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Oxytocin decreases diurnal and nocturnal arterial blood pressure in the conscious unrestrained spontaneously hypertensive rat

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ABSTRACT

In this study, we assessed the effects of oxytocin (OT) on mean arterial blood pressure (MAP), heart rate (HR), and locomotor activity (LA) in male spontaneous hypertensive rats (SHR) and Sprague-Dawley (SDR) controls using telemetry. OT was given by intravenous injections of 0.1, 0.2 or 0.4 mg/kg to assess short term acute effects or by daily subcutaneous injections of 0.5 or 1.0 mg/kg for 5 days. Compared to the saline infusion, (i) intravenous OT, regardless of concentration, increased MAP in SHR and SDR, (ii) HR increased, but was periodically lower in both strains with 0.2 or 0.4 mg/kg, and (iii) no effects of OT on LA were observed. Subcutaneous injections demonstrated that (i) 1.0 mg/kg for 5 days lowered diurnal MAP and HR in SDR and SHR, persisting for 6 days, (ii) 1.0 mg/kg decreased nocturnal HR in SDR, (iii) 0.5 and 1.0 mg/kg decreased MAP with minor effects on HR in the SHR, and lastly (iv) OT decreased LA mainly during the diurnal cycle in both strains. Our main results show that OT induces significant beneficial effects on cardiovascular function over several diurnal and nocturnal cycles in the SHR, with the most prominent effect being a robust decrease in MAP.

1. Introduction

The physiological role of oxytocin (OT) is traditionally associated with female reproductive function, where this nonapeptide produced primarily within cell bodies of magnocellular neurons in the supraoptic and paraventricular nuclei of the hypothalamus, stimulates uterine contraction and milk ejection. In humans and rats, OT is secreted into the plasma during suckling, and corresponding increases in OT levels are found in brain [1]. Higher levels of OT observed in plasma of lactating females are associated with imperturbation and less aggression and anxiety, and women breastfeeding exhibit reductions in both secretion of cortisol and blood pressure [2–4]. Treatment with OT also induces changes in patterns of motor activity in the rat, with behaviors shifting from highly exploratory and movement along the periphery of an open-field arena to reduced spontaneous locomotor activity towards the center [5], suggesting sedative and anxiolytic-like effects [6].

OT is a ubiquitous hormone originating from several sites of synthesis and exhibiting an array of behavioral and physiological functions. The observation that OT is found in equal concentrations in the plasma of both sexes clearly highlights physiological roles of OT beyond that of reproductive function. The connection between high levels of OT and its effect on blood pressure became clear following the observation that heart and the vasculature are also sites of synthesis of OT, where this peptide exerts robust effects on the cardio-renal axis, including electrolyte excretion and regulation of heart rate and blood pressure [7,8]. Results of most studies in humans and animals would support the observation that systemically administered OT generally induces a reduction in arterial blood pressure, regardless of the species or sex, presence or absence of anaesthesia, or route of administration [9–11]. Reports have shown that the decrease in blood pressure also occurs in the presence of reduced heart rate, or without affecting heart rate, whereas evidence indicates that this is met with corresponding intact baroreflex function, including increases is vascular resistance and tachycardia [12]. In ex vivo studies, acute administration of OT

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to isolated perfused dog atria reduces the rate and force of contraction [13]. On the other hand, increases in mean arterial pressure (MAP) following OT administration have been reported, although this may be to the fact that OT administered at high concentrations will bind to the vasopressin receptor and induce a pressor response [14,15].

The effects of OT on cardiovascular function have been well-documented in the conscious rat. Most protocols to date have been designed to record blood pressure at single time points, and during specific and convenient times of the circadian cycles. Use of tail-cuff methods, although minimally invasive, suffer from the main disadvantages of being indirect and requiring restraining of the animal. Restraint stress is an important physiological concern in the spontaneously hypertensive rat (SHR) since this strain exhibits heightened cardiovascular reactivity to immobilization in restraint chambers [16]. Measurement of cardiovascular function using an indwelling catheter tethered to an outside transducer limits the usefulness of this technique by short term patency of the catheter and restricted mobility of the rat. Radiotelemetry monitoring, on the other hand, circumvents the problems inherent to these techniques and can be used to monitor long-term cardiovascular function and locomotor activity with minimal animal handling. However, regardless of the technique used to monitor cardiovascular function, restrain stress remains inevitable if drugs or peptides are administered in the conscious rat.

In the present study, we examined the effects of acute and repeated administration of OT on MAP, heart rate and locomotor activity in the SHR rat model of arterial hypertension. To our knowledge, the effects of repeated administration of OT over consecutive diurnal and nocturnal cycles using radiotelemetry have not determined in this model of hypertension. Further, we chose to assess the effects of OT in the 8-week-old SHR rats because this strain exhibits a blunted baroreflex function marked by a delayed return in arterial pressure in response to stress [17]. In addition, continuous measurement of cardiovascular function particularly during the sleep cycle is to our interest because previous studies have shown that OT is secreted during slow-wave sleep, resulting in an increase in parasympathetic activity [18]. In this study, we evaluate the following hypotheses: (i) acute intravenous OT treatment decreases MAP and HR in the SHR; (ii) daily subcutaneous OT treatment decreases HR and MAP in the SHR during both diurnal and nocturnal cycles; and (iii) reductions in HR and MAP persist in the SHR after the last subcutaneous injection of OT. Our main findings show that OT decreases MAP during entire consecutive circadian cycle in the SHR, while a robust decrease in diurnal HR is observed in SDR.

2. Materials and methods

2.1. Animals

The experiments were conducted in accordance with the *Guidelines of the Canadian Council on Animal Care* and with the approval the Animal Care Committee of the Centre Hospitalier de l'Université de Montréal. Male spontaneously hypertensive rats (SHR, n = 10) and age-matched Sprague-Dawley (SDR, n = 10) normotensive controls were purchased at the age of 8 weeks (225–250 g) from Charles River laboratories (St-Constant, PQ, Canada). Only male rats were selected because OT binding to its receptor is influenced by estrogen and progesterone, which can depress the anti-hypertensive effects of OT [19]. Normotensive SD rats were used as controls to provide a wider basis for baseline values since Wistar Kyoto (WKY) rats are not always a suitable model because of genetic variations and evidence of left ventricular hypertrophy [20,21]. Animals were housed 2 or 3 per cage at a room temperature of 20−23° C under a 12-hour: 12-hour light-dark cycle beginning at 7 am. Rats were allowed free access to food and tap water.

2.2. In vivo arterial pressure measurement by radiotelemetry

After a one-week period of acclimatization, rats were anesthetised with isoflurane and implanted with TA12PA-C40 radiotelemeters (Data Sciences International, St. Paul, MN) in the abdominal aorta for the direct measurement of systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP), heart rate (HR), and locomotor activity (LA). Rats were then given a 10-day recovery period from the surgery before obtaining pre-injection baseline BP, HR, and LA measurements. The analysis of data was performed using Telemetry Analyzer software (TA version 3.2.2, JCL Consultants Inc., Longueuil, Qc, Canada).

2.3. Acute and chronic OT administration on cardiovascular function and locomotor activity

The acute effects of OT on cardiovascular function and LA were first determined. In this series of experiments, OT (Peptide 2.0 Inc. Chantilly, VA, dissolved in 0.3 ml of physiological saline, 0/9%) was administered on separate occasions at the concentrations of 0.1, 0.2, and 0.4 mg/kg as a single intravenous (i.v.) bolus in the tail vein of restrained rats.These concentrations of OT were selected based on earlier observations that it induces a diuretic effect in Wistar rats [8]. Measurement of MAP, HR and LA were then recorded over a 90-minute period following the injection and compared to a control infusion in which only saline was administered. For the chronic administration, OT was injected subcutaneously (s.c.) at the concentrations of 0.5 and 1 mg/kg on a daily basis over 5 consecutive days. Following the last injection, MAP, HR and LA were recorded for an additional 5 diurnal and nocturnal cycles. For these experiments, all data were expressed as change (Δ) in MAP, HR, and LA for each group and compared to baseline values.

2.4. Statistical analysis

All data and presented as mean ± SEM. Statistical analysis was carried out using a one-way ANOVA with repeated values followed by Newman-Keuls multiple comparison test. Data obtained from the chronic injection studies are expressed as change (delta) from baseline values. For baseline comparisons, statistical analysis was performed using the Student *t*-test. All statistical calculations were performed using software (Microsoft Excel, Graph Pad Prism). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Cardiovascular function at baseline in the SHR rat

Table 1 shows representative cardiovascular function in SDR and SHR prior to the injections of OT. HR was significantly lower in SHR compared to control SDR. However, all measurements of arterial blood pressure, as expected, were significantly elevated in SHR compared to SDR. Rate pressure product, an index of cardiac workload (HR multiplied by systolic pressure) was significantly elevated in SHR rats compared to SDR. The product of HR and MAP was also elevated in the SHR.

3.2. Acute intravenous effects of OT cardiovascular function and locomotor activity

The acute changes in MAP, HR, and LA following injections of OT at the concentrations of 0.1, 0.2, and 0.4 mg/kg were measured for a 90-minute period. There were no significant differences in