Sumatriptan reduces exercise capacity in healthy males: a peripheral effect of 5-hydroxytryptamine agonism?

Gerald P. McCANN, Helen CAHILL, Stephen KNIPE, Douglas F. MUIR, Paul D. MacINTYRE and W. Stewart HILLS
Department of Medicine and Therapeutics, University of Glasgow, Gardiner Institute, Church Street, Glasgow G11 6NT, Scotland, U.K.

ABSTRACT
5-Hydroxytryptamine (5-HT; serotonin) has been implicated in the perception of exercise-induced fatigue. Sumatriptan is a selective 5-HT1B/D receptor agonist which does not cross the blood–brain barrier. The aim of the present study was to determine the effect of sumatriptan on exercise capacity. Ten healthy male subjects (mean age 28.4 ± 10.8 years) performed a maximal treadmill exercise test according to the Bruce protocol with expired gas analysis on two occasions. Either 6 mg of sumatriptan or placebo was administered subcutaneously in a randomized, double-blind, placebo-controlled, cross-over design. Exercise time was greater after placebo compared with sumatriptan [914 and 879 s respectively; 95% confidence interval (CI) of difference 12–18 s; P = 0.008]. There was no significant effect on peak oxygen consumption (placebo, 50.6 ± 6.3 ml·min⁻¹·kg⁻¹; sumatriptan, 51.7 ± 7.6 ml·min⁻¹·kg⁻¹). Sumatriptan administration resulted in decreases in both heart rate (sumatriptan, 188 ± 14 beats/min, placebo, 196 ± 12 beats/min; 95% CI of difference 12–6, 2–6; P = 0.008) and respiratory exchange ratio (sumatriptan, 1.23 ± 0.06; placebo, 1.26 ± 0.07; 95% CI of difference 0.05, 0.01; P = 0.01) at peak exercise. There were no significant differences in blood pressure, heart rate or submaximal oxygen consumption between sumatriptan and placebo treatments at any stage of exercise. Thus sumatriptan reduces maximal exercise capacity in normal males. The failure to demonstrate any haemodynamic or cardiorespiratory effect suggests that sumatriptan enhances perception of fatigue by a peripheral mechanism affecting 5-HT modulation.

INTRODUCTION
5-Hydroxytryptamine (5-HT; serotonin) has been proposed as a mediator of the central component of exercise-induced fatigue. Increases in brain 5-HT levels have been observed in rats exercised until exhaustion, and administration of 5-HT agonists reduces exercise capacity; conversely, 5-HT antagonists prolong exercise capacity [1,2]. In humans, the administration of a selective 5-HT receptor re-uptake inhibitor (paroxetine [3] or fluoxetine [4], which increase 5-HT levels at all serotonergic synapses) leads to reduced exercise time to exhaustion at an exercise intensity of 70% of maximal oxygen consumption (VO2). In these studies no differences in metabolic variables [such as blood glucose, body temperature, VO2 or respiratory exchange ratio (RER)] were seen to support a peripheral effect of these drugs, and the authors concluded that fatigue was increased secondary to a central effect of increased 5-HT [3,4].

Sumatriptan is a highly selective 5-HT1 receptor agonist which has been shown to be effective in the treatment of acute migraine [5]. When administered subcutaneously, sumatriptan is absorbed rapidly, achieving peak plasma concentrations in 12–13 min; in addition,
bioavailability approaches 100% and the half-life is approx. 2 h [6,7]. The mechanism of action of sumatriptan in the treatment of migraine remains controversial. The most likely mechanisms are either reversal of cranial arterial vasodilation by direct stimulation of 5-HT1B receptors or inhibition of pro-inflammatory neuro-peptide (substance P, calcitonin-gene-related peptide) release by stimulation of pre-synaptic 5-HT1D autoreceptors located on perivascular trigeminal afferents [8]. Sumatriptan is hydrophilic and does not enter the central nervous system in substantial quantities unless there is disruption of the blood–brain barrier [6,9–11].

Side effects from sumatriptan are generally minor, e.g. flushing and tingling sensations [5], although in vivo and in vitro studies have confirmed a direct vasoconstrictive effect on the coronary and pulmonary circulations after sumatriptan administration [12,13]. The haemodynamic changes seen with sumatriptan in healthy, ambulatory controls are modest, with increases in blood pressure, measured non-invasively, of 10–12 mmHg that persist for 30–60 min [14].

The aim of the present study was to examine the effects of a single subcutaneous therapeutic dose of sumatriptan on aerobic exercise capacity. Sumatriptan’s highly selective receptor profile and favourable pharmacokinetics allow us to assess the peripheral effect, rather than a direct central (brain) effect, of 5-HT1 agonism on fatigue during maximal exercise testing.

MATERIALS AND METHODS

Ten healthy, non-migraineur male subjects were recruited to participate in the study. Exclusion criteria were: cigarette smokers, hypertension, known hypercholesterolaemia, ischaemic heart disease or presence of cardiovascular symptomatology. None of the subjects was sedentary and all participated, to varying degrees, in some form of regular exercise. A brief medical history and examination were carried out prior to participation in the study, which was carried out in accordance with the Declaration of Helsinki (1989), and written informed consent was obtained. All procedures were approved by the West Ethics Committee of the West Glasgow Hospitals University NHS Trust.

Protocol

Subjects were studied in a randomized, double-blind, placebo-controlled cross-over fashion. Subjects were instructed to fast for at least 4 h prior to each test and to abstain from any caffeine-containing drinks on the day of testing. On arrival at the laboratory, height and weight were recorded before subjects were attached to a 12-lead ECG (Quinton 4000 Stress Test Monitor) to record heart rate and to monitor for signs of ischaemia or arrhythmias. Blood pressure was measured by auscultation over the brachial artery in both seated and standing positions using a standardized Accoson Sphygmomanometer.

Either 6 mg of sumatriptan or placebo (water) was administered, subcutaneously, into the deltoid region of the arm by a nurse who was not otherwise involved in the study. Subjects remained seated for 12 min, after which time expired gas analysis commenced (CPX/D Systems; Medical Graphics Corporation, Minneapolis, MN, USA). Gas analysers and pneumotachs were calibrated using standard gas mixtures and a 3 litre syringe immediately before each exercise run. A 3 min period was then allowed for familiarization to the mouthpiece, and baseline data were obtained. Blood pressure and heart rate were again recorded in the seated and standing positions immediately prior to exercise. The subjects were then asked to exercise until exhaustion on a treadmill (Quinton Q65 series 90) following a standard Bruce Protocol [15]. Verbal encouragement was given throughout by the same investigator blinded to the study medication.

At the end of each incremental stage (every 3 min) and immediately post-exercise, blood pressure was measured. Heart rate, $\dot{V}O_2$, RER and ventilation were recorded continuously. The rate pressure product (systolic blood pressure × heart rate; RPP) was calculated for the last 30 s of each exercise stage. When subjects had run for as long as possible the total exercise time was recorded and they were allowed to recover for 4 min, during which time heart rate and blood pressure were measured at 1 min intervals. The maximal rate of perceived exertion (RPE) on a Borg scale [16] and the reason for termination of the test were noted when the mouthpiece and noseclip were removed. Any symptoms experienced after the injection, throughout the duration of the test or during recovery were noted.

After a washout period of at least 72 h but within 7 days, subjects returned for their second test. The two tests were performed for each subject at the same time of day to avoid any diurnal variation, and all tests were medically supervised.

Statistical analyses

All statistical analyses were performed with the aid of the Minitab 12.1 software package. Paired $t$-tests were used to compare all variables between sumatriptan and placebo runs. Results are expressed as means±S.D. with 95% confidence intervals (CIs), and significance was stated as $P < 0.05$.

RESULTS

No serious adverse events were observed during the study; however, side effects were experienced following sumatriptan administration. A total of eight symptoms (four of flushing, two of nausea, one of headache and one
Table 1  Summary of haemodynamic variables

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sumatriptan</td>
<td>Placebo</td>
<td>Sumatriptan</td>
</tr>
<tr>
<td>Rest (pre)</td>
<td>69 ± 12</td>
<td>74 ± 19</td>
<td>125 ± 12</td>
</tr>
<tr>
<td>Rest (post)</td>
<td>72 ± 13</td>
<td>72 ± 15</td>
<td>132 ± 8†</td>
</tr>
<tr>
<td>Peak ex.</td>
<td>188 ± 12</td>
<td>196 ± 14*</td>
<td>170 ± 25</td>
</tr>
<tr>
<td>Recovery</td>
<td>111 ± 16</td>
<td>117 ± 16*</td>
<td>172 ± 212</td>
</tr>
</tbody>
</table>

Significance of differences:

* P < 0.05, ** P < 0.01 for sumatriptan compared with placebo; † P < 0.05 for pre-drug compared with post-drug.

Table 2  Summary of maximal variables

<table>
<thead>
<tr>
<th></th>
<th>Sumatriptan Mean difference</th>
<th>Placebo Mean difference</th>
<th>(95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise time (s)</td>
<td>879 ± 124</td>
<td>914 ± 128</td>
<td>35.6 (12.1, 59.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>Peak $\dot{V}O_2$ (ml·min$^{-1}$·kg$^{-1}$)</td>
<td>51.7 ± 7.6</td>
<td>50.4 ± 6.3</td>
<td>1.0 (−1.04, 3.10)</td>
<td>0.29</td>
</tr>
<tr>
<td>RER</td>
<td>1.23 ± 0.06</td>
<td>1.26 ± 0.07</td>
<td>0.032 (0.05, 0.01)</td>
<td>0.01</td>
</tr>
<tr>
<td>RPE</td>
<td>18.1 ± 0.01</td>
<td>17.8 ± 0.92</td>
<td>0.375 (−0.358, 1.108)</td>
<td>0.265</td>
</tr>
</tbody>
</table>

of jaw pain) were reported in five subjects. None of these side effects prevented participation in the exercise test, and most diminished prior to commencement of exercise. No side effects were reported after placebo. There was no order effect between test 1 and test 2 for either maximal $\dot{V}O_2$ [51.5 versus 50.8 ml·min$^{-1}$·kg$^{-1}$ (95% CI of difference −0.46, 2.80; P = 0.4)] or total exercise time [892.5 versus 900.9 s (95% CI of difference −43.5, 26.7; P = 0.60)]. Generalized fatigue or leg fatigue was stated as the primary reason for cessation of exercise in both tests in all subjects.

**Haemodynamic variables**

There were no significant differences in heart rate or blood pressure at rest between sumatriptan and placebo treatments. Systolic and diastolic blood pressure increased significantly (6.3% and 10.4% respectively) after administration of sumatriptan, and there were also non-significant increases in both (4.3% and 7.4% respectively) after administration of placebo (Table 1). Systolic and diastolic blood pressure and RPP did not differ between sumatriptan and placebo at any time point either at rest or during exercise, whereas heart rate was significantly lower after sumatriptan at peak exercise and at 3 min of recovery (Table 1). There were no significant differences in heart rate at the end of each stage of exercise.

**Exercise capacity**

Indicators of maximal exercise capacity are summarized in Table 2. Total exercise time was significantly reduced after administration of sumatriptan compared with placebo, although there was no difference in maximal $\dot{V}O_2$. Individual exercise times are displayed in Figure 1. This shows that only one subject exercised for longer after sumatriptan (by 8 s), whereas nine out of 10 subjects performed more exercise after placebo (range 1–81 s). Peak exercise heart rate and RER were significantly lower after sumatriptan injection when compared with placebo. Comparative measurements of RPE were not significantly different, although there was a trend for values to be higher in the sumatriptan run (Table 2).

There were no significant differences in submaximal...
precursor, the essential amino acid tryptophan, since the onset of exercise time [1,2]. Levels of 5-HT led to decreased exercise capacity, in terms of exercise time in normal males during maximal incremental treadmill exercise. The magnitude of the reduction was small, 35.6 s, or 3.9% compared with the placebo run, but highly significant, with nine of the ten subjects exercising less after sumatriptan. Maximum heart rate and RER were both lower and there was a non-significant increase in RPE after sumatriptan administration, without an effect on maximal or submaximal $V\text{O}_2$. Blood pressure responses were similar after placebo and sumatriptan. These data strongly suggest that subjects experienced more fatigue during exercise after sumatriptan administration and consequently stopped earlier, thus limiting their maximum heart rate and RER.

Many animal studies have been carried out in an attempt to quantify the serotonergic response to exercise [17]. Most have found that levels of both 5-HT and its metabolite, 5-hydroxyindoleacetic acid, increase following an acute bout of exercise [18]. These earlier studies, though not confirming an aetiological role of 5-HT in the perception of fatigue, did give rise to the important realization that exercise could affect factors controlling 5-HT synthesis and turnover. Since 5-HT is well known to affect the sleep–arousal cycle, lethargy and mood, it seemed logical to investigate the relationship with exercise. Further experiments in rats using various 5-HT agonists and antagonists confirmed the link; increased levels of 5-HT led to decreased exercise capacity, in terms of exercise time [1,2].

Brain 5-HT synthesis is dependent on the supply of its precursor, the essential amino acid tryptophan, since the enzyme tryptophan hydroxylase is not saturated under physiological conditions [19,20]. Tryptophan circulates largely bound to albumin and it is only the smaller proportion, the unbound or free tryptophan, that is transported across the blood–brain barrier via a carrier that it shares with other large neutral branched-chain amino acids (BCAAs). It was proposed that, during prolonged exercise, there would be an increase in the uptake of tryptophan across the blood–brain barrier, for the following reasons [19]: (1) BCAAs are taken up and oxidized for energy in contracting skeletal muscle, thus decreasing the competition for the carrier across the blood–brain barrier; and (2) exercise causes an increase in plasma non-esterified fatty acids, which displace tryptophan from albumin, thereby increasing the free fraction of tryptophan. Therefore, with increasing duration of exercise, the greater unbound fraction of tryptophan leads to greater production of central 5-HT and consequently, it is proposed, a feeling of fatigue.

The most compelling evidence to support a role for 5-HT activity contributing to fatigue in humans is provided by the fact that the selective 5-HT receptor reuptake inhibitors, fluoxetine [4] and paroxetine [3,21], reduce time to exhaustion during treadmill or bicycle exercise at a fixed workload. In these studies no other variable measured, such as $V\text{O}_2$, blood glucose or blood lactate, was significantly different during placebo and drugs runs, suggesting that the effect seen was not due to a peripheral action of these pharmacological agents. However, not all studies which have attempted to alter 5-HT synthesis or activity have demonstrated consistent results. Administration of the 5-HT antagonists pizotifen (5-HT$_{1B}$) [22] or ritanserin (5-HT$_{2A}$) [23] did not increase exercise capacity in humans, although a 5-HT$_{1B}$ agonist reduced exercise capacity in rats [1]. Administration of tryptophan, which should increase its own uptake across the blood–brain barrier and consequently increase 5-HT synthesis centrally, has not been shown to lower exercise tolerance [24]. Similarly, supplementation with BCAAs, which decreased the tryptophan/BCAA ratio and should decrease the uptake of tryptophan centrally and reduce 5-HT synthesis, did not increase time to exhaustion in 10 endurance-trained cyclists [21]. Also, alterations in plasma free tryptophan and BCAAs did not alter perceived physical exertion levels during treadmill running at a fixed speed [25]. Overall, these studies suggest that 5-HT activity does influence the perception of fatigue, but there is no conclusive evidence that this effect is mediated centrally.

Several possible mechanisms exist by which sumatriptan may have reduced exercise time in the present study. Subjects may have stopped earlier because they experienced side effects after drug administration. This is unlikely, since only five of the subjects reported symptoms, and all subjects stated fatigue as the primary reason for termination of the test. It is also unlikely that this effect was mediated via 5-HT$_{1B}$ receptors inducing
Sumatriptan reduces exercise capacity

an increase in ventricular afterload, since there was no effect on blood pressure or RPP at rest or any stage of exercise compared with placebo. A third possibility is that sumatriptan acts centrally by binding directly to 5-HT_{10} or 5-HT_{1p} receptors, which have been shown to be present in autoradiographic studies of human brain tissue [26,27]. However, because sumatriptan is hydrophilic, it only crosses the intact blood–brain barrier in minute quantities (approximately 0.05% of drug) that are thought to be clinically and pharmacologically insignificant [6,9–11]. The most likely explanation for the mechanism of action of sumatriptan in the present study involves stimulation of peripheral 5-HT_{10} autoreceptors located on perivascular trigeminal afferents. This mechanism of action has been proposed for the therapeutic effect in migraine, reducing release of inflammatory neuropeptides at these sites [28]. Sumatriptan has also been shown to have neurogenic blocking properties in animal models, reducing trigeminal ganglion activation in response to chemical stimulation [29]. It is possible, due to the central connections to the trigeminal nucleus caudalis in the medulla oblongata, that subcortical levels of monoamines may be affected, as has been shown in rats [30]. In that study, rats given high scubcutaneous doses of sumatriptan (0.6 mg/kg) demonstrated reduced hypothalamic concentrations of 5-HT and increased turnover of both dopamine and 5-HT. Although this dose is very high compared with that used in the treatment of migraine (approximately 0.08 mg/kg), the plasma concentration achieved (70 ng/ml) was similar to that seen in humans after a single 6 mg subcutaneous injection (72.4 ng/ml) [30,31]. Whether such an effect would be seen in humans is debatable, and impractical to confirm given our current inability to measure brain levels of neurotransmitters without invasive procedures. The results of the present study support the hypothesis that 5-HT enhances fatigue, but this occurs primarily by a peripheral mechanism rather than a direct action centrally (brain), and the magnitude of the effect is small.

Conclusions

The results of the present study demonstrate that the administration of a 5-HT agonist reduces exercise capacity by a small but significant amount. The pharmacological properties of sumatriptan suggest that the increased perception of fatigue is mediated by a peripheral mechanism, probably at pre-synaptic 5-HT_{10} autoreceptors. Stimulation of these peripheral receptors may have secondary effects on brain monoamines.

Limitations

As shown in Table 2, a number of subjects experienced side effects after sumatriptan injection, which may have unveiled the blinded nature of the study. Invasive haemodynamic monitoring was not performed, which may have affected the exercising blood pressures recorded; there were no apparent differences between placebo and sumatriptan when measured at rest. Much of the discussion in this paper is based on data from animal studies, and there are definite species differences in both 5-HT receptor distribution and pharmacology. Our study differs from most others in this field in that we have employed maximal incremental exercise in the protocol, rather than exercise to exhaustion at a fixed workload, as the primary endpoint. We feel that this has advantages, since the peripheral mechanisms involved in fatigue (e.g. glycogen depletion) are limited.

Future research

Further studies with other selective 5-HT agonists may elucidate the exact mechanism by which 5-HT affects exercise performance. If our theory is correct, a selective 5-HT_{1p} agonist which does not cross the blood–brain barrier should have no effect on exercise capacity, conversely, a 5-HT_{10} antagonist should increase exercise duration.

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