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Clonidine reduces plasma melatonin levels

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Clonidine, an α-adrenoceptor agonist, reduces human plasma melatonin levels when administered intravenously at 2–3 μg kg^{-1} to sleeping volunteers. Measurement of plasma melatonin levels after administration of clonidine could be the basis for a clinical in-vivo test of α-adrenoceptors.

In mammals, synthesis and secretion of melatonin by the pineal gland is initiated and maintained through stimulation of the β_1-adrenoceptors of the pinealocytes by noradrenaline released from peripheral postganglionic sympathetic neurons; this occurs mainly at night (Ariens Kappers 1960; Wurtman et al 1971; Deguchi & Axelrod 1972; Klein & Weller 1973; Parfitt et al 1976; Zatz et al 1976). Although the neurotransmitters and receptors remain to be identified, melatonin production also seems to be under peripheral sympathetic regulation in man, because: (i) bedtime administration of propranolol (120–140 mg p.o.) can block the night-time rise of plasma melatonin levels (Vaughan et al 1976; Hanssen et al 1977; Moore et al 1979; Lewy 1983), (ii) cervical cordotomy disrupts the nocturnal increase in human urinary melatonin levels (Kneisley et al 1978), and (iii) patients with sympatholytic diseases, such as Shy-Drager syndrome and idiopathic orthostatic hypotension, have markedly reduced plasma melatonin (Vaughan et al 1979) and urinary 6-hydroxymelatonin levels (Tetsuo et al 1981). Martin et al (1984) have reported decreased 6-hydroxymelatonin excretion in Korsakoff's psychosis. We now report reduction of human plasma melatonin levels after administration of clonidine, an α-adrenoceptor agonist.

Methods

Four healthy volunteer subjects (three males, ages 21–24 and one female, age 57) were studied after having given written consent and with the approval of the appropriate ethical committee. Clonidine (2·0, 2·5 or 3·0 μg kg^{-1}) was administered intravenously shortly after sleep onset (between midnight and 0200h). Blood was sampled through an indwelling venous cannula every 30 min between midnight and 0500h. Samples were also taken at these intervals on a baseline (placebo control) night after administration of saline. Subjects did not know which night they received clonidine or which night they received saline. Per cent reduction of plasma melatonin was determined by dividing the value obtained 1 h after infusion of clonidine by the value obtained at the same clock time on the control (baseline) night. In addition, the 24-year-old male subject received clonidine 2·7 μg kg^{-1} p.o. at 2350h on another occasion. Plasma melatonin was measured using the gas chromatographic-negative chemical ionization mass spectrometric assay of Lewy & Markey (1978). This assay uses a deuterated internal standard and has a high degree of specificity, accuracy and sensitivity.

Results and discussion

There was a highly linear dose-response relationship between the amount of clonidine administered and the reduction in the concentration of plasma melatonin 1 h later. One h after infusion of clonidine or saline, respectively (which was at the beginning of or within the nadir), plasma levels of melatonin were 65·5/82·5 pg ml^{-1} (79%) and 27·0/37·0 pg ml^{-1} (73%) after 2·0 μg kg^{-1}; 7·5/13·0 pg ml^{-1} (58%) after 2·5 μg kg^{-1}, and 13·4/35·5 pg ml^{-1} (38%) and 27·5/82·5 pg ml^{-1} (33·3%) after 3·0 μg kg^{-1}. Although the data points were few, the correlation coefficient ($r = -0·99$) was highly significant ($P < 0·01$).

Oral administration of clonidine to one volunteer at midnight also reduced melatonin secretion by between 20–50%, with a lag time of 1–2 h, a maximum difference at 4 h (50%) and a longer duration of action (5 h).

Peripherally, clonidine is a relatively selective agonist

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for presynaptic inhibitory α_2-adrenoceptors (Starke et al 1955). It also decreases central noradrenergic activity, as reflected in concentrations of cerebrospinal (CSF) 3-methoxy-4-hydroxyphenylglycol (MHPG) (Bertilsson et al 1977), which is associated with a reduction in sympathetic outflow and blood pressure (Kobinger & Walland 1967). The reduction in central noradrenergic activity appears to be a function of clonidine's action on central α_2-adrenoceptors that decrease noradrenergic neuronal firing (Svensson et al 1975) and release of noradrenaline. Clonidine also has a central postsynaptic stimulatory effect on growth hormone secretion (Siever et al 1982). (Unlike blood pressure and growth hormone, melatonin secretion appears to be exclusively under noradrenergic control and is more easily sampled than CSF MHPG.)

Our presumption is that clonidine is acting on presynaptic inhibitory α_2-adrenoceptors of the postganglionic sympathetic neurons innervating the pineal gland (Pelayo et al 1977), although we cannot rule out another, perhaps central, site of action (Alphs et al 1980). An inhibitory α_2-adrenoceptor might explain why it has been so difficult to stimulate melatonin production in some species using adrenergic agonists (Lewy 1983). Regardless of the anatomical locus of the clonidine effect, measurement of the clonidine-induced reduction in night-time secretion of melatonin could be used as a simple overnight in-vivo clinical test for inhibitory α-adrenergic receptor function.

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