Acute effects of medetomidine, a selective \( \alpha_2 \)-adrenoceptor agonist, on anterior pituitary hormone and cortisol secretion in man

Antero Kallio\(^1\), Markku Koulu\(^1\), Harry Scheinin\(^2\), Jorma Viikari\(^3\) and Mika Scheinin\(^1\)

Departments of Pharmacology and Clinical Pharmacology\(^1\), University of Turku, Farmos Group Ltd\(^2\), Research Centre, and Department of Medicine\(^3\), Turku University Hospital, Turku, Finland

Abstract. Single iv doses (25, 50 and 100 \( \mu \)g) of medetomidine, a selective \( \alpha_2 \)-adrenoceptor agonist of the imidazole type, were administered to 8 healthy male volunteers in a randomized, double-blind, placebo-controlled study. The concentration of hGH in plasma was powerfully and dose-dependently increased. The plasma level of cortisol was dose-dependently decreased, whereas TSH showed a slight but statistically significant increase. Plasma levels of PRL, FSH and LH were unaffected by the drug. Medetomidine appears to resemble other \( \alpha_2 \)-adrenoceptor agonists, notably clonidine, in its endocrine effects. Its high selectivity and short duration of action make it a suitable tool for studies of the physiology and pharmacology of \( \alpha_2 \)-adrenoceptors in man.

Medetomidine (4(5)-[1-(2,3-dimethylphenyl)ethyl]imidazole) is a novel imidazole derivative (Karjalainen 1981). The compound is highly lipophilic (Savola et al. 1986) and has high affinity for \( \alpha_2 \)-adrenoceptors and no or negligible binding to or direct effects on \( \mu \)- and \( \kappa \)-opiate, adenosine, D\(_2\), histamine, 5-hydroxytryptamine, muscarinic, benzodiazepine, or \( \beta \)-adrenergic receptors (Virtanen et al. 1988). Its \( \alpha_2/\alpha_1 \)-binding selectivity ratio has been determined to be 1620 (vs 220 for clonidine; Virtanen et al. 1988). In the pithed rat and in isolated organ preparations, medetomidine has displayed selective and potent \( \alpha_2 \)-receptor agonistic activity, with weak partial \( \alpha_1 \)-agonistic effects at high concentrations (Savola et al. 1986). In rats, medetomidine reduces the release and metabolism of noradrenaline (NA) in the central nervous system (CNS) (Scheinin et al. 1986), and also decreases the turnover of serotonin in several brain areas (Koulu et al. 1987). Its effects can be antagonized by \( \alpha_2 \)-adrenoceptor antagonists, but not by prazosin (Scheinin 1986; Savola et al. 1986; Virtanen et al. 1988).

In this randomized double-blind study, three different doses of medetomidine and saline placebo were administered to 8 healthy male volunteers in order to study the acute endocrine effects of the compound. The cardiovascular and sedative effects of medetomidine observed in this study have been previously published (Scheinin et al. 1987).

Subjects and Methods

Procedure

The subjects were 8 healthy male volunteers (age 24–33 years, weight 72–90 kg, height 177–186 cm). The health of the subjects was ascertained by detailed medical history, physical examination, clinical chemistry tests and electrocardiography. One was a smoker (subject No. 3). The protocol of the study was approved by the Ethics Committee of Turku University Hospital and the...
Finnish National Board of Health, and each subject gave his written informed consent to the investigation. None of the volunteers had received any medication for at least two weeks preceding the study. Alcoholic beverages were not allowed for 36 h prior to each session, and the subjects fasted and desisted from smoking since 10.00 h on the preceding night.

The subjects arrived at the hospital at 7.30 h. Intravenous cannulae were inserted into both cubital fossae, and they were kept open with a dilute solution of heparin. The experiments were performed in a quiet, dimly lit room.

The doses of medetomidine and saline placebo were administered using two replicated Latin squares, with subjects and investigators unaware of the schedule. The doses were given in a volume of 5 ml as 5-min iv infusions after a minimum of 30 min supine rest.

Blood samples for the determination of hormone levels were drawn at -15, 15, 30, 45, 60, 90, 120 and 180 min from the beginning of the infusion. The samples (in polypropylene tubes with K2EDTA) were immediately chilled on ice, centrifuged, and the plasma stored at -70°C until assayed.

**Assays**

Plasma levels of hGH, cortisol, PRL, TSH, FSH and LH were determined using commercially available radio-immunoassay kits (all from Farmos Diagnostica, Farmos Group Ltd, Finland). The reproducibility of the assays was tested using pooled plasma samples from previous clinical studies, representing high and low physiological levels. The resulting intra-assay CV range was 0.7–8.5%. All samples from one experimental session were analysed within a single assay.

**Statistical analysis**

The results are presented as means ± sd. The statistical analysis was performed using analysis of covariance (ANCOVA) for repeated measurements, with two within-factors (dose and time), computed with BMDP2V programmes (BMDP Statistical Software Inc, USA). When pooled orthogonal components showed nonsphericity, Greenhouse-Geisser probability values were used (Keselman & Keselman 1984). Log-transformed data were used, when variances were unequal (cortisol and hGH). When a statistically significant drug effect or dose x time interaction was present (hGH, TSH, cortisol) (Table 1), the analysis was continued by performing separate ANCOVAs for each pair of dose levels, in order to characterize the dose-dependency of the effect in more detail.

**Results**

The concentration of hGH in plasma was powerfully and dose-dependently increased after medetomidine ($P < 0.001$; Table 1; Fig. 1). The maximal average increase (after 100 µg) was from 0.19

<table>
<thead>
<tr>
<th>Variable</th>
<th>Factor 1 = dose</th>
<th>Factor 2 = time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log hGH</td>
<td>F 36.14</td>
<td>68.03</td>
<td>19.68</td>
</tr>
<tr>
<td>(N = 7)</td>
<td>$P &lt; 0.0001$</td>
<td>$&lt; 0.0001^*$</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Log cortisol</td>
<td>F 3.30</td>
<td>0.92</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>$P 0.041$</td>
<td>0.40*</td>
<td>0.43*</td>
</tr>
<tr>
<td>TSH</td>
<td>F 3.73</td>
<td>5.45</td>
<td>2.70</td>
</tr>
<tr>
<td>(N = 7)</td>
<td>$P 0.032$</td>
<td>0.0004</td>
<td>0.0008</td>
</tr>
<tr>
<td>PRL</td>
<td>F 1.95</td>
<td>6.45</td>
<td>1.16</td>
</tr>
<tr>
<td></td>
<td>$P 0.15$</td>
<td>0.005*</td>
<td>0.35*</td>
</tr>
<tr>
<td>FSH</td>
<td>F 0.65</td>
<td>2.39</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>$P 0.52^*$</td>
<td>0.04</td>
<td>0.66*</td>
</tr>
<tr>
<td>LH</td>
<td>F 0.24</td>
<td>7.49</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>$P 0.72^*$</td>
<td>$&lt; 0.0001$</td>
<td>0.60*</td>
</tr>
</tbody>
</table>

* Greenhouse-Geisser probability value.

![Fig. 1.](https://example.com/fig1.png)

Average hGH levels in plasma after medetomidine. Symbols: ○, saline placebo; ●, 25 µg; △, 50 µg; ▲, 100 µg. Standard deviations have been omitted for clarity (see text for typical examples).
between Average elevated variation after No. 0.006, unaffected effect dependent interact ces analyses. and out significantly ± No. (P 2.02 Fig. µg) 100 Cortisol 0.20 The The = µg). 1.65 ± 1.00 mIU/l at +15 min to 2.02 ± 1.12 mIU/l at 60 min. One subject (subject No. 7) showed high basal values of TSH throughout the study (7.40, 5.00, 3.80, and 3.55 mIU/l) and was therefore excluded from these statistical analyses. Significant drug-related TSH differences were observed between placebo and 50 and 100 µg (P = 0.009 and 0.0004).

The plasma levels of PRL, FSH and LH were unaffected by the drug, showing only time-related variation (Table 1).

± 0.20 µg/l at −15 min to 20.00 ± 8.23 µg/l at +45 min. ANCOVA revealed significant differences between each successive dose level (P = 0.02, 0.006, and 0.02, respectively). Owing to initially elevated growth hormone levels in each session (12.2, 10.1, 8.4, and 6.3 µg/l), one subject (subject No. 1) was omitted from these statistical analyses.

Cortisol in plasma showed a biphasic time-related trend (Fig. 2): following an initial decrease after all doses, medetomidine appeared to counteract the increase in cortisol levels in a dose-dependent manner (P = 0.04; Table 1). The drug effect was significant between placebo and 100 µg (P = 0.007) as well as between 25 µg and 100 µg (P = 0.02).

The plasma levels of TSH were slightly but significantly increased after drug administration (P = 0.008 for drug x time interaction; Table 1; Fig. 3). The maximal average increase (after 100 µg) was from 1.65 ± 1.00 mIU/l at +15 min to 2.02 ± 1.12 mIU/l at 60 min. One subject (subject No. 7) showed high basal values of TSH throughout the study (7.40, 5.00, 3.80, and 3.55 mIU/l) and was therefore excluded from these statistical analyses. Significant drug-related TSH differences were observed between placebo and 50 and 100 µg (P = 0.009 and 0.0004).

The plasma levels of PRL, FSH and LH were unaffected by the drug, showing only time-related variation (Table 1).

Discussion

The essential role of noradrenergic mechanisms in the regulation of hGH release is well established (for reviews, see Tuomisto & Männistö 1985; Müller 1987). Activation of α2-receptors by clonidine and other α2-agonists stimulates hGH secretion (Lal et al. 1975; Brown et al. 1985; Grossman et al. 1987). The anatomical location of these receptors has been a matter of some debate (Tuomisto & Männistö 1985). Theoretically, α2-receptor agonists can either directly stimulate the secretion of hGH (or an hGH-releasing factor) by a postsynaptic action, or they can inhibit noradrenaline release presynaptically. In the latter case, noradrenaline itself would actually exert a tonic inhibition on hGH secretion. This would also mean that blockade of the postsynaptic adrenergic receptors (of either the α- or the β-type) would remove this tonic inhibition and thereby stimulate hGH release. However, α- or β-receptor blocking agents have generally failed to stimulate basal hGH release (Massara & Camanni 1972; Saxton et al. 1981; Struthers et al. 1986), suggesting that the action of α2-agonists is postsynaptic in man (Koulu 1986). Also, experimental evidence in rats suggests a postsynaptic mechanism (Krušich et al. 1982).

The dose-dependent stimulation of hGH release observed in our study is in good agreement...
with reports in which clonidine and other $\alpha_2$-adrenergic agonists have been shown to stimulate hGH release (Lal et al. 1975; Brown et al. 1985; Grossman et al. 1987).

Controversial results have been obtained in studies on the noradrenergic control of ACTH secretion and plasma cortisol. Lanes & Hurtado (1982) and Lanes et al. (1983) found an acute inhibition of ACTH and cortisol secretion after oral clonidine in prepubertal children and normal adults, whereas Lal et al. (1975) found no effect of intravenous clonidine on serum cortisol. In a recent report, oral clonidine and a more selective oxazoline $\alpha_2$-receptor agonist, S 3341, had no effects on plasma cortisol under basal conditions (Grossman et al. 1987). On the other hand, it has been reported that central $\alpha_1$-receptors mediate stimulation of ACTH secretion (Al-Damluji et al. 1987).

The well-established circadian rhythm in plasma cortisol levels is superimposed by episodic ACTH-stimulated cortisol peaks throughout the day (Hellman et al. 1970; Brandenberger & Follenius 1973). The episodic release of cortisol together with circadian variation could at least partly explain the controversial results obtained in different laboratories. In our study, the circadian fall in plasma cortisol levels was followed by a slight increase in the placebo session. This increase was apparently not related to marked mental stress, since no concomitant increases in other stress-sensitive hormones, hGH and prolactin, were observed, but could rather be explained as episodic cortisol secretion. Medetomidine appeared to counteract this increase in a dose-dependent manner, suggesting an inhibitory role of $\alpha_2$-receptors in the regulation of cortisol secretion.

There is little information on the role of noradrenaline in the regulation of TSH release in humans (Tuomisto & Männistö 1985). The increase in plasma TSH levels observed in our study might indicate a stimulatory role of $\alpha_2$-receptors in the regulation of TSH release. However, the observed increase was rather small and probably biologically insignificant, and could be a result of altered TSH clearance from plasma or some other factor not related to receptor-mediated regulation of TSH release. Therefore, no conclusive evidence for $\alpha_2$-receptor-mediated stimulation of TSH release can be drawn from our results.

Only time-related trends were observed in the plasma levels of PRL, FSH and LH. The results are compatible with earlier reports that also failed to demonstrate any effect of clonidine or guanfacine on PRL, FSH or LH in normal men (Lal et al. 1975; Lancranjan 1980).

In conclusion, medetomidine appears to resemble other $\alpha_2$-adrenoceptor agonists in its endocrine effects. Its high selectivity and short duration of action make it a suitable tool for studies of the physiology and pharmacology of $\alpha_2$-adrenoceptors in man.

Acknowledgments

The authors are grateful to Ms Eija Lehtovirta and Ms Merja Love for technical assistance, and to Mr Juhani Tuominen, LicPh, for performing the statistical analysis.

References


Received March 28th, 1988.
Accepted May 13th, 1988.

Dr Antero Kallio,
Department of Pharmacology,
University of Turku,
SF-20520 Turku,
Finland.