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Attenuating effect of melatonin on pyridoxal-stimulated release of adrenomedullary catecholamines in the rat

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ABSTRACT

Aims: To investigate the ability of melatonin (MEL) to suppress adrenomedullary catecholamine (CAT) release in the rat, with pyridoxal (PL) being used as an adrenomedullary stimulus and liver and gastrocnemius muscle glycogenolysis acting as indices of CAT release.
Main methods: MEL (1–4 mg/kg, i.p.) and PL (300 mg/kg, i.p.) were administered separately or together to male Sprague–Dawley rats (275–300 g), and blood samples for the assay of plasma glucose and CATs were periodically collected for up to 3 h after PL. Immediately thereafter, the liver and gastrocnemius muscle were surgically removed and used for the assay of glycogen. The role of adrenoceptors in PL-induced glycogenolysis was examined by parallel experiments in which idazoxan (IDX, 1 mg/kg), propranolol (PRO, 2 mg/kg) or metoprolol (MET, 2 mg/kg) were administered alongside MEL. In addition, MEL (4 mg/kg) was co-administered with taurine (TAU, 2.4 mmol/kg), a known adrenomedullary membrane stabilizer.
Key findings: MEL attenuated the release of adrenomedullary CATs and accompanying liver and gastrocnemius muscle glycogenolysis due to PL in a dose-dependent manner. A co-treatment with MEL and an adrenoceptor blocker had a greater attenuating effect on PL-induced glycogenolysis and hyperglycemia than MEL but without impinging on the CAT levels seen with MEL alone. Evidence of maximal inhibitory action by MEL on PL-induced plasma CAT elevation was suggested by the about equal levels of plasma CATs after treatments with MEL and with MEL plus TAU.
Significance: The present study demonstrates the modulatory effect of MEL of exogenous origin on adrenomedullary CAT secretion when present in supraphysiological concentrations.
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Introduction

Melatonin (MEL) is an indoleamine produced by pinealocytes in the pineal gland of higher animals from tryptophan, an amino acid, or serotonin, a neurotransmitter, and cyclically released according to a daily cycle of light and darkness (Claustrat et al. 2005; Reiter 1991). Since the availability of MEL is stimulated by darkness and suppressed by ambient light entering the retina, this compound has been implicated in the central regulation of biological functions such as the circadian rhythm (Sumova et al. 1995), sleep–wake process, body temperature and behavioral performance (Dollins et al. 1994). In addition MEL may modulate the hypothalamic–pituitary axis to inhibit the secretion of both gonadotropin (Debeljuk et al. 1970) and adrenocortical hormones (Heiman and Porter 1980). Evidence also exists to suggest that MEL, either from endogenous or exogenous sources, can exert an inhibitory action on the adrenomedullary content and outflow of catecholamines (CATs) in humans (Arangino et al. 1999; Cagnacci et al. 2000) and animals (Esquifino et al. 1994; Mahata and De 1991; Maitra et al. 2000a,b; Wang et al. 1999a,b) in a dose-related manner (Mahata and De 1991; Maitra et al. 2000b), and according to the duration of the photoperiod (Maitra et al. 2000a,b). Furthermore, this hormone has been found to elevate the liver and muscle glycogen contents in nonexercised rats and to spare the glycogen stores in the liver and muscle of exercised rats through changes in carbohydrate and lipid utilization (Mazepa et al. 2000; Sánchez-Campos et al. 2001).

The present investigation was undertaken in rats to determine whether MEL can attenuate the release of adrenomedullary CATs following chemical stimulation with pyridoxal (PL), a vitamin B_6 vitamer with proven sympathoadrenomedullary activity (Lau-Cam et al. 1991) and, hence, able to influence peripheral glycogen stores and circulating glucose levels as a result of an increase in circulating CATs. Since CATs are known to induce glycogenolysis by activating α- and β-adrenoceptors on target organs and tissues (Hutson et al. 1976; Kjaer et al. 2000; Onoagbe 1993), changes in liver and gastrocnemius muscle glycogen contents and in plasma glucose levels were also measured in animals treated with α- and β-adrenoceptor antagonists before PL.

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Materials and methods

Animals

A total of 126 male Sprague–Dawley rats, 275–300 g in weight, were obtained from Taconic Farms, Germantown, NY. The animals were housed in groups of 3 in standard plastic cages with cedar wood shavings beds and open-mesh wire covers. During an acclimation period of 5 days, the animals were kept in a room maintained at a temperature of 21 ± 3 °C and a 12 h light–dark cycle, with lights on from 6:00 a.m. to 6:00 p.m. The animals had free access to a commercial rodent diet (Purina® Lab Chow, Ralston Purina Co., St. Louis, MO) and filtered tap water. The food, but not the water, was withdrawn 14 h prior to an experiment. All procedures involving animals were approved by the Institutional Animal Care and Use Committee at St. John's University and followed guidelines set by the United States Department of Agriculture.

Chemicals

The following chemicals were obtained from the sources indicated: amyloglucosidase (30–60 U/mg of protein, from *Aspergillus niger*), glycogen (Type IX, from bovine liver), glucose (anhydrous, ≥99.5%), sodium pentobarbital, citric acid, disodium EDTA, sodium fluoride, (−)-epinephrine bitartrate, (−)-norepinephrine hydrochloride, dopamine hydrochloride, 3,4-dihydroxybenzylamine hydrobromide, ACS reagent grade Tris base, potassium bicarbonate and sodium octanesulfonate were purchased from Sigma Chemical Co., St. Louis, MO. ACS reagent grade sodium acetate, disodium phosphate, perchloric acid (69–72%), phosphoric acid (85%), acid-washed aluminum oxide, glacial acetic acid, and HPLC grade water were obtained from Mallinckrodt Baker, Inc., Phillipsburg, NJ.

Pharmacological agents

Idazoxan hydrochloride (IDX), MEL, metoprolol tartrate (MET), propranolol hydrochloride (PRO), pyridoxal hydrochloride (PL) and taurine (TAU) were obtained from Sigma Chemical Co., St. Louis, MO.

Treatments

Treatment solutions were prepared in either 10% ethanol (MEL) or water for injection (remaining pharmacological agents) and administered by the intraperitoneal route to experimental groups consisting of 6 rats each. The doses used were: PL 100–300 mg/kg, MEL 1–4 mg/kg (as a single dose or in two equal portions given 15 min apart), TAU 300 mg/kg (in two equal portions given 15 min apart), PRO 2 mg/kg, IDX 1 mg/kg and MET 5 mg/kg. Single doses of MEL were given 30 min before a treatment with PL; divided doses were given at 30 min and 15 min prior to PL. The adrenoceptor antagonists were given, singly or as a pair, 30 min before PL. TAU was concurrently administered with MEL. In experiments where multiple treatments were used, the agents were given 30 min apart, with the last agent being given 30 min before one with PL. The control group received only physiological saline (PHS). After the completion of the treatments, each animal was kept in a separate cage for the remaining on the experiment. To insure reproducibility of results, all experiments were started at 12:00 p.m. each time, in an air-conditioned room maintained at 21 ± 3 °C, and completed in about 4 h. To minimize the influence of ambient noise and light, the cages were kept covered with a piece of white cloth throughout an experiment.

Plasma collections

Blood samples were collected at predetermined intervals (0, 30, 60, 120 and 180 min after PL) from the tail tip into 2 ml polyethylene microtubes containing a small amount of disodium EDTA plus sodium fluoride, mixed well, and centrifuged at 5000 rpm for 10 min. The resulting plasma fractions were transferred to clean polyethylene microtubes and stored at −70 °C pending their analysis for glucose and CATs.

Liver and gastrocnemius muscle collection

Immediately after the collection of the last blood samples, the rats were sacrificed with a high (70 mg/kg) intraperitoneal dose of pentobarbital sodium, and their abdomen cut open to expose their livers, which were removed as described by Wollenberger et al. (1960) using metal tongs previously cooled in liquid nitrogen. A similar procedure was used to remove the gastrocnemius muscle, which was accessible after making a longitudinal incision along the left or right femur. The liver and gastrocnemius muscle samples were rapidly immersed in liquid nitrogen, wrapped in aluminum foil, and kept in a deep freezer at −70 °C pending their analyses for glycogen content.

Assessment of plasma glucose elevation

The plasma glucose was measured at 0, 30, 60, 120 and 180 min after a treatment with PL using a commercial assay kit (Procedure No. 510, from Sigma Chemical Co., St. Louis, MO) based on the glucose oxidase–peroxidase method of Raabo and Terkildsen (1960). Results are reported as mg/dl of plasma.

Assessment of liver and gastrocnemius muscle glycogen mobilization

The content of glycogen in the liver and gastrocnemius muscle was measured by the method of Keppler and Decker (1974) following its enzymatic hydrolysis to glucose. For this purpose, a portion of frozen tissue (~1 g) was cut with a razor blade into small pieces, and homogenized with ice-cold 0.6 N perchloric acid (5 ml) using a hand-held electric blender. A portion of homogenate (0.2 ml) was transferred to an ice-cold centrifuge tube and mixed with 1 M potassium bicarbonate (0.1 ml) and amyloglucosidase solution (45 U/ml in 0.2 M acetate buffer, pH 4.8) (0.2 ml). The tube and its contents were mechanically shaken at 40 °C for 2 h, centrifuged at 3000 rpm for 10 min, and an aliquot of the supernatant (0.05 ml) was used to measure glucose as described for the plasma samples. The respective glycogen content, derived by reference to a glycogen (mg/g) vs. glucose (mg/dl) calibration curve, is reported as mg/g of wet tissue.

Assessment of adrenomedullary catecholamine release

The levels of plasma epinephrine, norepinephrine and dopamine were measured in a plasma sample from blood collected 1 h after PL administration, by the HPLC method with electrochemical detection of Williams et al. (1985). As a preliminary step, the plasma samples were subjected to a clean-up procedure on alumina as described by Wang et al. (1999a,b). To this effect, the plasma (0.5 ml), 1.5 M tris buffer pH 8.6 containing 0.07 M EDTA (0.5 ml), acid-washed alumina (10 mg) and the working internal standard solution (3,4-dihydroxybenzylamine, 5 ng/ml) (0.02 ml) were added in succession to a 2 ml self-stoppered polyethylene microtube, mechanically shaken for 30 min, and centrifuged at 2000 rpm for 10 min. The liquid phase was discarded, and the remaining alumina was washed twice with distilled water (1 ml) and once with 0.2 M acetic acid (0.1 ml). The acidic extract was immediately analyzed for its CAT content by HPLC.

The plasma CATs were analyzed on a liquid chomatograph consisting of model 510 pump (Waters Associates, Milford, MA), model 5100A coulometric detector fitted with model 5020 conditioning cell and model 5010 analytic cell (ESA Inc., Bedford, MA), model AS-4000 Intelligent autosampler (Hitachi Instruments, Inc., San Jose, CA) and Pharmacia model LKB REC 1 strip chart recorder (Kipp &

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