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Effects of Prolactin-Releasing Peptide on Tuberoinfundibular Dopaminergic Neuronal Activity and Prolactin Secretion in Estrogen-Treated Female Rats

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Key Words

Prolactin-releasing peptide · Tuberoinfundibular dopaminergic neuron · Prolactin · Thyrotropin-releasing hormone · DOPAC · Striatum

Abstract

Both systemic and central effects of a newly discovered prolactin (PRL)-releasing factor (PRF), prolactin-releasing peptide (PrRP), were determined in this study. Systemic injection of PrRP (1 and 10 μg/rat, i.v.) stimulated PRL secretion in ovariectomized, estrogen-treated rats similar to the effect of another PRF, thyrotropin-releasing hormone (TRH). Pretreatment with a dopamine D_2 receptor antagonist, sulpiride (1 μg/rat, i.v.), potentiated the stimulatory effect of both PrRP and TRH on PRL secretion. Using the double-labeling immunohistochemical method, PrRP-immunoreactive terminals were found in close contact with tyrosine-hydroxylase-immunoreactive neurons in the hypothalamic arcuate nucleus. Central administration of PrRP (0.1–1,000 ng/rat, i.c.v.) stimulated tuberoinfundibular but not nigrostriatal dopaminergic neuronal activity in 15 min. Levels of 3,4-dihydroxyphenylacetic acid (DOPAC) in the median eminence and striatum were used as indices for tuberoinfundibular dopaminergic (TIDA) and nigrostriatal dopaminergic neuronal activities, respectively. The serum PRL level, however, was not significantly changed. Similar treatment with TRH (10 ng/rat, i.c.v.) stimulated and inhibited TIDA neuronal activity and serum PRL, respectively, at 30 min. In summary, PrRP may play a role in both the central and peripheral control of PRL secretion.

Introduction

Prolactin (PRL) secretion from the anterior pituitary is under dual control from the hypothalamus: a tonic inhibition by dopamine secreted from the tuberoinfundibular dopaminergic (TIDA) neurons and a phasic stimulation by a yet unidentified PRL-releasing factor (PRF) [2, 4]. Although many candidates have been proposed, e.g. thyrotropin-releasing hormone (TRH) [35], vasoactive intestinal peptide (VIP) [28], angiotensin II (AII) [1], oxytocin [17], arginine vasopressin [34], and an unidentified factor in the posterior pituitary [10], none fulfils all required criteria of PRF. Thus, the search for the authentic PRF continues.

Recently, Hinuma et al. [8] used the reverse pharmacology technique that searches for endogenous ligands of orphan receptors expressed in anterior pituitary cells and isolated a novel peptide from the bovine hypothalamus. They named the peptide PRL-releasing peptide (PrRP)

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because it stimulates PRL release from primary cultured rat anterior pituitary cells. Subsequent immunohistochemical and in situ hybridization studies reveal that the distribution of PrRP-immunoreactive (ir) or PrRP mRNA-containing neurons in the CNS are mainly concentrated in the dorsomedial hypothalamus and caudal medulla [3, 11, 14, 19, 23, 37]. Although PrRP-ir nerve terminals are present in several nuclei in the hypothalamus, few are present in the external zone of the median eminence (ME) [19, 37], the final common route for hypothalamic hypophysiotropic hormones. This finding suggests that PrRP may use a novel route for its control of pituitary PRL secretion if its PRF status is authenticated, e.g. through secretion into the third ventricle and uptake by tanycytes.

Despite the original claim [8], subsequent studies [29, 30] reported that PrRP exhibits either no or a much smaller effect on PRL release in anterior pituitary cells harvested from male and female rats. Results from in vivo studies also varied between gender and different estrous stages of the animals. For instance, intravenous (i.v.) injection of PrRP induced significant PRL secretion in anesthetized female rats at various estrous stages [22], or on estrus alone [36]. Furthermore, one study [22] also showed a positive PRL response in the male rat (less than that in the female), while another [36] found no effect in the male and in proestrous or diestrous female rats. Another study [13] found no effect at all in both conscious male and lactating female rats. Thus, the role of PrRP as a PRF is questioned.

From the distribution of PrRP and its receptor in the CNS, it is suggested that PrRP may have additional functions other than being a releasing hormone [5, 27]. While intracerebroventricular (i.c.v.) injection of PrRP fails to stimulate PRL secretion in rats, it stimulates the secretion of LH, FSH [30], oxytocin, vasopressin [20] and ACTH [21].

Since PRL is under both inhibitory and stimulatory control from the hypothalamus, it is conceivable that coordination between the two signaling pathways prior to a significant PRL secretion, e.g. the estrogen-induced afternoon PRL surge, should exist. A rhythmic signal originating from the suprachiasmatic nucleus that inhibits TIDA neuronal activity and stimulates the release of a putative PRF has been proposed [18, 24, 25, 31]. The exact nature of the rhythmic signaling pathway, however, has not been ascertained. Cholinergic [31], opiodergic [32] and serotonergic [15] inputs have been proposed. In addition, the effects of several putative PRFs, e.g. TRH [12], VIP [9], oxytocin [39] and AII [38], on TIDA neuronal activity have been determined. However, all these factors exhibit a paradoxically stimulatory effect on TIDA neurons.

To further delineate the role of PrRP as a PRF, we used both i.v. and i.c.v. injections of PrRP in this study to determine its possible effects on PRL secretion and on TIDA neuronal activity. The anatomical relationship between PrRP-ir terminals and TIDA neurons was also determined.

Materials and Methods

Animals and Surgical Preparations

Adult female Sprague-Dawley rats weighing between 220 and 250 g were purchased from the Yang-Ming University Animal Center and housed in a temperature (23 ± 1 °C)- and light (lights on between 06.00 and 20.00 h)-controlled animal room with free access to rat chow and water. All rats were ovariectomized (OVX), and 1 week later, implanted subcutaneously with silicone capsules (3.18 mm o.d., 1.57 mm i.d., 20 mm active length; A-M Systems, Everett, Wash., USA) containing 17β-estradiol (E_2; Sigma Chemical, St. Louis, Mo., USA; 150 μg/ml corn oil, Sigma) for 6 more days before being used for experiments. Animals bearing similar estrogen implants had plasma E_2 levels at the proestrous level [6].

For serial blood sampling, each rat was implanted with an intra-atrial catheter made of silicone tubing (0.64 mm o.d., 0.3 mm i.d., 3.5 cm in length; A-M Systems) and polyethylene tubing (0.97 mm o.d., 0.58 mm i.d., 6 cm in length; A-M Systems) via the jugular vein 2 days before the experiment as described previously [22]. For i.c.v. injection, we implanted a stainless steel cannula (23-gauge, 10 mm) into the lateral cerebroventricle of each rat 6 days before the experiment using a stereotaxic instrument (Kopf 900, Tujunga, Calif., USA). The rats were anesthetized with ether and Equithesin for catheterization and cannulation, respectively.

For immunohistochemical staining of PrRP- and TH-ir neurons and terminals in brain tissues, the conventional immunoperoxidase method using a commercially available avidin-biotin system (Vector Laboratories, Burlingame, Calif., USA) and diaminobenzidine as the chromogen were adopted. Nickel ammonium sulfate was added in the staining of PrRP that rendered it a dark blue color. The antisera for PrRP (Phoenix Pharmaceuticals, Mountain View, Calif., USA) and TH (Chemicon, Temecula, Calif., USA) were obtained from commercial sources. OVX + E_2 rats were used for preparing brain tissue slices (30 μm) both in the morning and afternoon.

Experimental Procedures

In the first series of experiments, various doses (0.1–10 μg) of either PrRP31 (Phoenix) or TRH (Phoenix) were injected into OVX + E_2 rats through the intra-atrial catheters in the morning and serial blood samples (0.3 ml each) before and after the injection were collected. The effects of PrRP and TRH (1 μg each) before and after treatment with sulpiride (1 μg, i.v.; RBI, Natick, Mass., USA), a dopamine antagonist, were also determined. After each blood sampling, an equal amount of warmed (37 °C), heparinized (50 IU/ml) saline was replaced through the catheter, which was also used as the vehicle for administration of PrRP, TRH and sulpiride. Each blood sample was centrifuged to get rid of the cell component and the plas-

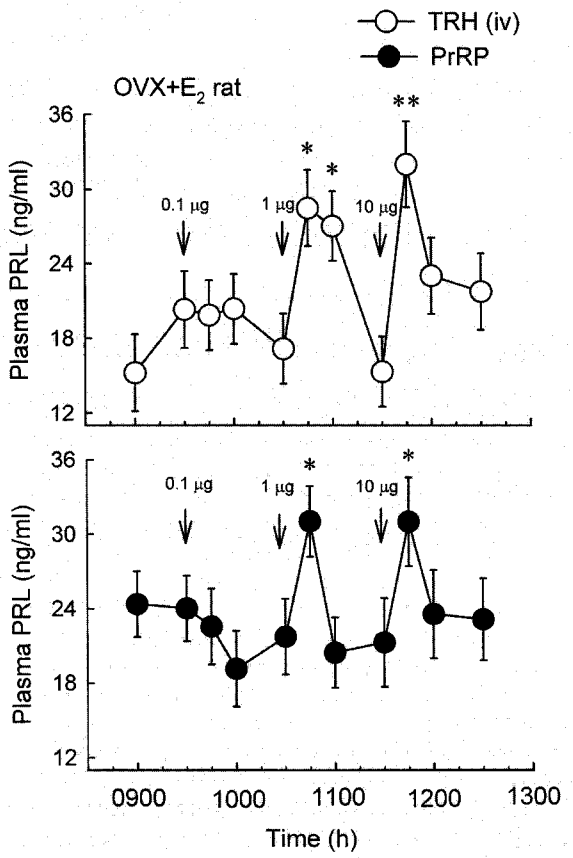

Fig. 1. Dose-dependent responses of plasma PRL to TRH and PrRP. OVX + E_2 rats received repeated injections of TRH or PrRP (0.1–10 μg/0.3 ml, i.v.) in the morning. Serial blood samples (0.3 ml each) were taken before and at 15, 30 and 60 min afterwards. Data are expressed as the mean ± SEM (n = 5–6 rats). * $p < 0.05$; ** $p < 0.01$, compared with preinjection level.

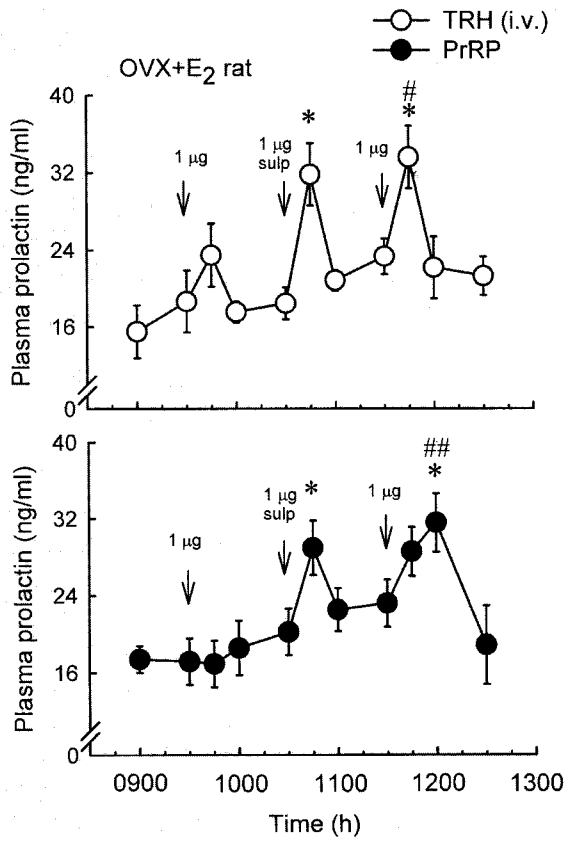

Fig. 2. Potentiation effect of sulpiride on TRH- and PrRP-stimulated PRL secretion. OVX + E_2 rats received i.v. injection of PrRP or TRH (1 μg each) before and after treatment with sulpiride (sulp; 1 μg/0.3 ml/rat). Serial blood samples were taken every 15–30 min. Data are expressed as the mean ± SEM (n = 5–6 rats). * $p < 0.05$, compared with preinjection level; # $p < 0.05$, ## $p < 0.01$, compared with respective PRL level 15 min after the first injection of TRH or PrRP (at 09:45 h).

ma was stored at −20 °C for later determination of its PRL levels by RIA.

In the second series of experiments, various doses of PrRP (0.1–1,000 ng/3 μl, i.c.v.) were given to OVX + E_2 rats and the rats were decapitated at various time points afterwards (15–60 min). TRH (10 ng, 30 min) was also used for comparison.

A trunk blood sample of each rat was individually collected and centrifuged to obtain the serum, and then stored at −20 °C for later determination of its PRL level. The brain was removed immediately from the skull and frozen on dry ice. Thick (600 μm), coronal sections were made by using a tabletop freezing microtome, thaw-mounted onto slides, and kept frozen over dry ice. The ME and striatum (ST) were removed from the sections using a modified micropunch technique [33], and stored individually in 40 μl solution containing 0.775 m*M* sodium octylsulfate, 0.5 m*M* EDTA, 0.17 *M* NaH_2PO_4, and 10% methanol at pH 2.8.

The concentrations of 3,4-dihydroxyphenylacetic acid (DOPAC) in the ME and ST were determined by HPLC with electrochemical detection as previously described [9, 18, 24, 31–33, 38, 39]. In brief, the frozen tissue was first thawed, sonicated and centrifuged. The supernatant was injected into an HPLC system (BAS LC-480, with a PM-80 pump, Rheodyne 7125 injector, Bioanalytical Systems, West Lafayette, Ind., USA). The mobile phase was the same as the solution used for storing the ME. The flow rate of the pump was set at 0.8 ml/min, and the oxidizing potential at +0.75 V. The tissue pellets were dissolved in 1.0 *N* NaOH and assayed for protein content by Lowry assay [16].

Both serum and plasma PRL levels were determined by RIA. The materials for PRL RIA were kindly provided by Dr. A.F. Parlow of the National Hormone and Pituitary program of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK, USA), as described previously [9, 18, 24, 31–33, 38, 39].

Statistical Analysis

The differences among different groups in the neurochemical studies were determined by one-way ANOVA, followed by Student-Newman-Keuls' multiple-range test. A $p < 0.05$ was considered a significant difference.

Results

Blood Sampling Study

Intra-atrial injection of 0.1 μg PrRP or TRH had no significant effect on PRL secretion in OVX + E_2 rats at 15–60 min. A slight decrease in the plasma PRL level was found after giving PrRP (fig. 1). Both PrRP and TRH in 1 and 10 μg doses significantly stimulated PRL secretion at 15 min and the effects of TRH lasted 30 min ($p < 0.05$; fig. 1). A clear dose-dependent response, however, was not observed for either agent.

Injection of sulpiride induced brief, but significant PRL secretion at 15 min ($p < 0.05$; fig. 2). Both effects of TRH and PrRP on PRL secretion were potentiated by prior treatment with sulpiride given 60 min earlier ($p < 0.01$; fig. 2).

Immunohistochemical Staining

PrRP-ir neurons were observed mainly in the dorsomedial hypothalamic nucleus (fig. 3A) and in the solitary tract of the caudal medulla (data not shown) as reported [3, 19]. Dense terminals were found mainly in areas such as the bed nucleus of stria terminalis, hypothalamic periventricular region, paraventricular nucleus, and supraoptic nucleus as reported [11, 19, 37]. With dual labeling, we found that PrRP-ir terminals and boutons were in close apposition with TH-ir neurons in the dorsomedial arcuate nucleus (fig. 3B, C).

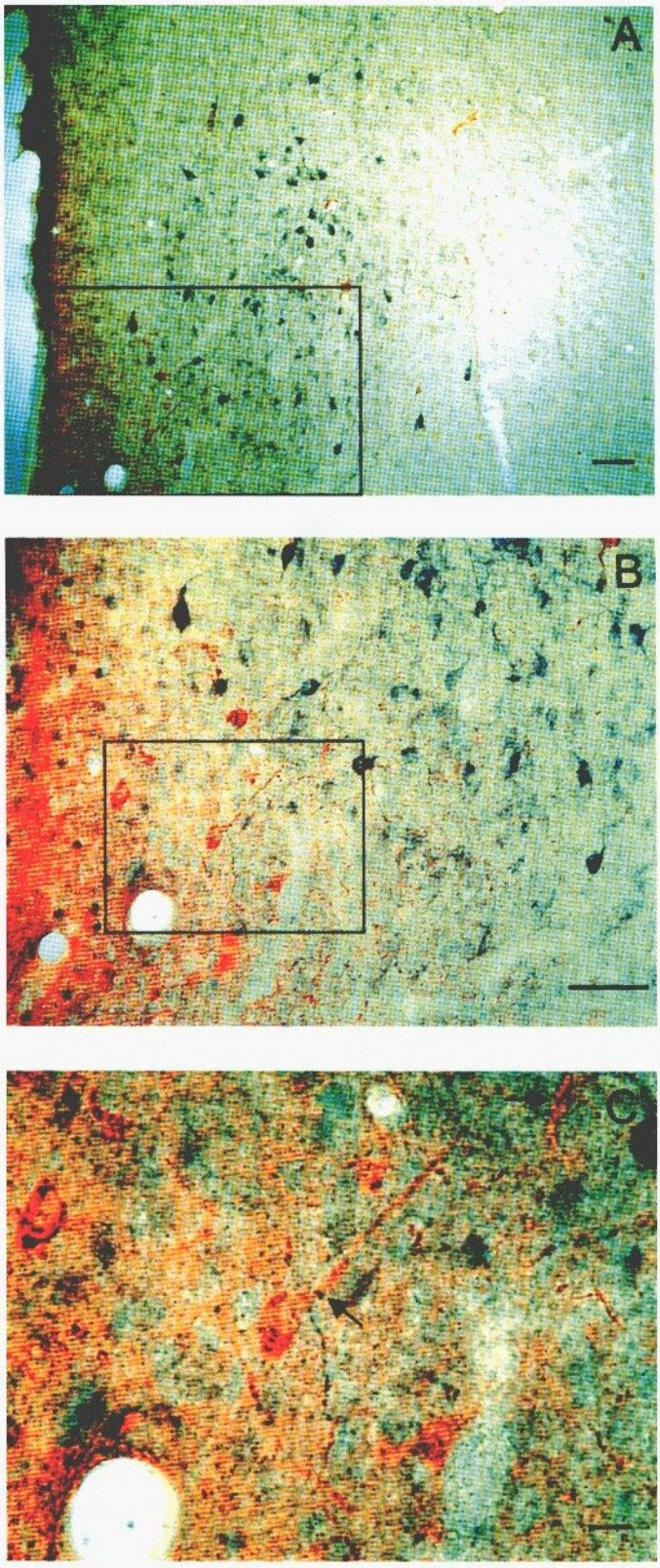

Fig. 3. Double immunohistochemical staining of PrRP (blue)- and TH (brown)-ir neurons and terminals in the medial basal hypothalamic region. **A** Abundant PrRP-ir neurons were present in the dorsomedial nucleus of the hypothalamus with scattered TH-ir neurons. **B** Higher (2×) magnification of the lower left corner of **A** showing more TH-ir neurons in the dorsomedial part of the arcuate nucleus. **C** An even higher (2×) magnification of the lower left corner of **B** showing close apposition of PrRP-ir fibers and boutons on TH-ir neurons. The scale bars in **A** and **B** are 50 μm; the one in **C** is 20 μm.

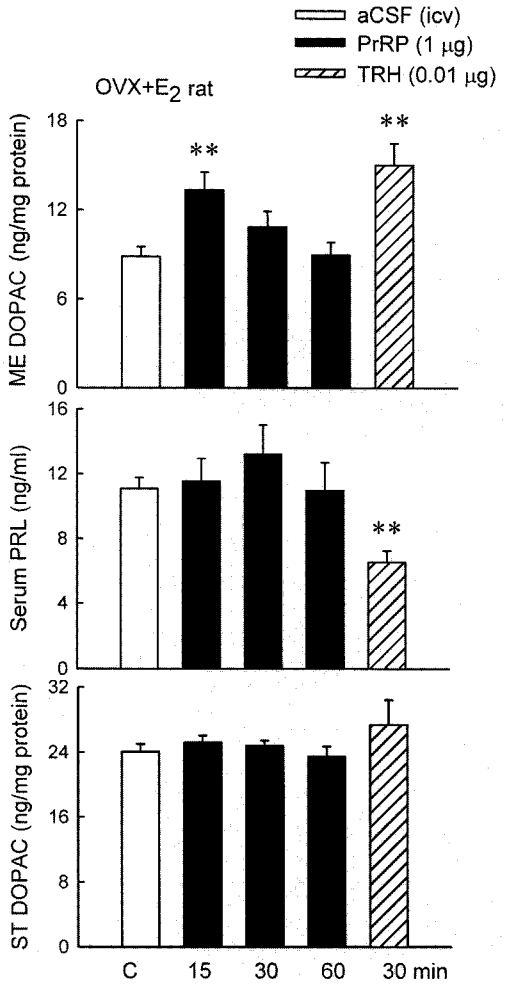

Fig. 4. Time-dependent effect of PrRP and TRH on ME and ST DOPAC and serum PRL levels. OVX + E_2 rats received i.c.v. injection of PrRP (1 μg/3 μl) and were decapitated at 15, 30 or 60 min afterwards. The control rats received artificial CSF (aCSF) instead and were decapitated at various time points. Another group received a TRH (0.01 μg) injection and the rats were decapitated at 30 min. Data are expressed as the mean ± SEM (n = 6–7 rats). ** $p < 0.01$, compared with the artificial CSF control.

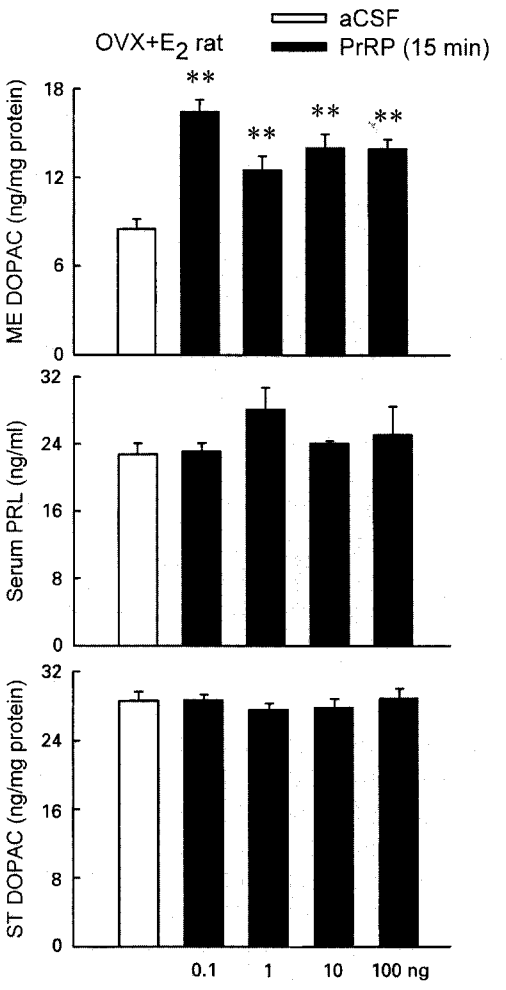

Fig. 5. Dose-dependent effect of PrRP on ME and ST DOPAC and serum PRL levels. OVX + E_2 rats received i.c.v. injection of PrRP (0.1–100 ng/3 μl) and were decapitated at 15 min afterwards. The control rats received artificial CSF (aCSF; 3 μl) instead. Data are expressed as the mean ± SEM (n = 6–7 rats). ** $p < 0.01$, compared with the artificial CSF control.

Neurochemical Studies

i.c.v. administration of PrRP (1 μg/3 μl) significantly stimulated ME DOPAC levels at 15, but not at 30 or 60 min ($p < 0.01$; fig. 4). Serum PRL and ST DOPAC levels, however, were not affected at all (fig. 4). In contrast, TRH at 0.01 μg stimulated and inhibited ME DOPAC and serum PRL levels, respectively, at 30 min ($p < 0.05$; fig. 4).

PrRP given in lower doses (0.1–100 ng/3 μl, i.c.v.) all exhibited significant stimulatory effects on ME DOPAC levels sampled at 15 min ($p < 0.01$; fig. 5). Serum PRL and ST DOPAC levels were again not affected (fig. 5).

Discussion

Effects of a newly discovered peptide, PrRP, on PRL secretion and TIDA neuronal activity were determined. Given peripherally, PrRP exhibited a stimulatory effect on PRL secretion, while given centrally, it stimulated TIDA neuronal activity without significantly affecting PRL secretion. The physiological role of PrRP as a PRF remains to be determined.

Systemic injection of PrRP stimulated a transient PRL secretion in OVX + E_2 rats and its effect was similar but not any more significant than that of TRH. It is well known that estrogen can stimulate PRL secretion through various mechanisms, i.e. increase in PRL synthesis, reduction in dopamine inhibition and increase in PRF stimulation. The estrogen-primed animal model used in this study appears to be appropriate for PrRP. This finding confirms some previous studies [22], but not others [13, 36].

Earlier studies [7, 26] have shown that a transient decrease of dopamine's action can potentiate the effects of TRH on PRL secretion. A transformation of PRL from storage to a releasable pool in lactotrophs of the anterior pituitary has been proposed [7, 26]. Similar changes in the release of hypothalamic DA and PRF may be the underlying mechanism preceding a PRL surge. We then used sulpiride, a short-acting dopamine antagonist, between two injections of PrRP to test if PrRP also had this property. Indeed, sulpiride treatment potentiated both the effects of PrRP and TRH on PRL secretion. Although this pharmacological approach may not prove the authenticity of any PRF, it indicates that both PrRP and TRH are worthy candidates.

That TRH given centrally can have a stimulatory effect on TIDA neuronal activity and an inhibitory one on PRL secretion has previously been reported [12] and confirmed in this study. Similar findings are also obtained with other putative PRFs, e.g. VIP [9], oxytocin [39] and AII [38]. The paradoxical effects of these PRFs on PRL secretion, i.e. direct stimulation on the anterior pituitary and indirect inhibition via hypothalamic dopamine, cannot be satisfactorily explained at this time. Compartmentalization in their release (separate innervation to the arcuate nucleus and to the ME) and/or differential timing in their action, i.e. direct stimulation of PRL secretion first and secondary inhibition of PRL via dopamine later, are two possible explanations.

It is then of interest to find that PrRP-ir terminals exhibited close apposition with TH-ir neurons in the arcuate nucleus and central administration of PrRP also stimulated the TIDA neurons. Although PrRP in doses ranging from 0.1 to 1,000 ng were effective in stimulating ME DOPAC levels, its action was transient and did not last longer than 15 min. We have performed another dose-response study using 30 min as the sampling time and obtained no significant response at all (data not shown).

In comparison with other putative PRFs, i.e. TRH, VIP, oxytocin and AII, the action of PrRP on TIDA neuronal activity is much shorter (15 vs. 30–60 min) [9, 12, 38, 39]. Furthermore, i.c.v. injection of other PRFs all induce a concomitant decrease in the serum PRL level, while PrRP did not. One explanation is that the duration of the effect of PrRP on TIDA neurons was too short to have a significant effect. The other may be that the change in serum PRL was too small or too transient to be detected.

Judging by its distribution in the CNS, i.e. dense terminals in periventricular structures but not in the external zone of the ME, PrRP does not act like a conventional hypothalamic releasing factor. Nevertheless, it did exhibit a potential influence on PRL secretion and on TIDA neuronal activity when administered centrally or peripherally. It is indeed an interesting PRF candidate that warrants further study.

Acknowledgments

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