Melatonin decreases glucocorticoid blood concentration in the rat and palm squirrel, acting directly on the adrenal gland

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ABSTRACT
We have investigated the effect of the prolonged administration of melatonin on the plasma concentration of glucocorticoids in rats and palm squirrels, whose hypothalamo-pituitary-adrenal axis and renin-angiotensin system were suppressed by the simultaneous administration of dexamethasone and captopril. Dexamethasone and captopril administration for two weeks markedly lowered the blood level of corticosterone in rats and cortisol in palm squirrels. The injection of melatonin during the second week of treatment caused a further significant lowering in the glucocorticoid plasma concentration. These findings suggest that melatonin exerts a sizeable glucocorticoid antisecretagogue effect in rats and squirrels, acting directly on the adrenal glands.

Melatonin is a multifunctional hormone, mainly secreted by the pineal gland, the effects of which on the hypothalamo-pituitary-adrenal (HPA) axis are well established (14). To summarize, melatonin is reported to be a potent inhibitor of the central branch of the HPA axis (16), as well as to reset dysregulation of this axis, at least in the rat (7). However, there is a marked disagreement as far as the direct effect of this hormone on the secretory activity of adrenal cortex is concerned. In fact, both stimulating (2, 4, 13, 15) and inhibitory effects have been described (5, 9, 11, 17). All these studies were carried out using dispersed or cultured adrenocortical cells, i.e. experimental models which do not reproduce in vivo physiological conditions. It, therefore, seemed worthwhile to study the effect of the prolonged melatonin administration on the blood concentrations of glucocorticoid in rats and palm squirrels, whose HPA axis and renin-angiotensin system (RAS) were pharmacologically interrupted.

Adult Sprague-Dawley male rats (200–250 g body weight, obtained from Charles-River; Como, Italy), and palm squirrels (Funambulus pennanti, Wrougton) (300–350 g body weight, obtained from the breeding facilities of our Zoology Department) were housed two per cage, kept under a 12:12 h light-dark cycle, and maintained on a standard diet and tap water ad libitum. After being adapted to the laboratory conditions for 15 days, the animals were divided into three equal groups (rats: n=10; palm squirrels: n=50), which were treated as follows: 1) dexamethasone (2.5 mg/kg; Sigma Chemical Company, St. Louis, MO, U.S.A.) and captopril (8.3 mg/kg; Squibb, Rome, Italy) for 14 days; they were subcutaneously injected twice a day, at 1 a.m. and 1 p.m. to counteract circadian rhythm of glucocorticoids secretion which depends on both HPA axis and
RAS; 2) same treatment as group 1, but on the 8th
day melatonin (0.4 mg/kg; Sigma) was adminis-
tered together with dexamethasone and captopril;
and 3) subcutaneous injection of the 0.9% NaCl
vehicle for 14 days (control group). Under middle
ether anaesthesia, blood samples were collected
from the tail (rats) or retro-orbital vein (palm
squirrels) at day 0, 7 and 14 of treatment. Corti-
costerone (rats) and cortisol (palm squirrels)
were extracted, and their concentration estimated
by radioimmunoassay (RIA) and enzyme
immunoassay (EIA), as previously detailed (3, 8).
Data were expressed as means ± SEM, and their
statistical comparison was done by the paired
sample t-test (P values < 0.05 were considered
significant).

The prolonged simultaneous administration of
dexamethasone and captopril lowered plasma
concentration of cortisol in rats and cortisol in palm squirrels by about 50% and 57%,
respectively (Figs. 1 and 2). These figures were
attained after the first week of treatment and
maintained themselves after the second week (data
not shown). Melatonin administration during
the second week evoked a further lowering in cor-
ticosterone (about 25%) and cortisol blood levels
(about 35%) (Figs. 1 and 2).

The maintenance of a normal adrenal glucocor-
ticoid secretory activity is known to depend on
the correct functioning of the HPA axis and RAS
both in rats (10) and palm squirrels (1), and our
study confirms this contention. Melatonin
decreases blood glucocorticoid concentration in
HPA axis- and RAS-suppressed animals, thereby
suggesting that this hormone acts directly on the
adrenal cortex. This view is in keeping with the
demonstration of the presence of melatonin
binding sites in the mammalian adrenal gland (6, 12).

In conclusion, our study provides evidence
that, like in vitro (5, 9, 11, 17), also in vivo
melatonin inhibits glucocorticoid secretion acting
directly on the adrenal cortex. The mechanism
and the physiological relevance of this effect of
melatonin remain, however, to be investigated.

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