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Control of Prolactin Secretion by Excitatory Amino Acids

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This article provides an overview of the increasing number of observations indicating that excitatory amino acids are involved in the control of prolactin secretion. The information available suggests that these amino acids exert a stimulatory action on hypophysial prolactin. Administration of a glutamate receptor agonist induces significant increase in prolactin release in rats, monkeys, and rams. In contrast, noncompetitive antagonists of *N*-methyl-D-aspartate receptors decrease plasma levels and attenuate the preovulatory surge of prolactin. It appears that the endogenous glutamatergic system participates not only in the regulation of basal secretion of prolactin, but also in the control of physiological prolactin responses induced by the suckling stimulus or by stress. Recent findings suggest that the glutamatergic innervation of the hypothalamic paraventricular nucleus is involved in the mediation of the neural signal of the suckling stimulus–induced prolactin release as well as in the mediation of the stress-induced release of prolactin.

Key Words: Prolactin; glutamate; paraventricular nucleus; stress; suckling stimulus; excitatory amino acids.

Overview of Pituitary Prolactin Secretion and its Regulation

Nowadays, it is well established that pituitary prolactin secretion is under a tonic and predominant inhibition exercised by the medial–basal hypothalamus. Therefore, prolactin secretion is restrained in vivo by the action of hypothalamic prolactin inhibiting factor(s) (PIF). Based on the observations that dopamine is present in high concentration in both the median eminence *(1)* and the blood collected from the long portal vesels *(2–4)*, and that drugs, affecting catecholamine metabolism, have always altered pituitary prolactin secretion *(5–7)*, it has been concluded that dopamine is the hypothalamic PIF. Experimental evidence that dopamine can dose-dependently inhibit prolactin release from pituitary mammotropes in vitro, has strongly supported this conclusion *(8–10)*. Subsequently, receptors for dopamine have been detected on pituitary cell membranes *(11–14)*, which belong to the D_2 subclass of the dopamine receptor family *(15,16)*. Hence, all of the required conditions have been documented to be present for considering dopamine as the major hypothalamic PIF.

One could conclude that, by having an established PIF, the simplest way to increase prolactin release would be to reduce hypothalamic inhibition. However, previous as well as recent evidence have strongly suggested that the prevailing view about the exclusive inhibitory control of prolactin secretion appears to be overly simplistic. There are conflicting reports about the changes in dopaminergic neuronal activity during surges of prolactin, like suckling-, stress-, and estrogen-induced responses *(17)*, suggesting that there is an alternate regulatory mechanism. Therefore, it can be assumed that there are two major mechanisms by which hypothalamic neuronal activity can enhance prolactin release from the pituitary gland: (1) inhibition of PIF and/or (2) stimulation of a prolactin-releasing factor (PRF) (Fig. 1).

Two major compounds, thyrotropin-releasing hormone (TRH) and vasoactive intestinal peptide (VIP), have previously been considered as physiologically relevant PRFs of hypothalamic origin. TRH- and VIP-producing nerve cells are localized in the parvocellular portion of the hypothalamic paraventricular nucleus, and terminate in the external zone of the median eminence. The peptides are secreted into the portal blood and have high affinity membrane receptors on mammotropes. However, the physiological role of TRH and VIP is still fairly puzzling. TRH can stimulate prolactin release both in vivo and in vitro only when dopaminergic input has been previously reduced or is absent. On the other hand, recent findings suggest that VIP is also produced by mammotropes themselves, and is established as an autocrine stimulatory factor of prolactin release *(17)*. This raises a concern about the role of hypothalamic TRH and VIP in the economy of prolactin secretion in vivo.

At the same time there is abundant evidence in the literature that the mammotropes are also influenced by the neural and intermediate lobes of the pituitary gland *(18)*. Secretory products of these lobes can reach the anterior lobe through the short portal vessels, which represent a vascular communication between these lobes and the anterior lobe (Fig. 1).

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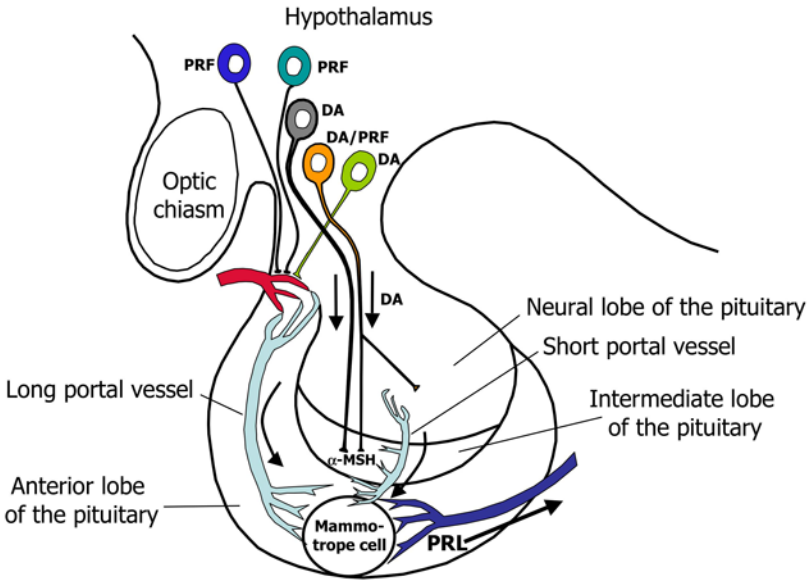

Fig. 1. Schematic illustration of the hypothalamic control of pituitary prolactin secretion by prolactin releasing factors (PRF) and dopamine (DA) and its metabolites reaching the mammotrope cell via long and short portal vessels.

Several observations have suggested that oxytocin and vasopressin, and possibly other less-well-characterized compounds as well, after being released at the posterior and/or intermediate lobe of the pituitary gland, can reach the anterior lobe and may participate in the control of prolactin secretion. Attempts have been made to chemically characterize the "major" prolactin releasing activity present in the neurointermediate lobe extract, but the only conclusion that has been drawn was that it is distinct from TRH, angiotensin II, VIP, arginine vasopressin, and oxytocin *(19–21)*.

A dopamine-derived compound, R-salsolinol (SAL), is a recently identified putative endogenous PRF, which can be detected in the neurointermediate lobe of pituitary gland as well as in the median eminence of male and female rats *(22)*. SAL appears to be a selective and potent stimulator of prolactin secretion both in vivo and in vitro without having any effect on the secretion of other pituitary hormones. Moreover, in lactating dams there is a sharp increase in SAL content of the neurointermediate lobe and the median eminence due to suckling stimulus. Using an antagonist of SAL, it has recently been shown that SAL may also participate in the immobilization as well as the formalin stress–induced prolactin responses *(23)*. However, the exact site and the mechanism of action of SAL influencing pituitary prolactin secretion is still enigmatic and remains to be investigated further. But the possibility that the two main hypophysiotropic regulatory factors are relative to each other, and members of the same synthetic/metabolic pathways, may give a new insight into the tonic inhibitory as well as the stimulatory regulation of pituitary prolactin secretion.

In summary (Fig. 1), it is clear now that PIF and PRF from the hypothalamic neuroendocrine neurons can not only be released at the level of the median eminence, but also at the level of the neurointermediate lobe. Thus, mammotropes are regulated by blood-borne factors arriving from two different directions. At the same time, these final common regulatory pathways of prolactin secretion can be influenced by ascending as well as descending pathways arriving to the hypothalamus and terminating at the level of both the median eminence and the neurointermediate lobe, where several other hypothalamic neurons release their hypophysiotropic factors like somatostatin, γ-aminobutyric acid, neurotensin, oxytocin, angiotensin II, dopamine and its derivatives, including salsolinol. At the same time they can also affect the same neuronal pathways at the level of the neuroendocrine hypothalamic cell groups, like arcuate, and paraventricular nuclei, where the inhibitory and stimulatory factors are most likely produced.

This article provides an overview of the increasing number of observations indicating that excitatory amino acids are involved in the control of prolactin secretion. The information available suggests that these amino acids participate in the regulation of basal secretion of prolactin as well as in the control of physiological prolactin responses such as rise in plasma prolactin induced by the suckling stimulus and stress-induced prolactin release. Data about the hypothalamic site of action of the excitatory amino acids are also presented.

Regulation of Basal Secretion of Prolactin by Excitatory Amino Acids

Both systemic and intracerebroventricular administration of the glutamate receptor agonist induces significant increase in prolactin release in male *(24)* and female rats *(25)*, adult female and prepubertal male rhesus monkeys

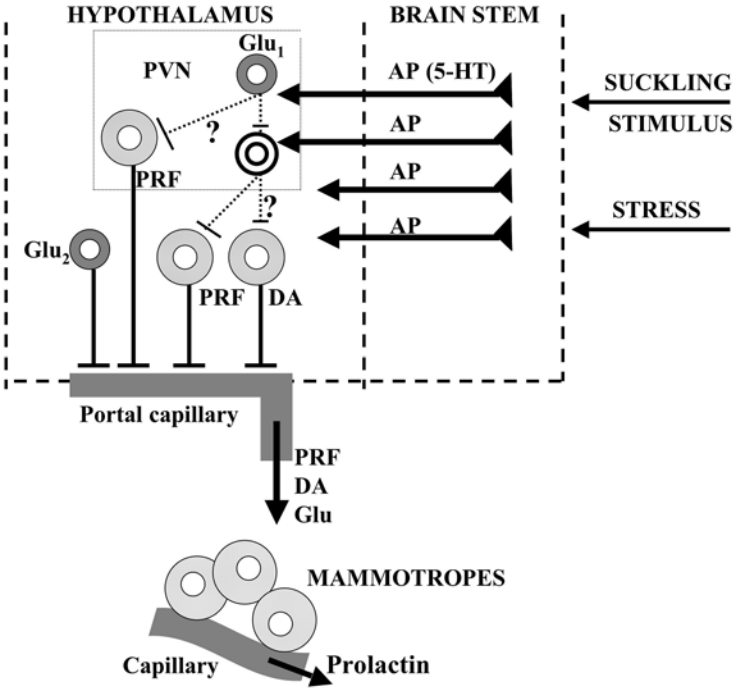

Fig. 2. Schematic drawing illustrating in a very simplified form the connections of a glutamatergic interneuron (Glu1) in the hypothalamic paraventricular nucleus (PVN) involved in the mediation of the suckling stimulus- and stress-induced prolactin release. Glu2: hypophysiotropic releasing hormone–producing neuron containing also glutamate; AP-s indicate ascending pathways of the brain stem terminating in the hypothalamus; 5-HT: ascending serotonergic pathway arising from the dorsal raphe nuclei and projecting to the paraventricular nucleus; DA: dopamine; PRF: prolactin releasing factor.

(26), and rams *(27)*. Likewise, injection of an agonist for the *N*-methyl-D-aspartate (NMDA) receptor or kainate into the third ventricle stimulates prolactin release in both cycling and lactating animals *(28)*. Furthermore, administration of sodium-D-aspartate, which is the precursor of NMDA, also induces a dose- and time-dependent elevation in serum prolactin concentration. In contrast, noncompetitive antagonists of NMDA receptors decrease plasma levels in female rats *(29)* and attenuate the preovulatory surge of prolactin *(30)*. It has to be noted that experiments conducted in vitro on isolated adenohypophysis or adenohypophysis coincubated with the hypothalamus showed that the release of prolactin is partially mediated through a direct action of D-aspartate on the pituitary gland and also indirectly through the hypothalamus *(31)*. In accordance with this, immunohistochemical studies revealed that receptors for NMDA are localized not only in the brain, but also in hormone-secreting cells of the anterior lobe, including mammotropes *(32)*.

Thus, in the light of the available information, it may be assumed that glutamate participates in the control of basal secretion of pituitary prolactin. The site of this action of glutamate is at present unclear. Presumably primarily hypothalamic structures are involved in the mediation of this effect. However, a direct action of glutamate on prolactin cells seems to be likely too, especially if one takes into account the most recent findings indicating that gonadotropin-releasing hormone, corticotropin-releasing hormone, and thyrotropin-releasing hormone and somatostatin neurons projecting to the median eminence contain vesicular glutamate transporter 2, a marker of glutamatergic neurons *(33–35)*. These observations suggest that glutamate may be released from the terminals of these hypophysiotropic neurons directly into the hypophysial portal vascular system and can act directly on mammotropes (Fig. 2).

Involvement of Glutamate in the Regulation of the Suckling-Induced Prolactin Release

The suckling-induced prolactin release is a widely studied neuroendocrine reflex, comprising a neural afferent and humoral efferent component. Its neural afferentation is known to be composed of classic sensory as well as central autonomic neuronal networks terminating in the hypothalamus that activate the humoral efferent side, which results in the release of prolactin from the anterior lobe of the pituitary gland. Separation of the mothers from their pups for 4 h results in a fall of plasma prolactin levels. When they are reunited, plasma prolactin level begins to rise within a few minutes *(17)*.

It appears that the endogenous glutamatergic system has an important role in the suckling-induced prolactin rise and in the constantly high prolactin levels in lactating rats. Zelena et al. *(36)*, using the combination of NMDA and non-NMDA receptor antagonists, have observed that the combination

of the two receptor antagonists administered iv efficiently diminished the suckling-induced plasma prolactin concentration of continuously suckling mothers. Parker and Crowley *(37)* have reported that administration of the non-NMDA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) in the third ventricle of suckling rats blocked the release of oxytocin and prolactin induced by suckling. Acute intravenous treatment of lactating mothers with phencyclidine, a non-competitive antagonist of the NMDA class of glutamate receptor, could only delay prolactin, but it blocked oxytocin response to the suckling stimulus *(38)*.

The hypothalamic paraventricular nucleus region appears to be a key structure in the mediation of the suckling stimulus–induced release of prolactin. Lesion of the whole nuclei interferes with the hormone response induced by suckling *(39)*. Frontal knife cut behind this nucleus, horizontal knife cut below the cell group, or lesion of the medial (periventricular and parvocellular) subdivision of the nucleus blocks the prolactin response to suckling *(40)*.

Several observations suggest that glutamate is a prime candidate that provides a major excitatory signal to hypothalamic paraventricular nucleus neurons. This cell group is rich in glutamate immunoreactive axons and synapses *(41–43)*, in glutamate receptor mRNA and protein expression *(44–47)*, in glutamate/agonist binding *(48)*, as well as it contains glutamatergic neurons and vesicular glutamate transporter 2 protein immunoreactive fibers *(49,50)*. All three subtypes of ionotropic glutamate receptors and certain subtypes of metabotropic glutamate receptors are present in the cell group *(51,52)*. According to Wuarin and Dudek *(53)* excitatory amino acid antagonists almost completely inhibit synaptic responses in both the magnocellular and parvocellular subdivision of the paraventricular nucleus. Van den Pol et al. *(43)* have found that spontaneous excitatory postsynaptic potentials in this cell group were markedly attenuated by application of the non-NMDA receptor antagonist CNQX. We have also looked at the involvement of the glutamatergic innervation of the paraventricular nucleus in the prolactin response to the suckling stimulus *(54)*. Non-NMDA and NMDA receptor antagonists were injected bilaterally into the paraventricular nucleus of lactating rats 15 min prior to the end of a 4-h separation of the dams from their pups. The litters were returned and the mothers exposed to the suckling stimulus. Bilateral injection of the non-NMDA receptor antagonist into the hypothalamic paraventricular nucleus blocked the elevation in plasma prolactin concentration induced by the suckling stimulus. In contrast, bilateral administration of the NMDA receptor antagonist into the paraventricular nucleus or bilateral injection of the non-NMDA receptor antagonist into the dorsomedial nucleus area or the arcuate nucleus did not interfere with the prolactin response to the suckling stimulus. These findings indicate that the glutamatergic innervation of the paraventricular nucleus is involved in the mediation of the neural signal of the suckling stimulus inducing prolactin release.

The glutamatergic fibers terminating in the paraventricular nucleus partly originate from glutamatergic neurons of several diencephalic and telencephalic structures, and partly belong to glutamatergic interneurons that have been shown to be present in the paraventricular nucleus *(49)*. Glutamatergic neurons originating from the brain stem and projecting to the paraventricular nucleus have not been detected *(49)*. If one takes into account that the signal of the suckling stimulus is mediated through the spinal cord and the brain stem up to the hypothalamus, it can be assumed that the glutamatergic innervation of the paraventricular nucleus to be involved in the mediation of the suckling stimulus most probably belongs to the glutamatergic interneurons of the cell group. Our findings suggest that these interneurons take part in forwarding the stimulatory influence of the suckling stimulus reaching the paraventricular nucleus. They presumably participate in the mediation of the stimulatory effect of the serotonergic afferents terminating in the paraventricular nucleus (Fig. 2). A large number of observations suggest that serotonergic elements arising from the raphe nuclei and terminating in the hypothalamic paraventricular nucleus *(55)* are primarily involved in leading the suckling stimulus to this cell group *(40,56–60)*.

Further investigations are needed to study where the neural afferent component of the suckling stimulus–induced release of prolactin is transformed into a humoral efferent reflex arch expressed via changes in the secretion of prolactin releasing and/or release inhibiting factors (vasoactive intestinal peptide, oxytocin, vasopressin, salsolinol, dopamine) produced by hypothalamic neurons *(17,22)*.

Participation of Glutamate in the Prolactin Response to Stress

Glutamate appears to be involved not only in the suckling stimulus–induced release of prolactin, but also in the prolactin response to stress. In male rats, combined, but not separate, blockade of NMDA and AMPA/kainate subtypes of glutamate receptors administered ip prevented the rise in plasma prolactin in response to foot-shock stress. In contrast, foot shock, as well as restraint stress–induced prolactin release, were inhibited even by separate blockade of NMDA glutamate receptors in female rats *(25,61)*. None of the treatments affected prolactin release during immobilization or ether stress *(61)*. It is well known that stress-induced prolactin release is inhibited by serotonin receptor antagonists *(62,63)*. There are findings *(25)* suggesting that the prolactin release evoked by restraint involves glutamate/NMDA receptors linked to a serotonergic pathway.

Recently, we have tested the involvement of the glutamatergic innervation of the paraventricular nucleus in the prolactin response to formalin stress *(64)*. Non-NMDA or NMDA receptor antagonists were injected bilaterally into the paraventricular nucleus of freely moving male rats and 15 min later the animals were exposed to formalin stress by

injecting formalin under the skin. Blood samples for prolactin were taken at different time points before and after administration of formalin. Non-NMDA receptor antagonist, when injected into the paraventricular nucleus inhibited the formalin-induced rise in plasma prolactin. A similar effect was not observed if an NMDA receptor antagonist was administered into the paraventricular nucleus or a non-NMDA receptor antagonist was injected outside the cell group. The findings indicate that the glutamatergic innervation of the paraventricular nucleus participates in the mediation of the formalin-induced prolactin release. When taking into account our mentioned observations, the serotonergic system is involved in the prolactin response to stress and the serotonergic innervation of the paraventricular nucleus participates in the mediation of the suckling stimulus-induced release of prolactin *(40)*, one might assume that the action of the serotonergic fibers on the glutamatergic interneurons of the paraventricular nucleus is presumably involved in the mediation of the formalin stress–induced release of prolactin.

In summary (Fig. 2), a significant amount of information has been accumulated indicating that excitatory amino acids participate in the neural control of hypophysial prolactin secretion both in the regulation of basal secretion as well as in the control of physiological prolactin responses. Recent findings indicate that the glutamatergic innervation of the hypothalamic paraventricular nucleus participates in the mediation of the neural signal of the suckling stimulus or of stress inducing prolactin release. At present, it is not known where the neural signals are transformed into a humoral efferent reflex answer expressed via changes in the secretion of prolactin releasing and/or release inhibiting factors produced by hypothalamic neurons.

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