GH, ACTH and cortisol (Cowen et al. 1990; Lesch et al. 1992). Changes in plasma PRL are less consistent and may be complicated by the significant dopamine receptor affinity possessed by many 5-HT_{1A} receptor agonists (Cowen et al. 1990). However, if anything, 5-HT_{1A} receptor agonists have been found to increase plasma PRL (Anderson et al. 1990; Cowen et al. 1990; Lesch 1992). Accordingly, apart from the increase in plasma GH, the effects of sumatriptan do not resemble those of a 5-HT_{1A} receptor agonist.

An ability of a 5-HT-receptor agonist to lower plasma PRL is unexpected, since increases in 5-HT neurotransmission are generally associated with a facilitation of PRL release (Tuomisto and Mannisto 1985; Meltzer and Nash 1988). It is possible, however, to explain this finding if sumatriptan, in fact, lowers 5-HT release by activating 5-HT_{1D} terminal autoreceptors (Middlemiss et al. 1988; Schlicker et al. 1989; Wilkinson and Middlemiss 1992). This would be expected to decrease 5-HT release and may thereby decrease PRL secretion. 5-HT_{1D} receptors are also found post-synaptically in certain brain regions (Lowther et al. 1992) This raises the possibility that the increase in plasma GH produced by sumatriptan may be caused by activation of post-synaptic 5-HT_{1D}-receptors. This hypothesis implies, however, that post-synaptic 5-HT_{1D}-receptors do not play a significant role in the regulation of PRL release; otherwise it might be supposed that, as with plasma GH, sumatriptan would have increased rather than decreased plasma PRL levels.

Like Rolandi et al. (1992), we found no change in plasma cortisol following subcutaneous sumatriptan. However, Eckland et al. (1992) have reported a decline in plasma cortisol and ACTH following oral sumatriptan given in the morning. The reason for this discrepancy is not clear. Cortisol has a pronounced diurnal variation and the timing of sumatriptan administration might be important. Our study was conducted in the afternoon when cortisol levels are lower and it is possible that this might make an inhibitory effect of sumatriptan on cortisol harder to detect. It is also possible that the route of administration of sumatriptan (oral versus subcutaneous) might be important. At any event the current data suggest that under certain circumstances sumatriptan can also lower cortisol and ACTH levels. Whether this might also reflect a reduction in 5-HT neurotransmission through terminal autoreceptor stimulation remains to be determined (Eckland et al. 1992).

It should be noted that while earlier ligand-binding studies failed to demonstrate the presence of 5-HT_{1B} receptors in the human brain, more recent investigations have identified a 5-HT_{1B} receptor with an amino acid sequence that has over 90% homology with its rodent counterpart (see Peroutka 1992). However, the pharmacological properties of this receptor are quite different from the rodent 5-HT_{1B} receptor and are currently indistinguishable from the human 5-HT_{1D} receptor (Oksenberg et al. 1992). At present, therefore, it is also possible that the neuroendocrine effects of sumatriptan could be attributable to activation of human type 5-HT_{1B}-receptors or to 5-HT_{1B} and 5-HT_{1D} receptors acting in concert.

In summary, sumatriptan produces a novel profile of neuroendcrine response which could be a consequence of activation of 5-HT_{1D} and/or 5-HT_{1B} receptors located both on 5-HT nerve terminals and at sites post-synaptic to 5-HT neurones. Clearly these proposed mechanisms of action of sumatriptan are speculative and will need to be examined in the light of studies with other selective 5-HT_{1D} receptor agonists and antagonists.

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