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Research report

An endogenous dopaminergic tone acting on dopamine D_3 receptors may be involved in diurnal changes of tuberoinfundibular dopaminergic neuron activity and prolactin secretion in estrogen-primed ovariectomized rats

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ABSTRACT

The diurnal rhythm of tuberoinfundibular dopaminergic (TIDA) neuron activity, i.e., high in the morning and low in the afternoon, is prerequisite for the afternoon prolactin (PRL) surge in proestrous and estrogen-primed ovariectomized (OVX) female rats. Whether dopamine acts via D_3 receptors in regulating the rhythmic TIDA neuron activity and PRL secretion in estrogen-primed OVX (OVX + E_2) rats is the focus of this study. Intracerebroventricular (icv) injection of a D_3 receptor agonist, PD128907 (0.1–10 μg/3 μl), in the morning significantly reduced the basal activity of TIDA neurons and increased plasma PRL level. The effects of PD128907 were reversed by co-administration of U99194A, a D_3 receptor antagonist, but not by raclopride, a D_2 receptor antagonist. To determine whether endogenous dopamine acts on D_3 receptors involved in the diurnal changes of the activities, we used both U99194A, a D_3 receptor antagonist, and an antisense oligodeoxynucleotide (ODN) against D_3 receptor mRNA in the study. U99194A (0.1 μg/3 μl, icv) given at 1200 h significantly reversed the lowered TIDA neuron activity and the afternoon PRL surge at 1500 h. Moreover, OVX + E_2 rats pretreated with the antisense ODN (10 μg/3 μl, icv) for 2 days had the same effects as the D_3 receptor antagonist on TIDA neuron activity and the PRL surge. The same treatment with sense ODN had no effect. In conclusion, an endogenous DA tone may act on D_3 receptors to inhibit TIDA neuron activity and in turn stimulate the PRL surge in the afternoon of OVX + E_2 rats.

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1. Introduction

Dopamine (DA) is a central neurotransmitter with myriad functions [35]. In addition to acting postsynaptically, DA also acts presynaptically to modulate its own dynamics via autoreceptors [15]. Both D_2 and D_3 receptor subtypes have been shown to act as autoreceptors in midbrain dopaminergic neurons [6,16,37]. Moreover, DA is also a well-established prolactin (PRL)-inhibiting hormone that is synthesized by hypothalamic tuberoinfundibular dopaminergic (TIDA) neurons and released in the external zone of median eminence [2]. This DA is then transported to the anterior pituitary by hypothalamo-hypophysial portal veins and exhibits a tonic inhibition on PRL secretion.

The presence of DA autoreceptors in TIDA neurons has been suggested, but the presence of DA receptor subtypes and their actions have been controversial [27,30]. Earlier studies using systemic injections of various DA agonists in male rats have shown that D_1 and D_2 receptor agonists inhibit and stimulate the basal activity of TIDA neurons, respectively [3,4,8–10]. However, using local injection of DA and a D_3 receptor agonist, 7-OH-DPAT, into lateral cerebroventricle or into dorsomedial arcuate nucleus (dmARN) where TIDA neurons reside [21,26], we found that DA acting on D_3 receptors inhibits the TIDA neuronal activity of ovariectomized plus estrogen-primed (OVX + E_2) rats [22]. Using extracellular single-unit recording of dmARN neurons in brain slices obtained from OVX + E_2 rats, we have consistently shown that DA inhibits the firing rates of 66–74% [18,19,21,39] and 7-OH-DPAT inhibits 80.9% [22] of recorded dmARN neurons. Another D_3 receptor agonist, PD128907, also inhibits 86.3% of DA-responsive dmARN neurons [18]. Furthermore, in brain slices obtained from OVX + E_2 rats pretreated with antisense oligodeoxynucleotides (ODNs) against D_2 or D_3 receptor mRNA, the inhibitory effects of DA on dmARN neurons were significantly reduced from 67.6% in control group to 43.6% in D_2 ODN-treated group and from 59.5% in control group to 38.5% in D_3 ODN-treated group [19]. Combined treatment of both D_2 and D_3 antisense ODNs reduced the rate even further from 60.5% to 18.4% [19]. Taken together, we have shown that DA acts on both D_2 and D_3

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receptors to inhibit TIDA neuronal activity in OVX + E_2 rats, which is much the same as DA does in midbrain dopaminergic neurons, but differs from those obtained in male rats using systemic treatments.

The TIDA neuronal activity also exhibits a diurnal rhythm in female but not in male rats [33]. The rhythm, high in the morning and low in the afternoon, is prerequisite for the estrogen-induced diurnal PRL surge [25,32]. Various neuronal inputs have been shown to underlie the diurnal changes of TIDA neuronal activity, including cholinergic [32], opioidergic [34] and serotonergic [17]. Whether DA acting on D_3 receptors plays a role in the diurnal changes of TIDA neuronal activity and PRL secretion has not been determined, and is the focus of this study.

Intracerebroventricular (icv) injections of a D_3 receptor agonist, PD128907, a D_3 receptor antagonist, U99194A, and an antisense ODN against D_3 receptor mRNA were used in this study to test the hypothesis that exogenous and endogenous DA acting on D_3 receptors regulate TIDA neuronal activities both in the morning and afternoon. The results clearly show that DA acting on D_3 receptor is involved in the control of TIDA diurnal rhythm and PRL secretion.

2. Materials and methods

2.1. Animal source and treatments

Adult female Sprague-Dawley rats, weighting between 220 and 250 g, were purchased from Yang-Ming University Animal Center (Taipei, Taiwan) and were housed at a light (lights on between 06:00 and 20:00 h) and temperature (23 ± 1 °C) regulated room with free access to tap water and rat chow. All rats used in the experiments were ovariectomized (OVX) for one week, before being implanted subcutaneously with a capsule (silicone tubing, A-M systems, Everett, WA; id, 1.57 mm; od, 3.18 mm; active length, 20 mm) containing 17β-estradiol (E_2; 150 μg/ml corn oil; Sigma Chemical Co., St. Louis, Mo., USA) for a second week. The E_2 levels in the plasma of the capsule implanted animals have been reported at the proestrous level [14]. Each rat also received implantation of a single icv cannula (23-gauge stainless steel) in the lateral cerebroventricle using a stereotaxic instrument (DKI 900; David Kopf Instruments, Tujunga, CA, USA) at the time when E_2 capsule was implanted. Ether and equithesin (2 ml/kg BW, i.p.) were used as anesthetics in OVX and stereotaxic surgeries, respectively.

For icv injections of the chemicals, a 30-gauge needle connected to a microsyringe (10 μl) was inserted into the pre-implanted cannula in each conscious rat. The ODNs and various D_3 agonist/antagonists were slowly injected (3 μl/min) and the animals were decapitated at specific times afterwards under no anesthesia. The handlings and surgical procedures of animals were in accordance with the protocols approved by the Animal Care and Use committee of Chang Gung University.

2.2. Experimental designs and sample collections

In the first study, both time- and dose-dependent effects of PD128907, a D_3 receptor agonist, were determined in the morning around 1000 h. In the time-dependent study, groups of rats were sacrificed at 15, 30, 60 or 120 min after receiving injections of PD128907 (1 μg). The rats in the control group received injections of artificial cerebrospinal fluid (aCSF) and were decapitated at respective times afterwards. In the dose-dependent study, groups of rats were injected with various doses of PD128907 (0.01, 0.1, 1 or 10 μg, icv) and sacrificed at 15 min after the injections.

In the second study, PD128907 (0.1 μg) was administered alone or in combination with either a D_3 receptor antagonist, U99194A (0.1 or 1 μg), or a D_2 receptor antagonist, raclopride (0.1 or 1 μg), #in the morning. The rats were sacrificed at 15 min after the injections.

In the third study, both dose- and time-dependent effects of U99194A, a D_3 receptor antagonist, were determined in the afternoon around 1500 h. In the dose-dependent study, groups of rats received icv injection of U99194A (0.1 or 1 μg) at 1200 h and were sacrificed at 1500 h on the experimental day. The rats also received injections of an aromatic amino acid decarboxylase inhibitor, NSD1015 (100 mg/kg, i.p.), 30 min before being sacrificed. In the time-dependent study, groups of rats received icv injections of 0.1 μg U99194A at 1200, 1300, 1330 or 1400 h and they were all sacrificed around 1500 h on the same day.

In the fourth study, rats were divided into three groups and each group received icv injections of aCSF, antisense ODN against D_3 receptor mRNA (10 μg/3 μl) or sense ODN at 1000 h for 2 days prior to the experimental day. On the experimental day, each group was further divided into two: one was sacrificed at 1000 h and the other at 1500 h. Half of each subgroup received an extra injection of NSD1015 (100 mg/kg, i.p.) 30 min before being sacrificed.

All rats were sacrificed by decapitation at specific time points on the experimental day as described above. The brain of each rat was quickly removed from the skull and frozen on dry ice. Thick (600 μm) coronal brain sections were prepared with a cryostat and thaw mounted onto glass slides. The median eminence (ME) was removed from the slices by a modified micropunch technique [29]. The isolated ME from each rat was then placed individually in 40 μl of 0.15 M sodium phosphate buffer containing 0.65 mM sodium octanesulphonate, 0.5 mM EDTA, and 12% methanol, pH 2.6, and stored at −20 °C until assayed by high-performance liquid chromatography (HPLC) for its monoamine contents including DA, DOPAC and DOPA. The trunk blood of each rat was collected individually at decapitation and the serum was obtained after coagulation and centrifugation of the blood. The serum from individual rat was then stored at −20 °C until assayed for its PRL level using radioimmunoassay (RIA).

2.3. Resources of chemicals and preparations

PD128907, U99194A, raclopride were all purchased from RBI (Natick, MA., USA) and dissolved in distilled water. NSD1015 was purchased from Sigma–Aldrich (St. Louis, MO. USA) and dissolved in 0.9% saline solution. The D_3 antisense ODN was a synthetic 18-mer (5′-GCT-CAC-AGG-TGC-CAT-GGC-3′) DNA sequences complementing to the initial coding region of the D_3 receptor transcript of rats and therefore direct against the D_3 receptor mRNA in a sequence-specific manner. The D_3 sense ODN sequence was 5′-GCC-ATG-GCA-CCT-CTG-AGC-3′ and used as a control. All ODNs were phosphorothioate-modified to increase the resistance of the nucleotide from degradation by endogenous nucleases [1,36]. All sequences were adopted from previous studies [19,38] and were synthesized by a local company (Watson Biotechnology, Taipei, Taiwan). The ODNs were dissolved in aCSF with the concentration of 10 μg/3 μl. The composition of aCSF was as follows (in mM): NaCl 125.1, KCl 3.8, KH_2PO_4 1.2, $MgSO_4$ 1.3, $CaCl_2$ 2.4, $NaHCO_3$ 26, and dextrose 10.

2.4. Chemical assays and statistical analysis

The contents of DA, 3,4-dihydroxyphenylacetic acid (DOPAC) and 3,4-dihydroxyphenylalanine (DOPA) in the punched brain tissues were determined by HPLC with electrochemical detection (ECD) as previously described [17,22,25,32]. Protein quantities of punched brain tissues were measured by the Lowry method [24]. The data were expressed as ng of DOPAC or DOPA per mg protein. Serum PRL levels were determined by RIA using materials kindly provided by Dr. A.F. Parlow of the National Hormone and Pituitary Program of NIDDK, USA.

Statistical analyses were conducted using either one-way or two-way ANOVA. One-way ANOVA, followed by the Student–Newman–Keules' multiple-range test, was performed for all groups. Differences were considered significant at $p < 0.05$.

3. Results

3.1. Effects of exogenously administered D_3 receptor agonist and antagonist on basal TIDA neuronal activity and serum PRL level in OVX + E_2 rats

In the first study, icv injection of 1 μg of PD128907 induced a short-lived (15 min) decrease in ME DOPAC and increase in serum PRL levels in the morning (Fig. 1; $p < 0.05$). The effect was not significant at and after 30 min. Both 10 times higher and lower doses of PD128907, i.e., 10 and 0.1 μg, had the same effects on ME DOPAC and serum PRL levels (Fig. 2; $p < 0.05$, upper panel and $p < 0.01$, lower panel). However, serum PRL levels were significantly lower in rats receiving two higher doses of PD128907 (1 and 10 μg) than the ones receiving the lowest dose (0.1 μg; Fig. 2; $p < 0.05$).

In the second study, co-administration with U99194A (1 μg), a D_3 receptor antagonist, but not raclopride (0.1 and 1 μg), a D_2 receptor antagonist, reversed the effects of PD128907 on ME DOPAC and serum PRL level (Fig. 3; $p < 0.05$). The lower dose of U99194A (0.1 μg) was not effective. Although serum PRL levels in PD128907 + raclopride-treated group seem to be higher than those in PD128907-treated group, they are not statistically different (Fig. 3).

3.2. Involvement of endogenous DA acting on D_3 receptors in regulating the diurnal rhythm of TIDA neuronal activity and afternoon PRL surge in OVX + E_2 rats

In the aCSF-injected control groups, the ME DOPA or DOPAC levels at 1500 h were significantly lower than those at 1000 h (Figs. 4, 6 and 7; $p < 0.01$). In contrast, serum PRL levels were significantly higher (Fig. 6; $p < 0.01$). Icv injection of 0.1 but not 1 μg

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