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Short communication

Melatonin together with noradrenaline augments contractions of human myometrium

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Abstract

The hormone melatonin is known to influence the circadian rhythm, and it probably also mediates some of the physiological changes that occur in the body at night. Inasmuch as uterine activity is greater during darkness, we investigated whether melatonin could modulate uterine contractility. Biopsies were performed during caesarean sections to obtain uterine tissue from women who had reached full term. The obtained samples were mounted in organ baths, and spontaneous contractions were recorded. Melatonin alone did not change myometrial contractility, whereas melatonin in combination with noradrenaline potentiated contractions. These results may indicate that melatonin plays a role in the timing of labour, since labour often begins late in the evening.

Keywords: Melatonin; Myometrium, human; Pregnancy; Labor; Noradrenaline

1. Introduction

The hormone melatonin is produced in the pineal gland, and its main function is to co-ordinate the body's biological clock with nature's own timekeeper, the sun. Information from the sun, i.e., variation in light–dark conditions, is transferred as nerve signals to the pineal gland and, depending on the message conveyed by the information, melatonin production is turned on or off. Because of the lack of functional assays, few in vitro investigations have dealt with melatonin. However, it is known that the hormone has an aggregating effect on pigment cells (melanophores) and that it inhibits the release of dopamine in retinal neurones (Krause and Dubocovich, 1991).

In recent years, there have been reports that the effect of melatonin is sometimes dependent on noradrenaline; this has been noted in rat caudal artery (Krause et al., 1995; Viswanathan et al., 1990) and in fish melanophores (Mårtensson and Andersson, 1996). In the cited experiments, melatonin alone had no effect on either smooth muscle contraction or melanophore pigment aggregation. Instead, if an adrenergic stimulant was added before exposure to melatonin, the adrenergic response was potentiated. The noradrenaline-induced aggregation within melanophores is mediated by an α_2-adrenoceptor, whereas the contraction of vascular smooth muscle in rat caudal artery is mediated by a receptor population of both α_1- and α_2-adrenoceptors (Templeton et al., 1989).

It is known that uterine activity is greater during the hours of darkness, and also that labour has a tendency to begin late in the evening (Duscay and Yellon, 1991; Myers and Nathanielsz, 1993; Nathanielsz, 1994). The mechanism behind this phenomenon is unknown although, during human pregnancy, melatonin secretion steadily increases and reaches the highest level at the time of delivery (Kivelä, 1991).

Adrenergic receptors influence the contractility of the uterus, i.e., a mixed population of α_1- and α_2-adrenoceptors mediates increased contractility (Berg et al., 1986). The goal of the present study was to determine whether melatonin can influence human uterine contractility and if noradrenaline is a prerequisite component of the melatonin response.

2. Materials and methods

Myometrial biopsy specimens were taken from 16 women who delivered by caesarean section. The indication

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for caesarean section was humanitarian reasons, breech presentation or pelvic disproportion. The women (22–39 years old) had not received any medication prior to delivery, nor had they been given any agents or drugs that induce contraction. The caesarean section was performed with epidural or general anaesthesia in week 38–40 of gestation. The myometrial biopsies were taken at approximately 9:00 a.m. and thereafter immedediately placed in Ringer solution and taken to the Pharmacology Department. The myometrial samples were dissected free from connective tissues and divided into strips weighing about 100 mg each. The strips were prepared and mounted in special holders, and isometric tension was registered by using FTO3 transducers and a Grass polygraph. The preparations were suspended in Krebs' solution, aerated with 95% O_2 and 5% CO_2, and exposed to 1 μM propranolol (Inderal, 1 mg/ml, ICI). The tension was initially adjusted to 1 g, and the strips were then allowed to equilibrate in the buffer solution until they contracted spontaneously, which took approximately 1–2 h. When the contraction pattern became stable, an experiment was started by adding different combinations of drugs to the organ baths. The effects of all the added substances were then determined by comparing the recorded responses (i.e., the area under each contraction peak) with the spontaneous contractions recorded for the same preparation; in this way, each myometrial sample served as its own control.

Noradrenaline HCl and melatonin were purchased from Sigma, and fresh solutions were made for each experiment. Noradrenaline was dissolved in Krebs' buffer; melatonin was first dissolved in 95% ethanol to make a 10 mM stock solution and thereafter diluted with Krebs' buffer.

2.1. Statistical methods

All values are given as arithmetic means ± S.E.M. Levels of significance were tested by one-way analysis of variance (ANOVA). The significance levels are $^{*}P < 0.05$ and $^{**}P < 0.01$.

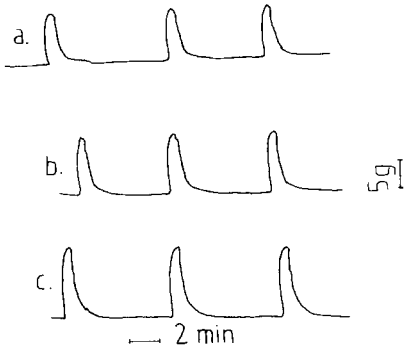

Fig. 1. Recordings of spontaneous myometrial contractions (a) and contractions induced by exposure to 0.1 μM noradrenaline (b), and a combination of 0.1 μM noradrenaline and 0.1 μM melatonin (c).

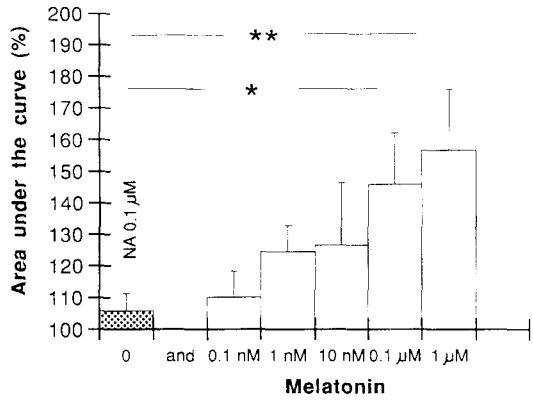

Fig. 2. The effects on myometrial contractions induced by various concentrations of melatonin in the presence of 0.1 μM noradrenaline. Values shown are means ± S.E.M. $n = 4–8$. $^{*}P < 0.05$, $^{**}P < 0.01$.

The experiment was approved by the Ethics Committee of Linköping University.

3. Results

After about 1–2 h in the organ bath, the myometrium started to contract spontaneously (Fig. 1a) and continued to do so for several hours, exhibiting only very small changes in the contraction pattern (data not shown). Noradrenaline increased these contractions (Fig. 1b), and the maximal augmentation, 53 ± 11%, was reached at a concentration of 10 μM noradrenaline. Melatonin did not induce any changes when administered alone (data not shown). However, when a combination of melatonin and a submaximal concentration of noradrenaline (0.1 μM) was introduced to the organ baths, and the concentrations of melatonin were subsequently increased (Fig. 1c), myometrial contractions were potentiated in a dose-dependent manner (Fig. 2). When the noradrenaline concentration was increased to 1 μM, contractions were augmented by 34 ± 18% (n.s.) and 66 ± 19% ($P < 0.01$) upon exposure to melatonin concentrations of 1 nM and 1 μM, respectectively.

4. Discussion

We found that melatonin alone had no effect on the contractions of human pregnant myometrium. However, melatonin did potentiate the response to noradrenaline, i.e., a submaximal concentration of noradrenaline was sufficient to allow a melatonin-induced potentiation of myometrial contractions.

The present results are similar to those for the effects of melatonin on rat caudal artery observed by Viswanathan et al. (1990), namely that melatonin prolonged and potentiated noradrenaline-induced contractions. As of yet, it is not known why noradrenaline is necessary for melatonin-induced contractions in caudal artery or human uterus. Nonetheless, results concerning the melatonin pharmacol-

ogy of melanophores may provide some clues. There is evidence that α_2-adrenoceptors in melanophores must be activated to allow the potentiation mediated by melatonin (Mårtensson and Andersson, 1996). This may also be the case in the human pregnant uterus and the adult rat caudal artery, since the presence of noradrenaline is a prerequisite for melatonin-induced contraction in these tissues, and both tissue types possess α_2-adrenoceptors that mediate a contractile response (Berg et al., 1986; Templeton et al., 1989). However, the interaction of the adrenergic and melatonin signals may also occur between the time of receptor activation and muscle contraction. Perhaps the integration of signals takes place along the signal transduction pathway, since both melatonin and the α_2-adrenoceptor share the same transduction mechanism, i.e., a decrease in cAMP.

In some cases melatonin may modulate adrenergic activity. For that to be possible, the information transferred by the melatonin molecule would have to be integrated with adrenergic signals. Such an integration would mean that melatonin could have considerable influence on myometrial contractility. It is known that serum levels of melatonin are high during pregnancy, and uterine activity is greater after the fall of darkness. Therefore, it is tempting to suggest that melatonin plays a role in labour, a process that often begins late in the evening: the higher level of melatonin may induce more forceful myometrial contractions, which in turn may initiate labour. Further research is needed to determine whether this is the case and, if so, whether melatonin can activate not only its own receptor, but α_2-adrenoceptors as well.

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