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Thalamic integration of social stimuli regulating parental behavior and the oxytocin system

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Abstract

Critically important components of the maternal neural circuit in the preoptic area robustly activated by suckling were recently identified. In turn, suckling also contributes to hormonal adaptations to motherhood, which includes oxytocin release and consequent milk ejection. Other reproductive or social stimuli can also trigger the release of oxytocin centrally, influencing parental or social behaviors. However, the neuronal pathways that transfer suckling and other somatosensory stimuli to the preoptic area and oxytocin neurons have been poorly characterized. Recently, a relay center of suckling was determined and characterized in the posterior intralaminar complex of the thalamus (PIL). Its neurons containing tuberoinfundibular peptide 39 project to both the preoptic area and oxytocin neurons in the hypothalamus. The present review argues that the PIL is a major relay nucleus conveying somatosensory information supporting maternal behavior and oxytocin release in mothers, and may be involved more generally in social cue evoked oxytocin release, too.

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1. Introduction

Social behaviors are regulated by specialized neural networks in the brain that respond to sensory information from the environment. These social neural networks were established early in evolution, long before cortical structures developed to mediate advanced social communication (Goodson, 2005; Royle et al., 2014). Even in mammals, these ancient subcortical networks continue to play critically important roles in the control of instinctive social and affiliative behaviors. One example of an evolutionarily ancient, yet highly conserved behavior that is regulated by subcortical neural networks responsive to social cues is parenting behavior, which is present in all mammalian species, although often only in the form of maternal behavior, as only females take care of the young in most mammalian species (Rilling and Young, 2014). Recent progress in parental neurobiology has determined chemically identifiable cell types of the maternal regulatory network within the preoptic area of the hypothalamus that are critically involved in parental responsiveness (Wu et al., 2014). Other, even earlier established brain regions involved in maternal neuroendocrine actions are the paraventricular and supraoptic nuclei of the hypothalamus, which contain the majority of the brain's oxytocin neurons (Feldman et al., 2016; Knobloch and Grinevich, 2014). These neurons are activated in mothers, and secrete their neuropeptide hormone into the blood in the pituitary to induce muscle contraction in the uterus during parturition and in the mammary glands during milk ejection (Burbach et al., 2006). These same neurons release oxytocin into the \brain where they influence the onset maternal motivation and bonding (Lee et al., 2009; Leng et al., 2008; Marlin et al., 2015; Rich et al., 2014; Ross and Young, 2009). More recently, many more general functions of oxytocin have been established in different social situations (Mitre et al., 2016; Neumann, 2008). Thus, oxytocin participates in gating of social reward (Hung et al., 2017), controlling anxiety (Li et al., 2016), pair bonding (Numan and Young, 2016), empathy based consolation behavior (Burkett et al., 2016), as well as olfactory memories (Ferguson et al., 2001; Stoop, 2016). Like parental behavior, these behaviors require social interactions, during which sensory information transfer takes place between individuals. The sensory inputs include a variety of different sensory systems, such as somatosensory, olfactory, auditory, and visual systems. These sensory systems all have cortical representations, through which the social brain network can be affected, probably via limbic connections. However, direct sensory inputs, which bypass the cerebral cortex, may also reach the social brain network to evoke simple parental reflexes as well as more complex social behaviors. This review will focus on a thalamic relay center, which is optimally located to integrate somatosensory and auditory inputs and may exert their effects on maternal and sociosexual brain centers in the preoptic area as well as on oxytocin neurons in the hypothalamus. Thus, we focus our discussion on the posterior intralaminar complex of the thalamus (PIL) as a potential relay station of certain maternal reflexes as well as potentially more complex parental, sexual, and social behaviors, although

a role of the PIL in regulating non-parental social behavior remains speculative. The PIL contains a unique neuropeptide, tuberoinfundibular peptide of 39 residues (TIP39), which will be described in detail, together with its receptor, the parathyroid hormone 2 receptor (PTH2 receptor). We will then discuss the neural pathways which convey sensory information to affect maternal responses. Finally, the broader implications for non-parental social behavior, the human relevance of the rodent data, and potential future research directions will be discussed.

2. The posterior intralaminar complex of the thalamus and its neuropeptide content

We originally identified the posterior intralaminar complex of the thalamus (PIL) (Dobolyi et al., 2003b) based on the distribution of the then newly identified tuberoinfundibular peptide of 39 residues (TIP39; Fig. 1) (Usdin et al., 1999). Subsequent studies revealed its likely role in integrating pup stimuli and activating MPOA neurons and potentially stimulating oxytocin release.

2.1. Tuberoinfundibular peptide of 39 residues (TIP39)

TIP39 (or parathyroid hormone 2) is a ligand of the previously orphan parathyroid hormone 2 receptor (Usdin and Dobolyi, 2009), a G-protein coupled receptor concentrated in hypothalamic and limbic brain regions (Dobolyi et al., 2006a; Faber et al., 2007; Wang et al., 2000). TIP39 is coded by a single gene in mouse, rat, bovine and human, from which other neuropeptides are not known to be synthesized (Dobolyi et al., 2002; John et al., 2002). The original description of the distribution of TIP39 established only two sites of expression, the periventricular gray-subparafascicular area in the medial thalamus and the medial paralemniscal nucleus in the lateral pons (Dobolyi et al., 2002). The PIL, as a third major site of expression of TIP39, only became apparent in a developmental study because TIP39 was the most abundant in the brain in this region before birth (Brenner et al., 2008). However, TIP39 disappears from the PIL in early postnatal period, therefore, it is not detectable there in adult male brains (Dobolyi et al., 2006b). The level of TIP39 is somewhat higher, but still very low in adult female rat (Dobolyi et al., 2006b). In turn, we observed a markedly significant increase of TIP39 expression in the PIL of mothers both at the mRNA (Fig. 2) and peptide level in the postpartum period, starting at parturition and lasting until weaning of the pups, indicating that TIP39 levels remain elevated throughout lactation (Cservenak et al., 2010; Cservenák et al., 2013). In addition, the pontine site of TIP39 expression, the medial paralemniscal nucleus (Varga et al., 2008), also showed maternal induction, albeit to a lesser degree than the PIL (Varga et al., 2012). Interestingly, TIP39 was not induced at all in the periventricular gray of the thalamus, rather a tendency for further decrease was found there (Cservenak et al., 2010; Cservenák et al., 2013), so the major site of expression of TIP39 in the forebrain of mothers is the PIL (Fig. 2G).

2.2. Topography and chemoarchitecture of the PIL

The PIL does not follow the borders of traditional nuclei based on cell morphology or clustering. Rather, it consists of the posterior intralaminar thalamic nucleus as well as the parvocellular (or lateral) subparafascicular nucleus. Furthermore, TIP39 neurons are present

ventrally in the lateral zona incerta below the lateral part of the medial lemniscus (Cservenák et al., 2013; Dobolyi et al., 2003b). This area can be well-characterized neurochemically by the presence and distribution of the calcium binding protein, calbindin (Fig. 1), which is present in all parts of the PIL, essentially delineating its boundaries (Cservenak et al., 2017a). The complexity of the structure is further enhanced by the subdivision of the parvocellular subparafascicular nucleus into a medial and a lateral subdivision defined topographically by the presence of galanin fibers and calcitonin gene-related peptide (CGRP)-containing cell bodies, respectively (Coolen et al., 2003). We have determined that TIP39 cell bodies are located medial to CGRP neurons in the area (Brenner et al., 2008; Dobolyi et al., 2005) suggesting that the PIL can be also divided into a medial and lateral subdivision and TIP39 neurons are located medially (Dobolyi et al., 2010). A chemo-architectonic analysis found that essentially all TIP39 neurons contained calbindin, while calbindin neurons were not present in brain areas immediately surrounding the PIL except for the dorsally located triangular subdivision of the posterior thalamic nucleus (Cservenak et al., 2017a). In contrast, the PIL did not contain parvalbumin neurons even though parvalbumin was present in several adjacent nuclei including the ventrally located substantia nigra, the dorsomedially located anterior pretectal nucleus, and with lower density, also in the dorsally located triangular subdivision of the posterior thalamic nucleus (Cservenak et al., 2017a). The distribution of both calcium ion binding proteins confirms that TIP39 neurons are mostly present in the medial subdivision of the PIL. Within this area, however, the TIP39 neurons have an even distribution. TIP39 neurons are not the only cell type within the medial PIL because there are some TIP39-negative calbindin neurons and TIP39-negative GABAergic neurons in the area as well (Cservenak et al., 2017a), and the presence of additional cell types cannot be excluded either.

2.3. Afferent neuronal connections of the PIL

The inputs to the PIL have been studied using retrograde tracer injections. Although the injections were performed in mother rats so that the position of the injection site can be verified using TIP39 immunohistochemistry, it is not known if the inputs terminate on TIP39 neurons. Nevertheless, the data are relevant when assessing the role of the PIL as a relay center. The PIL receives contralateral ascending input from the spinal cord, thoracic laminae IV-V and lumbar cells in laminae VI–VII, typically 5 neurons per millimeter. Additional ascending somatosensory input arrived from the gracile and cuneate nuclei, as well as the spinal trigeminal nucleus (Cservenak et al., 2017a). Furthermore, a number of retrogradely labeled cells were found in the ipsilateral external cortex of the inferior colliculus suggesting significant auditory input while less dense input arrived from the lateral parabrachial nucleus, periaqueductal gray, and deep layers of the superior colliculus (Cservenak et al., 2017a), findings which are consistent with a more restricted connectivity study focusing on auditory inputs to the subparafascicular area (Yasui et al., 1990). In addition, the PIL also receives some predominantly ipsilateral descending inputs, of which the largest one arrives from the ventromedial hypothalamic nucleus, particularly in its ventrolateral subdivision, while neurons in the infralimbic and insular cortices, the central amygdaloid nucleus, the substantia innominata, and the anterior portion of the lateral septal nucleus, the lateral preoptic area and zona incerta also send some projections to the PIL (Cservenak et al.,

2017a). Thus, the PIL is in optimal position to convey multimodal, somatosensory, auditory and possibly visual and viscerosensory information to upper brain sites.

2.4. Projections of TIP39 neurons in the PIL

TIP39 fibers are present in a variety of limbic, endocrine, nociceptive and auditory brain regions, including the medial prefrontal cortex, the nucleus accumbens, the lateral septum, the paraventricular thalamic nucleus, the fundus striati, the preoptic area (Fig. 3), the paraventricular hypothalamic (Fig. 3), dorsomedial and arcuate nuclei, the medial and central amygdaloid nuclei, the ventrolateral subdivision of the periaqueductal gray, deep layer of the superior and external cortex of the inferior colliculi, the lateral parabrachial nucleus, the locus coeruleus and subcoeruleus areas, the paraolivary nuclei, and the nucleus of the solitary tract. Disappearance of TIP39 fibers following lesions of TIP39 neuronal cell bodies suggested that thalamic TIP39 neurons project to limbic and hypothalamic regions of the forebrain (Dobolyi et al., 2003a; Palkovits et al., 2009b) while TIP39 neurons in the medial paralemniscal nucleus project to the lower brainstem (Dobolyi et al., 2003a). Subsequent retrograde tracer studies in mother rats (in which TIP39 is present, consequently identifiable in the PIL) determined that TIP39 neurons in the PIL project to the MPOA and to a lesser extent to the arcuate nucleus (Cservenák et al., 2013; Szabo et al., 2010) as well as to the PVN (Cservenak et al., 2017a). The distribution of TIP39 was similar to the distribution of retrogradely labeled neurons except for some retrogradely labeled cells lateral to the majority of TIP39 neurons. Furthermore, retrogradely labeled TIP39-negative cells were also present following all hypothalamic injections suggesting that neurons other than TIP39-positive ones also project to all these hypothalamic nuclei. It has not been directly determined whether a single TIP39 neuron projects to different target areas. However, the vast majority of TIP39 neurons were labeled following larger injections into both the MPOA and the PVN suggesting that at least some TIP39 neurons projects to both sites (Cservenak et al., 2017a; Cservenák et al., 2013). TIP39 neurons are likely excitatory glutamatergic as TIP39 neurons contain mRNA of vesicular glutamate transporter 2 but not that of glutamic acid decarboxylase (Cservenak et al., 2017a). In addition, TIP39 terminals contain glutamate and form conventional asymmetrical synapses on target neurons (Cservenak et al., 2017b).

3. Maternal behavior

Parental behaviors in humans are determined by complex regulatory mechanisms, which include emotional and cognitive neural processes. However, they also possess an instinctive component, which can be well studied in animal models (Lonstein and Fleming, 2002). In rodents, we can mostly speak about maternal behaviors as primarily mothers take care of the offspring in rats and mice (Dulac et al., 2014). Maternal behaviors can be divided into pup-directed behaviors (pup retrieval to the nest, anogenital licking of the pups, nursing postures, such as kyphosis), and additional behavioral changes including placentophagia immediately after parturition and increased food and fluid intake throughout lactation (Lonstein and Fleming, 2002; Numan and Insel, 2003). Maternal emotional changes include maternal aggression towards intruders, decreased anxiety in general, and reduced responsiveness of the hypothalamo-pituitary-adrenal axis in stress situations (Bosch and Neumann, 2012; Carter et al., 2001; Neumann, 2003). Maternal alterations also include hormonal changes,

such as the release of prolactin for lactation, driven by suppression of the dopaminergic neurons in the arcuate nucleus, which normally inhibits prolactin release from the pituitary (Freeman et al., 2000; Neville, 2006). Furthermore, GnRH secretion is suppressed during lactation leading to reduced estrogen serum level and lactational anoestrous characteristic of mothers (McNeilly, 2006).

3.1. Hormonal and neuronal inputs that induce maternal behaviors

In rats, maternal behaviors appear only at the end of pregnancy, initiated by the changes in concentrations of hormones associated with pregnancy and parturition. Estrogen levels are high throughout pregnancy while progesterone levels are also high but decrease in the last days of pregnancy. These changes in steroid hormone levels as well as elevated oxytocin and prolactin levels at parturition may also contribute to the appearance of maternal behaviors (Bridges et al., 1996; Knobil and Neill, 2006; Rilling and Young, 2014; Siegel, 1986). The action of these hormones likely involves the elimination of the inhibition of maternal behaviors evoked by pup odors (Numan and Insel, 2003). However, decreased levels of estrogen hormones are found throughout lactation (Lamming, 1994) and oxytocin and prolactin cannot maintain maternal behaviors in the absence of pup stimuli. In addition, the full range of maternal behaviors can be induced by prolonged pup exposure even in ovariectomized virgin females (Fleming and Rosenblatt, 1974; Rosenblatt, 1967). Somatosensory inputs from the nipples and ventral body surface evoked by suckling and pup exposure play the most important role in sensitization (Stern, 1989). The same somatosensory inputs are thought to maintain maternal behaviors in dams throughout the postpartum period (Febo et al., 2008; Numan and Woodside, 2010).

3.2. The preoptic area as a central element of maternal behavioral circuitry

The regulation and coordination of the above described maternal adaptations take place in the central nervous system. Several brain regions may be involved in specific aspects of maternal behaviors including the preoptic area, the lateral septum, the bed nucleus of the stria terminalis, the medial and cortical amygdaloid nuclei, the anteroventral periventricular nucleus, paraventricular hypothalamic nucleus (PVN), parts of the periaqueductal gray, the accumbens nucleus and the ventral tegmental area (Bridges, 2015; Numan and Young, 2016). The ventrolateral subdivision of the caudal periaqueductal grey, for example, has been shown to regulate kyphosis, the most effective body posture in rats for suckling pups, and maternal aggression (Lonstein et al., 1998). However, a number of different approaches provide convincing evidence that the preoptic area plays a central role in the initiation and maintenance of maternal behaviors (Dobolyi et al., 2014). Brain activity is elevated in the preoptic area in response to pup exposure based on immediate-early gene (Li et al., 1999; Lonstein et al., 1998; Stack and Numan, 2000), 2-deoxyglucose (Del Cerro et al., 1995) and fMRI techniques (Febo et al., 2005). The activated neurons in the preoptic area have a characteristic distribution. They are abundant in the medial preoptic nucleus (MPN), an area dorsolateral to the MPN, and also further dorsolaterally in the ventral subdivision of the bed nucleus of the stria terminalis (BNSTv) (Fleming et al., 1994; Kalinichev et al., 2000; Numan and Numan, 1995; Sheehan et al., 2000). These regions are often referred to as the medial preoptic area (MPOA). Electrical as well as axon-sparing excitotoxic lesions of the MPOA eliminate all maternal behaviors without affecting other, e.g. feeding, behaviors

(Gray and Brooks, 1984; Numan, 1986; Numan and Woodside, 2010) and similar effects were found following temporal pharmacological inactivation of MPOA (Arrati et al., 2006; Pereira and Morrell, 2009). In contrast to lesions, electrical stimulation of the MPOA increased maternal responsiveness (Morgan et al., 1997). Although additional preoptic neurons may also play a role in the control of maternal responsiveness, the involvement of the activated cells is particularly likely. The neurochemical characteristics of these maternally activated MPOA cells began to be explored recently. First, it was shown that the majority of them are GABAergic as they express glutamic acid decarboxylase (Lonstein and De Vries, 2000) even though the majority of the neurons in the MPOA are glutamatergic (Tsuneoka et al., 2013). Significant portions of the activated neurons also contained neuropeptides, specifically galanin, neurotensin, and/or tachykinin2 (Tsuneoka et al., 2013). Among these, the galanin neurons received particular attention because their manipulation strongly affected maternal behavior in mice. Their selective lesion markedly impaired parental responses while their optogenetic activation induced caring behavior even in males (Wu et al., 2014).

3.3. Anatomical pathways activating the preoptic maternal center

Despite all the advances on the control of maternal responsiveness, the available data are still scarce as to the neuronal input to the preoptic area that evokes and maintains maternal behaviors. The preoptic area receives olfactory input primarily through the medial amygdaloid nucleus, which may contribute to maternal behaviors (Walsh et al., 1996). However, maternal behaviors remain in the absence of olfactory input (Levy and Keller, 2009). In addition, neuronal activation in the preoptic area appears following suckling behavior (Fleming and Walsh, 1994; Hasen and Gammie, 2005; Lonstein et al., 1998), a response in which the role of the somatosensory suckling stimulus is not fully determined. When an anaesthetic was applied locally to the ventral region of the mother before suckling, c-Fos expression in MPOA was not decreased (Walsh et al., 1996). In turn, the combined elimination of both olfaction and ventral somatic sensory inputs in mothers decreased, but did not eliminate, c-Fos expression in MPOA (Numan and Numan, 1995). Moreover, c-Fos expression in the MPOA showed a significant increase in response to physical suckling stimulus, which would include exteroceptive sensory stimuli associated with pup exposure, compared with the patterns induced in response to pup exposure without physical contact (Li et al., 1999). These results are most consistent with the view that multiple sensory inputs from pups influence MPOA activation and maternal behavior. A number of brain regions projecting to the medial preoptic area have been identified in a detailed study on the afferent neuronal connections of the medial preoptic area (Simerly and Swanson, 1986). One of them, called the “central tegmental field” in that report, resembles a relay station of the milk-ejection reflex. Using the retrograde tracer, cholera toxin beta subunit, injected in the medial preoptic nucleus (Fig. 4), we suggested that the area identified as the posterior intralaminar complex of the thalamus (PIL) projects to the preoptic area, and that its neurons are activated by pup exposure in mother rats (Cservenák et al., 2013). Furthermore, we also showed that the same neurochemically identified neurons project to the paraventricular nucleus of the hypothalamus as well (Cservenak et al., 2017a).

4. The involvement of projections, and specifically TIP39-containing projections from the PIL in the control of maternal behaviors

4.1. Activation of neurons in the PIL of mother rats

The involvement of projections from the PIL to convey pup-driven somatosensory information to forebrain has been suggested by the activation of PIL neurons in mother rats. In 20-hour pup deprived rats, suckling induced marked c-Fos expression in the PIL (Cservenak et al., 2010). Pup exposure without physical contact elicited only a minimal c-Fos expression in the PIL suggesting that somatosensory input from the pups is required for robust activation (Cservenák et al., 2013). While Fos-ir neurons were evenly distributed within the PIL in the area where TIP39 neurons were present and also the area immediately lateral to it, almost none appeared in adjacent regions, implying that the PIL includes all pup-activated neurons in the area, which likely corresponds to the “lateral midbrain tegmentum” where c-Fos expressing neurons have been previously reported in response to suckling and during lactation (Li et al., 1999; Lin et al., 1998).

Almost all TIP39 neurons were activated by suckling, however, these cells accounted for only about a third of the activated neurons in the PIL, suggesting that not only TIP39 neurons are activated in the PIL of mothers (Cservenák et al., 2013). This finding raises the possibility that TIP39-positive and -negative PIL neurons could have similar but also distinct functions in the control of maternal behavior and maternal adaptations in general. Since our knowledge on the function of PIL projection neurons is minimal, their specific function should be addressed experimentally, for example using optogenetics in the future, as general somatosensory inputs, independent of TIP39 release, could drive aspects on maternal behavior via activation of PIL (Lonstein, 2005; Stern and Kolunie, 1993). Another critical study as to the mechanism of activation and maternal function of the TIP39 neurons specifically would be to determine whether thelectomy blocks the increased TIP39 expression in PIL of postpartum females. In rats, thelectomy does not interfere with maternal behavior (Numan and Numan, 1995) but could affect the induction of TIP39.

Pup exposure represents a complex stimulus for the mothers. Apart from nursing-related somatosensory inputs, visual, auditory, or olfactory exteroceptive stimuli, or hormonal changes associated with the presence of pups can induce maternal behaviors (Hashimoto et al., 2001; Terkel et al., 1979). Since the PIL receives auditory inputs (Cservenak et al., 2017b; Yasui et al., 1990), it is conceivable that auditory inputs from the pups also affects TIP39 neurons in the region. While physiologically relevant ultrasonic vocalization has not been tested, high-intensity auditory signal was shown to activate neurons in the PIL (Campeau and Watson, 2000), and specifically TIP39 neurons in the PIL allowing the possibility that pup-derived auditory input can be conveyed through these neurons as well (Palkovits et al., 2009a). Thus, TIP39 neurons in the PIL are ideally positioned to relay or even combine pup-derived somatosensory and auditory signals and transfer this information to the hypothalamus for maternal behaviors, and hormonal responses (Fig. 5).

4.2. Projections of TIP39 neurons to additional suckling-activated neurons in the forebrain

In the MPOA, the distribution of TIP39 fibers was very similar to that of c-Fos-positive neurons in pup-activated mothers. We used the potassium channel Kv2.1 to help define the plasma membrane, and showed that TIP39 containing fibers closely apposed c-Fos-expressing neurons in all regions of the MPOA (Cservenák et al., 2013). The percentage of Fos-expressing neurons that were closely apposed by TIP39 fibers was 78–85% depending on the specific MPOA region. As mentionned above, galanin neurons represent a large subclass of c-Fos-positive neurons in the MPOA whose crucial role in the control of maternal responsiveness has been demonstrated (Dulac et al., 2014; Wu et al., 2014). We determined that cell bodies of galanin neurons are closely apposed by TIP39 terminals. Furthermore, it was also demonstrated that galanin neurons are innervated by TIP39 projections as they contained TIP39-positive synapses (Cservenak et al., 2017b). We do not have direct evidence that galanin neurons contain the receptor of TIP39, the parathyroid hormone 2 receptor (PTH2 receptor). However, it was shown that the PTH2 receptor is present in the MPOA (Fig. 4B). Since PTH2 receptor-containing cell bodies are not reliably immunolabeled, X-gal histochemistry was used in mice expressing the beta-galactosidase enzyme driven be the PTH2 receptor promoter to describe the distribution of PTH2 receptor expressing neurons (Faber et al., 2007). This distribution was essentially identical to the distribution of PTH2 receptor mRNA expressing neurons detected by in situ hybridization histochemistry (Dobolyi et al., 2006a; Faber et al., 2007). Both methods suggest that the distribution of PTH2 receptors in the MPOA is similar to that of pup-induced c-Fos expressing neurons in the area.

4.3. Functional evidence of the role of TIP39 in the control of maternal motivation

To examine the function of TIP39, a peptide antagonist of the PTH2 receptor was developed (Kuo and Usdin, 2007) by modifying the sequence of TIP39 at 4 positions (HYWH-TIP39). The sequence encoding this antagonist was inserted into a lentivirus, which was injected into the preoptic area (Cservenák et al., 2013). The infected cells in the preoptic area–visualized by green fluorescent protein in the construct–secreted the antagonist continuously. The conditioned place preference test, used regularly in the study of addiction (Schwarz and Bilbo, 2013), is a particularly sensitive way to assess maternal motivation (Mattson et al., 2003; Seip and Morrell, 2009). Therefore, pup-conditioned place preference was used to evaluate a potential causal relationship between TIP39 signaling in MPOA and maternal motivation (Cservenák et al., 2013). The control virus-injected mothers spent significantly more time in the pup-associated cage than in the control cage (Cservenák et al., 2013) as expected from previous studies (Arrati et al., 2006; Pereira and Morrell, 2011), while nulliparous females did not show any significant cage preference suggesting a specific maternal effect. In contrast, the time spent in the different compartments, and also the number of animals demonstrating at least 20% difference between compartments did not differ for the mother rats infected with the antagonist producing virus (Cservenák et al., 2013) suggesting the involvement of the TIP39-PTH2 receptor system in pup attachement and maternal motivation. Fos-expressing neurons have been previously implicated in maternal motivation (Lonstein et al., 1998; Stack and Numan, 2000), probably via their projections to the nucleus accumbens and the ventral tegmental area (Numan et al., 2005). In addition, local preoptic injection of the virus did not affect serum prolactin levels arguing

against an indirect mechanism of action on maternal motivation via prolactin (Bridges et al., 1990), and further suggesting that preoptic TIP39 projections are involved in maternal motivation. The nature of this involvement, however, remains to be established. The treatment of the mother with the antagonist did not change retrieval behavior, suggesting that the primary appetitive aspect of maternal behaviour remained unaffected. Therefore, it is possible that the formation or retention of the conditioned place preference was influenced as inactivation of the MPOA is known to prevent the expression of preference for the pup-associated compartment (Pereira and Morrell, 2010). To address this question, acute injection of the PTH2 receptor antagonist into the MPOA would be necessary at different phases of the conditioning for pup-associated place preference, including its aquisition and its performance. In addition, the effect of thelectomy on the TIP39 system and the pup-associated place preference would also be relevant. It will be also interesting to investigate whether TIP39-positive and -negative projections of PIL are similarly or differentially involved in the formation of maternal attachment. These studies are now possible with novel viral tools available for the functional investigation of specific projections of overlapping cell populations (El-Shamayleh et al., 2016).

5. TIP39 projections from the PIL potentially regulate oxytocin neurons

5.1. The oxytocin neurons of the mammalian brain and their projections

Oxytocin neurons are found only in restricted parts of the hypothalamus, specifically in the paraventricular, supraoptic and so called accessory nuclei (Knobloch et al., 2012; Lee et al., 2009). There may be different types of oxytocin neurons, which possess different functions. The early studies distinguished magnocellular and parvocellular oxytocinergic neurons. Magnocellular neurons in both the supraoptic and paraventricular nuclei were suggested to project to the pituitary while parvocellular neurons to brain and spinal cord sites (Russell et al., 2003). Later on, magnocellular neurons were also shown to have collaterals with targets within the brain (Knobloch et al., 2012; Lee et al., 2009; Ross et al., 2009; Ross and Young, 2009). It is, however, very possible that different subclasses of oxytocin neurons exist as suggested by gene transcriptional (Romanov et al., 2017), and morphological/electrophysiological studies (Althammer and Grinevich, 2017; Eliava et al., 2016).

Extensive brain projections of oxytocin neurons were first expected based on the relatively widespread distribution of oxytocin receptors even though the presence of oxytocin immunoreactive fibers did not always match the location of the receptors (Bale et al., 2001; Trueta and De-Miguel, 2012). Recent connectivity data using molecular biological techniques suggested that oxytocin neurons project to these sites even if oxytocin cannot always be detected in them with immunohistochemical techniques (Grinevich et al., 2016). Our knowledge regarding the potentially diverse targets of the different oxytocin neurons is limited but the likely existence of several types of oxytocin neurons suggests that they may have different projections and functions in the central nervous system..

5.2. Inputs leading to oxytocin release

Oxytocin neurons are also known to have a variety of different inputs. These include hormonal inputs, as they possess prolactin and estrogen receptors (Kokay et al., 2006;

Laflamme et al., 1998). In fact, oxytocin neurons also contain oxytocin receptors, by which they may be synchronized following dendritic oxytocin release (Ludwig, 1998; Ludwig and Stern, 2015). In addition, oxytocin neurons also receive neuronal inputs. Studies using traditional retrograde tracers to establish afferent connections to the paraventricular nucleus (Campeau and Watson, 2000) provide limited information on specific inputs of oxytocin neurons as this nucleus, in addition to oxytocin neurons, also contains several different types of neurons with extensive inputs (Kiss, 1988). Despite the recent developments of methods allowing selective tracing of neuronal subtypes, however, selective inputs to oxytocin neurons, let alone to subtypes of oxytocin neurons have not been performed. Still, studies using anterograde tracers and describing synapses on oxytocin neurons identified a number of afferent projections to oxytocin neurons. Thus, oxytocin neurons receive glutamatergic, GABA-ergic, monoaminergic as well as peptidergic inputs (Brown et al., 2013). These inputs may provide information on salt-water balance, food intake and metabolic status, stress, as well as reproductive and social environment (Brown et al., 2013). In addition, signal from peripheral osmo- and baroreceptors can reach oxytocin neurons via visceral sensory centers of the brainstem, such as the A1 and A2 noradrenergic cell group (Sawchenko and Swanson, 1982). Since drugs acting on adrenergic receptors (mostly alpha 2 type) can affect oxytocin release during stress (Lipinska et al., 2008; Onaka, 2004) and reproductive situations as well (Bealer et al., 2010; Brunton and Russell, 2008b; Russell et al., 2008), brainstem nuclei containing monoaminergic cells including the nucleus of the solitary tract have been implicated in oxytocin release (Bealer and Crowley, 1998). However, more detailed analysis of the pathways leading to oxytocin release under reproductive circumstances suggests that they are not restricted to the ascending noradrenergic system.

Neuronal pathways activating the oxytocin system were first addressed by investigating the milk ejection reflex in animals. Suckling induces milk ejection, which was possible to measure simply by looking at the presence of milk in the stomach of previously fasted pups (Knaggs et al., 1972; Tindal et al., 1967). Later, intramammary pressure, or directly, blood oxytocin levels were measured for more precise analysis of the reflex (Dubois-Dauphin et al., 1985a; Hansen and Kohler, 1984; Wang et al., 1995). Importantly, pups would suckle even an anaesthetized mother, which allowed different manipulations, such as lesions and electrophysiological stimulation and/or recording in the mother’s nervous system (Fukuoka et al., 1984; Tindal and Knaggs, 1975). Any resulting deficit in milk ejection was confirmed with the peripheral addition of exogenous oxytocin as positive control. These approaches determined that the dorsal column-medial lemniscal system and the major thalamic relay station of spinal somatosensory stimuli, the ventral posterolateral nucleus were not involved in the milk-ejection reflex (Dubois-Dauphin et al., 1985b). Rather, the information in the mammary nerves is conveyed in the dorsal column of the spinal cord and ascends in the lateral funiculus (Fukuoka et al., 1984). It may relay in the lateral cervical nucleus and the superior and inferior colliculi (Dubois-Dauphin et al., 1985a, b). The pathway then unites in the lateral tegmentum of the midbrain because small lesions in this area block the milk ejection reflex (Juss and Wakerley, 1981). While lesions can determine the path of the projections, they are less suitable to determine the position of the relay neurons as destruction of fibers also eliminates the reflex response. In turn, neuronal cell bodies are more sensitive to low intensity microstimulation than fibers. Using this technique, an area

ventromedial to the medial geniculate body, but not the caudally located lateral midbrain tegmentum, was determined to contain effective injection sites of the milk-ejection reflex (Fig. 6A), while bilateral transection of the lateral tegmentum immediately caudal to this site also blocked milk ejection (Tindal and Knaggs, 1971, 1975). Chemical lesions of the area ventromedial to the medial geniculate body (called “peripeduncular nucleus” in the original paper), which preserves fibers but eliminates cell bodies inhibited lactation (Factor et al., 1993), further suggesting the presence of relay neurons at this position (Fig. 6B). Studies using neuronal tracers also supported that this area (called “parvicellular division of the subparafascicular and posterior intralaminar nuclei” and “lateral zona incerta”) projects to the paraventricular (Campeau and Watson, 2000), and supraoptic nuclei (Tribollet et al., 1985), respectively (Fig. 6C,D). The position of the brain sites that control milk ejection in these experiments is very similar to, and possibly overlapping with that of the PIL (Fig. 1,4,6). Therefore, we propose here that it is the same brain area, which is activated by suckling and is involved in the transmission of this information to promote maternal behaviors as well as oxytocin release, the latter leading to milk ejection and indirect enhancement of maternal behaviors (Okabe et al., 2017). We believe that the PIL is a complex brain region at the border of the diencephalon and mesencephalon making it difficult to precisely identify, which could be the reason of the different names in previous literature. In turn, the complexity of the area makes it also possible that its different parts may be involved in different functions. Specifically, it is possible that some neurons in the PIL regulate maternal behaviors while others are involved only in milk-ejection reflex.

5.3. TIP39 inputs of oxytocin neurons

TIP39 fibers and PTH2 receptors are present in the hypothalamic paraventricular and supraoptic nuclei (Fig. 4). PTH2 receptors are particularly abundant in the PVN (Dobolyi et al., 2012; Dobolyi et al., 2006a) where TIP39 terminals approach oxytocin neurons (Cservenak et al., 2017a). The number of close appositions between TIP39 terminals and oxytocin cell bodies is on average two per cell. Furthermore, the existence of synaptic contact has also been demonstrated with electron microscopy (Cservenak et al., 2017a) providing strong evidence for extensive innervation of oxytocin neurons by TIP39 terminals suggesting that TIP39 may have functional significance in the control of oxytocin release during lactation. Since the body weight of (even cross fostered) pups is reduced in the absence of a functional PTH2 receptor gene in mice (Coutellier et al., 2011b), a role of the TIP39-PTH2 receptor system in oxytocin release is likely. However, we do not have direct evidence for that, a question that should be addressed in the future. Furthermore, TIP39 neurons represent only a portion of PIL neurons that project to the PVN. In fact, the PIL probably corresponds to the relay station of the milk-ejection reflex based on the topographic localizations (see in 5.2.). Thus, all the relay neurons present in the PIL may have an even more significant role in the regulation of oxytocin release than only TIP39 neurons, an intriguing point, which also remains to be established. If functionally different oxytocin cell subclasses exist as described in 5.1, then a further complexity is possible as different cell populations in the PIL could innervate different types of oxytocin cells in the hypothalamus. Thus, it is possible that PIL neurons represent a significant mechanism for regulating the oxytocin system beyond motherhood, in a broad range of social context,

perhaps independently of TIP39. Future optogenetic studies are needed to explore this possibility.

6. Additional maternal adaptations of the brain and their potential control by TIP39-containing projections from the PIL

There is direct and indirect evidence that TIP39 may play a role in additional maternal adaptations, warranting further investigation of its role in modulating the maternal brain. Apart from the preoptic area and paraventricular hypothalamic nuclei, TIP39 terminals are present in some additional hypothalamic sites, including the arcuate nucleus (Dobolyi et al., 2003b), which is known to control prolactin release (Grattan, 2015). In fact, there is some evidence available that TIP39 is involved in suckling-induced prolactin release. Injection of the above described (see 4.3.) PTH2 receptor antagonist (Kuo and Usdin, 2007) HYWH-TIP39 into the cerebral ventricle dose-dependently inhibited suckling-induced prolactin release suggesting that TIP39 plays a physiological role in the regulation of prolactin secretion (Cservenak et al., 2010). Injection of a virus directly into the mediobasal hypothalamus, thereby producing the antagonist locally, also reduced suckling-induced prolactin release suggesting a local effect in the mediobasal hypothalamus (Cservenák et al., 2013). However, anatomical evidence suggests that TIP39 neurons do not directly act on dopaminergic neurons in the arcuate nucleus. Rather, TIP39 may excite local interneurons, which in turn inhibit tuberoinfundibular dopamine neurons to induce prolactin release from the pituitary (Cservenak et al., 2010).

The core body temperature of mothers is increased, particularly in the postpartum period (Eliason and Fewell, 1997; Gamo et al., 2016). Since TIP39 was suggested to increase body temperature in male mice and provide some protection in cold environment (Dimitrov et al., 2011), its role was tested in mothers as well. Evidence using mice lacking the PTH2 receptor suggests that TIP39 contributes to the elevated core body temperature of mothers (Gellen et al., 2017).

Direct functional evidence of the involvement of the TIP39-PTH2 receptor neuromodulator system is not available regarding other changes in the maternal brain. However, indirect data obtained in males suggest that TIP39 could have additional functions in mothers as well. A reduced anxiety is present during the postpartum period, possibly to better cope with increasing burden of raising the litter (Hillerer et al., 2011; Silva et al., 1997) while anti-depression-like behavior of rodent mothers has also been reported (Lonstein et al., 2014; Maguire and Mody, 2008). Since TIP39 injection into the cerebral ventricle caused anxiolytic- and antidepression-like effects in rats (LaBuda et al., 2004) while mice lacking TIP39 signaling showed increased anxiety (Coutellier et al., 2011a; Fegley et al., 2008), it is possible that maternally induced TIP39 may contribute to reduced anxiety- and depression-like behaviors in mothers. Stress coping strategies are also altered during late pregnancy and postpartum: mother rats demonstrate reduced responsiveness of the hypothalamo-pituitary-adrenal (HPA) axis including diminished synthesis and release of corticotropin releasing hormone (Carter et al., 2001; Neumann, 2001, 2003). Suckling was suggested to drive the hyporesponsiveness of the HPA axis in the postpartum period (Brunton and Russell, 2008a).

The involvement of TIP39 in this potential maternal alteration is conceivable because corticotropin-releasing hormone-containing neurons are affected by TIP39 in male mice (Dimitrov and Usdin, 2010).

There are additional maternal alterations where no functional evidence is available on the role of the TIP39-PTH2 receptor neuromodulator system, but the presence of TIP39 terminals and PTH2 receptor-expressing neurons form an anatomical basis of a potential functions that should be examined in future studies. For example, the suppression of GnRH secretion and consequently reduced estrogen level leading to lactational anoestrous is characteristic in mothers (McNeilly, 2006). The central common pathways for the regulation of GnRH neurons are kisspeptin neurons (Clarke et al., 2015; Uenoyama et al., 2016) located in the anteroventral periventricular and arcuate nuclei (Javed et al., 2015). Lactational anoestrus is primarily driven by the suckling stimulus during the first half of lactation and by negative energy balance during its second half (Tsukamura and Maeda, 2001) mediated by the kisspeptin system (Smith et al., 2010; Topaloglu et al., 2010). Since PTH2 receptors and TIP39 terminals are present in both the anteroventral periventricular and arcuate nuclei (Dobolyi et al., 2006a), it seems conceivable that TIP39-containing projections from the PIL could affect GnRH secretion via the kisspeptin neurons and play a role in lactational anoestrus.

Another specific behavioral characteristic of mothers is maternal aggression, that is defense of the litter by attacking a male intruder.. It is possible that TIP39 could affect maternal aggression as TIP39 fibers have been described in several nuclei, including the lateral septum, the paraventricular hypothalamic nucleus, and the ventral mamillary nucleus, which are involved in maternal aggression (Bosch and Neumann, 2012; Carter et al., 2001; Neumann, 2003). In fact, a previous study using partial lesions of the area corresponding to the PIL (Fig. 6) demonstrated impairment in both lactation and maternal aggression (Factor et al., 1993), suggesting common mechanisms at this level of processing. In turn, other postpartum maternal behaviors were not affected. It is conceivable, that the TIP39 could affect maternal aggression via the oxytocin system as it was recently demonstrated that oxytocin affects maternal aggression, probably via projections to the central amygdaloid nucleus (Bosch and Neumann, 2012). Therefore, it can be hypothesized that TIP39-mediated general somatosensory inputs from pups evoke oxytocin release in central amygdaloid nucleus to influence maternal aggression. To test this hypothesis, it would be interesting to inject TIP39 antagonist into the PVN to measure potential blockade of the occurrence of maternal aggression in postpartum rats, while also measuring other aspects of maternal behavior.

7. Potential non-maternal functions of TIP39 neurons in the PIL

7.1. Sexual activity

Sexual reflexes are driven by spinal reflexes with substantial descending control in both males and females (Pfaus, 1999). However, there is information related to sexual activity, which should be transferred to the brain via ascending pathways, such as reward value (Matthews et al., 2005), the initiation of post-ejaculatory interval (Schober and Pfaff, 2007) (Veening et al.), or attachment to the mate characteristic in monogamous species (Amadei et

al., 2017; Johnson and Young, 2015). One candidate for a forebrain relay station of sexual reflexes is the so-called peripeduncular area because electric stimulation applied to pudendal nerve evoked field potentials as well as single unit responses in this brain region (Carrer, 1978). Furthermore, lesion or synaptic blockade of this area eliminated female sexual behavior (Hansen and Gummesson, 1982; Lopez and Carrer, 1985a, b) as well as male sexual behavior (Hansen and Gummesson, 1982; Hansen and Kohler, 1984). Another previously suggested diencephalic relay station is the parvicellular subparafascicular nucleus, which was implicated in the processing of sensory information related to mating and ejaculation (Coolen et al., 2004). The activation of its neurons requires ejaculation in male rats while only sexual intercourse in females but the topographical localization of activated neurons is the same in both sexes (Veening et al.). Furthermore, the location of the brain region avtivated during sexual behavior is very similar to the PIL suggesting that some parts of the PIL could also be involved in conveying ascending sexual information following sexual intercourse. The activated neurons following male ejaculation were shown to contain TIP39 (Wang et al., 2006) arguing that they in fact may be the same cell types activated in mothers as well.

7.2. Oxytocin release following sexual intercourse

Oxytocin neurons are activated and oxytocin is released during sexual intercourse (Carmichael et al., 1987; Pfaus and Heeb, 1997; Ross et al., 2009; Waldherr and Neumann, 2007) suggesting that information from genitalia can reach oxytocin neurons in the hypothalamus. Experimental investigation of this neuronal pathway is more difficult than that of the milk ejection because sexual intercourse requires behaving, conscious animals. Therefore, the pathway is not fully established yet. It is, however, possible that the pathway from the genitalia joins the pathway from the nipples before reaching the paraventricular and supraoptic nuclei, specifically, they could both relay in the PIL. This hypothesis is supported by the finding that elimination of relay neurons in this area by electrolytic lesions (Hansen and Gummesson, 1982) or by local injections of ibotenic acid inhibited male ejaculation as well as the milk-ejection reflex in females (Hansen and Kohler, 1984) suggesting that the neuronal pathways conveying these types of information are convergent at this level of the brain to the same neurons, or the relay neurons are closely located in the area.

7.3. Non-reproductive social situations

Apart from reproductive actions, oxytocin can also be released in non-sexual social situations (Light et al., 2005; Nagasawa et al., 2015; Uvnas-Moberg, 1998). The type of sensory input that leads to oxytocin release can vary under social circumstances. Olfactory input may play an important role (Stoop, 2016) as oxytocin neurons receive input from the olfactory bulb, which could play a role in relaying olfactory information in a social situation (Gur et al., 2014). Auditory and visual inputs may also be important, especially in human. They could be transmitted to oxytocin neurons from the limbic system, e.g. through prefrontal cortical projections to the oxytocin neurons (Brown et al., 2013). In addition, affective somatosensory inputs play an important but sometimes not sufficiently emphasized role in oxytocin release as sensory nerve stimulation in anaesthetized animals can raise plasma oxytocin levels (Stock and Uvnas-Moberg, 1988). Pain as a stressor has long been known to induce oxytocin release (Neumann, 2002), however, affective touch (McGlone et

al.), such as strokes or massage have also been reported to increase oxytocin levels (Kurosawa et al., 1995; Lund et al., 2002). They may be important in mother/father–infant relations (Barrett et al., 2015; Matthiesen et al., 2001), which suggests the relevance of physical contact between the parents and their child, too. Very little is known about how affective somatosensory input reaches oxytocin neurons in adult-adult contexts or how they affect the social brain network directly. However, we recently demonstrated that TIP39 neurons in the PIL are activated in response to social situations. To avoid stress and aggression, familiar female rats were separated for a day. Following their reunion, significant c-fos activation was present in the PIL of both females (Cservenak et al., 2017a). Since TIP39 cannot be very well visualized in non-maternal females, the c-fos activated neurons were double labeled with calbindin, a marker of PIL neurons (see in 3.2.). Indeed, most of the c-fos activated neurons following the reunion of the females were calbindin-positive (Cservenak et al., 2017a). These findings suggest that PIL neurons, partly those that would be expressing TIP39 in mothers, may relay input, which can contribute to the activation of oxytocin neurons or directly the social brain network in non-reproductive social situations. Thus, it is possible that the same thalamus relay circuit that is critical for pup-induced activation of maternal responsiveness and oxytocin release supporting the milk ejection reflex my play a more general role in socially mediated oxytocin release in non-parental context. If this is the case, the PIL represents a novel relay center that not only is involved in transducing pup stimuli to regulate maternal neuroendocrinology and behavior, but may play an important, yet unexplored role in evoking oxytocin release in more general social contexts to influence a host of oxytocin-dependent social behaviors ranging from social bonding to empathetic consoling behavior. If true, this is consistent with previous assertions that the neural circuits underlying maternal responsiveness have become evolutionarily generalized to influence broader social bonding behaviors ranging from empathy and pair bonding to romantic attachment (Young, 2009; Young and Alexander, 2012). Further, as oxytocin is a strong candidate for improving social cognition in psychiatric disorders such as autism (Young and Barrett, 2015), the PIL TIP39 neurons represent a potential target for evoking endogenous oxytocin release in a clinical setting. Future studies should examine the role of the PIL relay in stimulating non-parental, socially-evoked central oxytocin release as well as consider the translational implications of stimulating the oxytocin system through targeted PIL circuit manipulations.

8. Conclusions

Different aspects of maternal behaviors are driven by sensory inputs from the pups. Somatosensory inputs including suckling play an essential part in the different components of maternal behaviors. In addition, auditory input may also be involved in eliciting maternal behaviors. The PIL, located in the posterior thalamus may integrate these inputs. It seems likely that TIP39 projections from the PIL participate in more than one of the above listed regulations and even a single TIP39 cell can have multiple functions. It raises the important question how the different functions can be independently regulated if they receive the same input. Since neither the cell-specific inputs nor the projections of TIP39 neurons and other projections neurons of the PIL are known at present, we can only speculate that the target areas determine how they interpret the incoming information from the PIL depending on

their state and/or the hormonal status of the animal. The fact that PIL neurons use a peptide, TIP39, suggest that their influence on the target areas depends on the state of motherhood as TI39 is expressed only during this period in adult female rats. TIP39 is an ideal candidate for this task as neuropeptides are signaling molecules in the nervous system that typically have slow actions but play important neuromodulatory functions during adaptive processes.

Although parental care in human is more complex than in animals as it involves emotional and cognitive cortical functions, the role of PIL in conveying somatosensory information may still be important in human as well. Touch evokes oxytocin release and physical contact with babies may contribute to parental attachment. Indeed, both TIP39 and the PTH2 receptor have a similar distribution in human and macaque as in rodents (Bagó et al., 2009). Such similarities between distributional patterns in the brains of primates and rodents have often been reported for other neuropeptides and neuropeptide receptors suggesting similar functions in different species (de Lacalle and Saper, 2000; Kostich et al., 2004). These data support the idea that the TIP39-PTH2 receptor system may also be involved in similar functions. However, judgment about the relevance of particular observations made in rodents to humans obviously requires detailed consideration of the specific functions and structures. Given the enthusiasm for targeting the oxytocin system in psychiatry (Shamay-Tsoory and Young, 2016), the PIL TIP39 circuit should be more intensively investigated as a potential entry point to manipulate the oxytocin system to enhance social cognition and behavior to explore its translational potential beyond the context of the maternal brain.

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References

Althammer F, Grinevich V. Diversity of oxytocin neurons: beyond magno- and parvocellular cell types? J Neuroendocrinol. 2017

Amadei EA, Johnson ZV, Jun Kwon Y, Shpiner AC, Saravanan V, Mays WD, Ryan SJ, Walum H, Rainnie DG, Young LJ, Liu RC. Dynamic corticostriatal activity biases social bonding in monogamous female prairie voles. Nature. 2017; 546:297–301. [PubMed: 28562592]

Arrati PG, Carmona C, Dominguez G, Beyer C, Rosenblatt JS. GABA receptor agonists in the medial preoptic area and maternal behavior in lactating rats. Physiol Behav. 2006; 87:51–65. [PubMed: 16297940]

Bagó AG, Dimitrov E, Saunders R, Seress L, Palkovits M, Usdin TB, Dobolyi A. Parathyroid hormone 2 receptor and its endogenous ligand tuberoinfundibular peptide of 39 residues are concentrated in endocrine, viscerosensory and auditory brain regions in macaque and human. Neuroscience. 2009; 162:128–147. [PubMed: 19401215]

Bale TL, Davis AM, Auger AP, Dorsa DM, McCarthy MM. CNS region-specific oxytocin receptor expression: importance in regulation of anxiety and sex behavior. J Neurosci. 2001; 21:2546–2552. [PubMed: 11264328]

Barrett CE, Arambula SE, Young LJ. The oxytocin system promotes resilience to the effects of neonatal isolation on adult social attachment in female prairie voles. Transl Psychiatry. 2015; 5:e606. [PubMed: 26196439]

Bealer SL, Armstrong WE, Crowley WR. Oxytocin release in magnocellular nuclei: neurochemical mediators and functional significance during gestation. Am J Physiol Regul Integr Comp Physiol. 2010; 299:R452–458. [PubMed: 20554931]

Bealer SL, Crowley WR. Noradrenergic control of central oxytocin release during lactation in rats. Am J Physiol. 1998; 274:E453–458. [PubMed: 9530128]

Bosch OJ, Neumann ID. Both oxytocin and vasopressin are mediators of maternal care and aggression in rodents: from central release to sites of action. Horm Behav. 2012; 61:293–303. [PubMed: 22100184]

Brenner D, Bago AG, Gallatz K, Palkovits M, Usdin TB, Dobolyi A. Tuberoinfundibular peptide of 39 residues in the embryonic and early postnatal rat brain. J Chem Neuroanat. 2008; 36:59–68. [PubMed: 18495420]

Bridges RS. Neuroendocrine regulation of maternal behavior. Front Neuroendocrinol. 2015; 36:178–196. [PubMed: 25500107]

Bridges RS, Numan M, Ronsheim PM, Mann PE, Lupini CE. Central prolactin infusions stimulate maternal behavior in steroid-treated, nulliparous female rats. Proc Natl Acad Sci U S A. 1990; 87:8003–8007. [PubMed: 2236014]

Bridges RS, Robertson MC, Shiu RPC, Friesen HG, Stuer AM, Mann PE. Endocrine communication between conceptus and mother: Placental lactogen stimulation of maternal behavior. Neuroendocrinology. 1996; 64:57–64. [PubMed: 8811667]

Brown CH, Bains JS, Ludwig M, Stern JE. Physiological regulation of magnocellular neurosecretory cell activity: integration of intrinsic, local and afferent mechanisms. J Neuroendocrinol. 2013; 25:678–710. [PubMed: 23701531]

Brunton PJ, Russell JA. The expectant brain: adapting for motherhood. Nat Rev Neurosci. 2008a; 9:11–25. [PubMed: 18073776]

Brunton PJ, Russell JA. Keeping oxytocin neurons under control during stress in pregnancy. Prog Brain Res. 2008b; 170:365–377. [PubMed: 18655896]

Burbach JPH, Young LJ, Russell JA. Oxytocin: Synthesis, Secretion, and Reproductive Functions. In: Neill JD, editorKnobil and Neill′s Physiology of Reproduction. Academic Press; Oxford: 2006.

Burkett JP, Andari E, Johnson ZV, Curry DC, de Waal FB, Young LJ. Oxytocin-dependent consolation behavior in rodents. Science. 2016; 351:375–378. [PubMed: 26798013]

Campeau S, Watson SJ Jr. Connections of some auditory-responsive posterior thalamic nuclei putatively involved in activation of the hypothalamo-pituitary-adrenocortical axis in response to audiogenic stress in rats: an anterograde and retrograde tract tracing study combined with Fos expression. J Comp Neurol. 2000; 423:474–491. [PubMed: 10870087]

Carmichael MS, Humbert R, Dixen J, Palmisano G, Greenleaf W, Davidson JM. Plasma oxytocin increases in the human sexual response. J Clin Endocrinol Metab. 1987; 64:27–31. [PubMed: 3782434]

Carrer HF. Mesencephalic participation in the control of sexual behavior in the female rat. J Comp Physiol Psychol. 1978; 92:877–887. [PubMed: 569667]

Carter CS, Altemus M, Chrousos GP. Neuroendocrine and emotional changes in the post-partum period. Prog Brain Res. 2001; 133:241–249. [PubMed: 11589134]

Clarke H, Dhillo WS, Jayasena CN. Comprehensive Review on Kisspeptin and Its Role in Reproductive Disorders. Endocrinol Metab (Seoul). 2015; 30:124–141. [PubMed: 26194072]

Coolen LM, Allard J, Truitt WA, McKenna KE. Central regulation of ejaculation. Physiol Behav. 2004; 83:203–215. [PubMed: 15488540]

Coolen LM, Veening JG, Petersen DW, Shipley MT. Parvocellular subparafascicular thalamic nucleus in the rat: anatomical and functional compartmentalization. J Comp Neurol. 2003; 463:117–131.

Coutellier L, Logemann A, Kuo J, Rusnak M, Usdin TB. TIP39 modulates effects of novelty-induced arousal on memory. Genes Brain Behav. 2011a; 10:90–99. [PubMed: 20796031]

Coutellier L, Logemann A, Rusnak M, Usdin TB. Maternal absence of the parathyroid hormone 2 receptor affects postnatal pup development. J Neuroendocrinol. 2011b; 23:612–619. [PubMed: 21535248]

Cservenak M, Bodnar I, Usdin TB, Palkovits M, Nagy GM, Dobolyi A. Tuberoinfundibular peptide of 39 residues is activated during lactation and participates in the suckling-induced prolactin release in rat. Endocrinology. 2010; 151:5830–5840. [PubMed: 20861230]

Cservenak M, Keller D, Kis V, Fazekas EA, Ollos H, Leko AH, Szabo ER, Renner E, Usdin TB, Palkovits M, Dobolyi A. A Thalamo-Hypothalamic Pathway That Activates Oxytocin Neurons in Social Contexts in Female Rats. Endocrinology. 2017a; 158:335–348. [PubMed: 27841935]

Cservenak M, Kis V, Keller D, Dimen D, Menyhart L, Olah S, Szabo ER, Barna J, Renner E, Usdin TB, Dobolyi A. Maternally involved galanin neurons in the preoptic area of the rat. Brain Struct Funct. 2017b; 222:781–798. [PubMed: 27300187]

Cservenák M, Szabó TR, Bodnár I, Lékó A, Palkovits M, Nagy GM, Usdin TB, Dobolyi A. Thalamic neuropeptide mediating the effects of nursing on lactation and maternal motivation. Psychoneuroendocrinology. 2013; 38:3070–3084. [PubMed: 24094875]

de Lacalle S, Saper CB. Calcitonin gene-related peptide-like immunoreactivity marks putative visceral sensory pathways in human brain. Neuroscience. 2000; 100:115–130. [PubMed: 10996463]

Del Cerro MC, Perez Izquierdo MA, Rosenblatt JS, Johnson BM, Pacheco P, Komisaruk BR. Brain 2-deoxyglucose levels related to maternal behavior-inducing stimuli in the rat. Brain Res. 1995; 696:213–220. [PubMed: 8574672]

Dimitrov E, Usdin TB. Tuberoinfundibular peptide of 39 residues modulates the mouse hypothalamic-pituitary-adrenal axis via paraventricular glutamatergic neurons. J Comp Neurol. 2010; 518:4375–4394. [PubMed: 20853513]

Dimitrov EL, Kim YY, Usdin TB. Regulation of hypothalamic signaling by tuberoinfundibular peptide of 39 residues is critical for the response to cold: a novel peptidergic mechanism of thermoregulation. J Neurosci. 2011; 31:18166–18179. [PubMed: 22159128]

Dobolyi A, Dimitrov E, Palkovits M, Usdin TB. The neuroendocrine functions of the parathyroid hormone 2 receptor. Front Endocrinol (Lausanne). 2012; 3:121. [PubMed: 23060860]

Dobolyi A, Grattan DR, Stolzenberg DS. Preoptic inputs and mechanisms that regulate maternal responsiveness. J Neuroendocrinol. 2014; 26:627–640. [PubMed: 25059569]

Dobolyi A, Irwin S, Makara G, Usdin TB, Palkovits M. Calcitonin gene-related peptide-containing pathways in the rat forebrain. J Comp Neurol. 2005; 489:92–119. [PubMed: 15977170]

Dobolyi A, Irwin S, Wang J, Usdin TB. The distribution and neurochemistry of the parathyroid hormone 2 receptor in the rat hypothalamus. Neurochem Res. 2006a; 31:227–236. [PubMed: 16570212]

Dobolyi A, Palkovits M, Bodnar I, Usdin TB. Neurons containing tuberoinfundibular peptide of 39 residues project to limbic, endocrine, auditory and spinal areas in rat. Neuroscience. 2003a; 122:1093–1105. [PubMed: 14643775]

Dobolyi A, Palkovits M, Usdin TB. Expression and distribution of tuberoinfundibular peptide of 39 residues in the rat central nervous system. J Comp Neurol. 2003b; 455:547–566. [PubMed: 12508326]

Dobolyi A, Palkovits M, Usdin TB. The TIP39-PTH2 receptor system: unique peptidergic cell groups in the brainstem and their interactions with central regulatory mechanisms. Prog Neurobiol. 2010; 90:29–59. [PubMed: 19857544]

Dobolyi A, Ueda H, Uchida H, Palkovits M, Usdin TB. Anatomical and physiological evidence for involvement of tuberoinfundibular peptide of 39 residues in nociception. Proc Natl Acad Sci U S A. 2002; 99:1651–1656. [PubMed: 11818570]

Dobolyi A, Wang J, Irwin S, Usdin TB. Postnatal development and gender-dependent expression of TIP39 in the rat brain. J Comp Neurol. 2006b; 498:375–389. [PubMed: 16871538]

Dubois-Dauphin M, Armstrong WE, Tribollet E, Dreifuss JJ. Somatosensory systems and the milk-ejection reflex in the rat. I. Lesions of the mesencephalic lateral tegmentum disrupt the reflex and damage mesencephalic somatosensory connections. Neuroscience. 1985a; 15:1111–1129. [PubMed: 3840236]

Dubois-Dauphin M, Armstrong WE, Tribollet E, Dreifuss JJ. Somatosensory systems and the milk-ejection reflex in the rat. II. The effects of lesions in the ventroposterior thalamic complex, dorsal columns and lateral cervical nucleus-dorsolateral funiculus. Neuroscience. 1985b; 15:1131–1140. [PubMed: 3840237]

Dulac C, O'Connell LA, Wu Z. Neural control of maternal and paternal behaviors. Science. 2014; 345:765–770. [PubMed: 25124430]

El-Shamayleh Y, Ni AM, Horwitz GD. Strategies for targeting primate neural circuits with viral vectors. J Neurophysiol. 2016; 116:122–134. [PubMed: 27052579]

Eliason HL, Fewell JE. Thermoregulatory control during pregnancy and lactation in rats. J Appl Physiol (1985). 1997; 83:837–844. [PubMed: 9292471]

Eliava M, Melchior M, Knobloch-Bollmann HS, Wahis J, da Silva Gouveia M, Tang Y, Ciobanu AC, Triana Del Rio R, Roth LC, Althammer F, Chavant V, Goumon Y, Gruber T, Petit-Demouliere N, Busnelli M, Chini B, Tan LL, Mitre M, Froemke RC, Chao MV, Giese G, Sprengel R, Kuner R, Poisbeau P, Seeburg PH, Stoop R, Charlet A, Grinevich V. A New Population of Parvocellular Oxytocin Neurons Controlling Magnocellular Neuron Activity and Inflammatory Pain Processing. Neuron. 2016; 89:1291–1304. [PubMed: 26948889]

Faber CA, Dobolyi A, Sleeman M, Usdin TB. Distribution of tuberoinfundibular peptide of 39 residues and its receptor, parathyroid hormone 2 receptor, in the mouse brain. J Comp Neurol. 2007; 502:563–583. [PubMed: 17394159]

Factor EM, Mayer AD, Rosenblatt JS. Peripeduncular nucleus lesions in the rat: I. Effects on maternal aggression, lactation, and maternal behavior during pre- and postpartum periods. Behav Neurosci. 1993; 107:166–185. [PubMed: 8447950]

Febo M, Numan M, Ferris CF. Functional magnetic resonance imaging shows oxytocin activates brain regions associated with mother-pup bonding during suckling. J Neurosci. 2005; 25:11637–11644. [PubMed: 16354922]

Febo M, Stolberg TL, Numan M, Bridges RS, Kulkarni P, Ferris CF. Nursing stimulation is more than tactile sensation: It is a multisensory experience. Horm Behav. 2008; 54:330–339. [PubMed: 18440003]

Fegley DB, Holmes A, Riordan T, Faber CA, Weiss JR, Ma S, Batkai S, Pacher P, Dobolyi A, Murphy A, Sleeman MW, Usdin TB. Increased fear- and stress-related anxiety-like behavior in mice lacking tuberoinfundibular peptide of 39 residues. Genes Brain Behav. 2008; 7:933–942. [PubMed: 18700839]

Feldman R, Monakhov M, Pratt M, Ebstein RP. Oxytocin pathway genes: evolutionary ancient system impacting on human affiliation, sociality, and psychopathology. Biol Psychiatry. 2016; 79:174–184. [PubMed: 26392129]

Ferguson JN, Aldag JM, Insel TR, Young LJ. Oxytocin in the medial amygdala is essential for social recognition in the mouse. J Neurosci. 2001; 21:8278–8285. [PubMed: 11588199]

Fleming AS, Rosenblatt JS. Maternal behavior in the virgin and lactating rat. J Comp Physiol Psychol. 1974; 86:957–972. [PubMed: 4833599]

Fleming AS, Suh EJ, Korsmit M, Rusak B. Activation of Fos-like immunoreactivity in the medial preoptic area and limbic structures by maternal and social interactions in rats. Behav Neurosci. 1994; 108:724–734. [PubMed: 7986366]

Fleming AS, Walsh C. Neuropsychology of maternal behavior in the rat: c-fos expression during mother-litter interactions. Psychoneuroendocrinology. 1994; 19:429–443. [PubMed: 7938344]

Freeman ME, Kanyicska B, Lerant A, Nagy G. Prolactin: structure, function, and regulation of secretion. Physiol Rev. 2000; 80:1523–1631. [PubMed: 11015620]

Fukuoka T, Negoro H, Honda K, Higuchi T, Nishida E. Spinal pathway of the milk-ejection reflex in the rat. Biol Reprod. 1984; 30:74–81. [PubMed: 6696966]

Gamo Y, Bernard A, Troup C, Munro F, Derrer K, Jeannesson N, Campbell A, Gray H, Miller J, Dixon J, Mitchell SE, Hambly C, Vaanholt LM, Speakman JR. Limits to sustained energy intake XXIV: impact of suckling behaviour on the body temperatures of lactating female mice. Sci Rep. 2016; 6:25665. [PubMed: 27157478]

Gellen B, Zelena D, Usdin TB, Dobolyi A. The parathyroid hormone 2 receptor participates in physiological and behavioral alterations of mother mice. Physiol Behav. 2017; 181:51–58. [PubMed: 28890271]

Goodson JL. The vertebrate social behavior network: evolutionary themes and variations. Horm Behav. 2005; 48:11–22. [PubMed: 15885690]

Grattan DR. The hypothalamo-prolactin axis. Journal of Endocrinology. 2015; 226:T101–T122. [PubMed: 26101377]

Gray P, Brooks PJ. Effect of lesion location within the medial preoptic-anterior hypothalamic continuum on maternal and male sexual behaviors in female rats. Behav Neurosci. 1984; 98:703–711. [PubMed: 6540591]

Grinevich V, Knobloch-Bollmann HS, Eliava M, Busnelli M, Chini B. Assembling the puzzle: pathways of oxytocin signaling in the brain. Biol Psychiatry. 2016; 79:155–164. [PubMed: 26001309]

Gur R, Tendler A, Wagner S. Long-term social recognition memory is mediated by oxytocin-dependent synaptic plasticity in the medial amygdala. Biol Psychiatry. 2014; 76:377–386. [PubMed: 24787950]

Hansen S, Gummesson BM. Participation of the lateral midbrain tegmentum in the neuroendocrine control of sexual behavior and lactation in the rat. Brain Res. 1982; 251:319–325. [PubMed: 7139329]

Hansen S, Kohler C. The importance of the peripeduncular nucleus in the neuroendocrine control of sexual behavior and milk ejection in the rat. Neuroendocrinology. 1984; 39:563–572. [PubMed: 6440046]

Hasen NS, Gammie SC. Differential fos activation in virgin and lactating mice in response to an intruder. Physiol Behav. 2005; 84:681–695. [PubMed: 15885244]

Hashimoto H, Saito TR, Furudate S, Takahashi KW. Prolactin levels and maternal behavior induced by ultrasonic vocalizations of the rat pup. Exp Anim. 2001; 50:307–312. [PubMed: 11515093]

Hillerer KM, Reber SO, Neumann ID, Slattery DA. Exposure to chronic pregnancy stress reverses peripartum-associated adaptations: implications for postpartum anxiety and mood disorders. Endocrinology. 2011; 152:3930–3940. [PubMed: 21846798]

Hung LW, Neuner S, Polepalli JS, Beier KT, Wright M, Walsh JJ, Lewis EM, Luo L, Deisseroth K, Dolen G, Malenka RC. Gating of social reward by oxytocin in the ventral tegmental area. Science. 2017; 357:1406–1411. [PubMed: 28963257]

Javed Z, Qamar U, Sathyapalan T. The role of kisspeptin signalling in the hypothalamic-pituitary-gonadal axis--current perspective. Endokrynol Pol. 2015; 66:534–547. [PubMed: 26662653]

John MR, Arai M, Rubin DA, Jonsson KB, Juppner H. Identification and characterization of the murine and human gene encoding the tuberoinfundibular peptide of 39 residues. Endocrinology. 2002; 143:1047–1057. [PubMed: 11861531]

Johnson ZV, Young LJ. Neurobiological mechanisms of social attachment and pair bonding. Curr Opin Behav Sci. 2015; 3:38–44. [PubMed: 26146650]

Juss TS, Wakerley JB. Mesencephalic areas controlling pulsatile oxytocin release in the suckled rat. J Endocrinol. 1981; 91:233–244. [PubMed: 7299324]

Kalinichev M, Rosenblatt JS, Nakabeppu Y, Morrell JI. Induction of c-fos-like and fosB-like immunoreactivity reveals forebrain neuronal populations involved differentially in pup-mediated maternal behavior in juvenile and adult rats. J Comp Neurol. 2000; 416:45–78. [PubMed: 10578102]

Kiss JZ. Dynamism of chemoarchitecture in the hypothalamic paraventricular nucleus. Brain Res Bull. 1988; 20:699–708. [PubMed: 3044519]

Knaggs GS, McNeilly AS, Tindal JS. The afferent pathway of the milk-ejection reflex in the mid-brain of the goat. J Endocrinol. 1972; 52:333–341. [PubMed: 5062727]

Knobil E, Neill JD. Knobil and Neill's Physiology of Reproduction. Academic Press; San Diego: 2006.

Knobloch HS, Charlet A, Hoffmann LC, Eliava M, Khrulev S, Cetin AH, Osten P, Schwarz MK, Seeburg PH, Stoop R, Grinevich V. Evoked axonal oxytocin release in the central amygdala attenuates fear response. Neuron. 2012; 73:553–566. [PubMed: 22325206]

Knobloch HS, Grinevich V. Evolution of oxytocin pathways in the brain of vertebrates. Front Behav Neurosci. 2014; 8:31. [PubMed: 24592219]

Kokay IC, Bull PM, Davis RL, Ludwig M, Grattan DR. Expression of the long form of the prolactin receptor in magnocellular oxytocin neurons is associated with specific prolactin regulation of oxytocin neurons. Am J Physiol Regul Integr Comp Physiol. 2006; 290:R1216–1225. [PubMed: 16410399]

Kostich WA, Grzanna R, Lu NZ, Largent BL. Immunohistochemical visualization of corticotropin-releasing factor type 1 (CRF1) receptors in monkey brain. J Comp Neurol. 2004; 478:111–125. [PubMed: 15349973]

Kuo J, Usdin TB. Development of a rat parathyroid hormone 2 receptor antagonist. Peptides. 2007; 28:887–892. [PubMed: 17207559]

Kurosawa M, Lundeberg T, Agren G, Lund I, Uvnas-Moberg K. Massage-like stroking of the abdomen lowers blood pressure in anesthetized rats: influence of oxytocin. J Auton Nerv Syst. 1995; 56:26–30. [PubMed: 8786276]

LaBuda CJ, Dobolyi A, Usdin TB. Tuberoinfundibular peptide of 39 residues produces anxiolytic and antidepressant actions. Neuroreport. 2004; 15:881–885. [PubMed: 15073536]

Laflamme N, Nappi RE, Drolet G, Labrie C, Rivest S. Expression and neuropeptidergic characterization of estrogen receptors (ERalpha and ERbeta) throughout the rat brain: anatomical evidence of distinct roles of each subtype. J Neurobiol. 1998; 36:357–378. [PubMed: 9733072]

Lamming GE. Marshall's Physiology of Reproduction. Vol. 3. Chapman & Hall; London: 1994.

Lee HJ, Macbeth AH, Pagani JH, Young WS 3rd. Oxytocin: the great facilitator of life. Prog Neurobiol. 2009; 88:127–151. [PubMed: 19482229]

Leng G, Meddle SL, Douglas AJ. Oxytocin and the maternal brain. Curr Opin Pharmacol. 2008; 8:731–734. [PubMed: 18656552]

Levy F, Keller M. Olfactory mediation of maternal behavior in selected mammalian species. Behav Brain Res. 2009; 200:336–345. [PubMed: 19146885]

Li C, Chen P, Smith MS. Neural populations in the rat forebrain and brainstem activated by the suckling stimulus as demonstrated by cFos expression. Neuroscience. 1999; 94:117–129. [PubMed: 10613502]

Li K, Nakajima M, Ibanez-Tallon I, Heintz N. A Cortical Circuit for Sexually Dimorphic Oxytocin-Dependent Anxiety Behaviors. Cell. 2016; 167:60–72. e11. [PubMed: 27641503]

Light KC, Grewen KM, Amico JA. More frequent partner hugs and higher oxytocin levels are linked to lower blood pressure and heart rate in premenopausal women. Biol Psychol. 2005; 69:5–21. [PubMed: 15740822]

Lin SH, Miyata S, Matsunaga W, Kawarabayashi T, Nakashima T, Kiyohara T. Metabolic mapping of the brain in pregnant, parturient and lactating rats using fos immunohistochemistry. Brain Res. 1998; 787:226–236. [PubMed: 9518626]

Lipinska S, Ebrowska-Badalla A, Lipinska J. Vasopressin and oxytocin release into CSF after sympathetic stimulation in rat. Endocr Regul. 2008; 42:77–78. [PubMed: 18624610]

Lonstein JS. Reduced anxiety in postpartum rats requires recent physical interactions with pups, but is independent of suckling and peripheral sources of hormones. Horm Behav. 2005; 47:241–255. [PubMed: 15708752]

Lonstein JS, De Vries GJ. Maternal behaviour in lactating rats stimulates c-fos in glutamate decarboxylase-synthesizing neurons of the medial preoptic area, ventral bed nucleus of the stria terminalis, and ventrocaudal periaqueductal gray. Neuroscience. 2000; 100:557–568. [PubMed: 11098119]

Lonstein JS, Fleming AS. Parental behaviors in rats and mice. Curr Protoc Neurosci. 2002; Chapter 8(Unit 8):15.

Lonstein JS, Maguire J, Meinlschmidt G, Neumann ID. Emotion and mood adaptations in the peripartum female:complementary contributions of GABA and oxytocin. J Neuroendocrinol. 2014; 26:649–664. [PubMed: 25074620]

Lonstein JS, Simmons DA, Swann JM, Stern JM. Forebrain expression of c-fos due to active maternal behaviour in lactating rats. Neuroscience. 1998; 82:267–281. [PubMed: 9483519]

Lopez HS, Carrer HF. Evidence for peripeduncular neurons having a role in the control of feminine sexual behavior in the rat. Physiol Behav. 1985a; 35:205–208. [PubMed: 4070384]

Lopez HS, Carrer HF. Further studies on peripeduncular-hypothalamic pathways involved in sexual behavior in the female rat. Exp Neurol. 1985b; 88:241–252. [PubMed: 3987855]

Ludwig M. Dendritic release of vasopressin and oxytocin. J Neuroendocrinol. 1998; 10:881–895. [PubMed: 9870745]

Ludwig M, Stern J. Multiple signalling modalities mediated by dendritic exocytosis of oxytocin and vasopressin. Philos Trans R Soc Lond B Biol Sci. 2015:370.

Lund I, Ge Y, Yu LC, Uvnas-Moberg K, Wang J, Yu C, Kurosawa M, Agren G, Rosen A, Lekman M, Lundeberg T. Repeated massage-like stimulation induces long-term effects on nociception: contribution of oxytocinergic mechanisms. Eur J Neurosci. 2002; 16:330–338. [PubMed: 12169113]

Maguire J, Mody I. GABA(A)R plasticity during pregnancy: relevance to postpartum depression. Neuron. 2008; 59:207–213. [PubMed: 18667149]

Marlin BJ, Mitre M, D'Amour JA, Chao MV, Froemke RC. Oxytocin enables maternal behaviour by balancing cortical inhibition. Nature. 2015; 520:499–504. [PubMed: 25874674]

Matthews TJ, Abdelbaky P, Pfaff DW. Social and sexual motivation in the mouse. Behav Neurosci. 2005; 119:1628–1639. [PubMed: 16420165]

Matthiesen AS, Ransjo-Arvidson AB, Nissen E, Uvnas-Moberg K. Postpartum maternal oxytocin release by newborns: effects of infant hand massage and sucking. Birth. 2001; 28:13–19. [PubMed: 11264623]

Mattson BJ, Williams SE, Rosenblatt JS, Morrell JI. Preferences for cocaine- or pup-associated chambers differentiates otherwise behaviorally identical postpartum maternal rats. Psychopharmacology (Berl). 2003; 167:1–8. [PubMed: 12607073]

McGlone F, Wessberg J, Olausson H. Discriminative and affective touch: sensing and feeling. Neuron. 82:737–755.

McNeilly AS. Suckling and the Control of Gonadotropin Secretion. In: Neill JD, editorKnobil and Neill′s Physiology of Reproduction. Academic Press; Oxford: 2006.

Mitre M, Marlin BJ, Schiavo JK, Morina E, Norden SE, Hackett TA, Aoki CJ, Chao MV, Froemke RC. A distributed network for social cognition enriched for oxytocin receptors. J Neurosci. 2016; 36:2517–2535. [PubMed: 26911697]

Morgan HD, Watchus JA, Fleming AS. The effects of electrical stimulation of the medial preoptic area and the medial amygdala on maternal responsiveness in female rats. Ann N Y Acad Sci. 1997; 807:602–605. [PubMed: 9071410]

Nagasawa M, Mitsui S, En S, Ohtani N, Ohta M, Sakuma Y, Onaka T, Mogi K, Kikusui T. Social evolution. Oxytocin-gaze positive loop and the coevolution of human-dog bonds. Science. 2015; 348:333–336. [PubMed: 25883356]

Neumann ID. Alterations in behavioral and neuroendocrine stress coping strategies in pregnant, parturient and lactating rats. Prog Brain Res. 2001; 133:143–152. [PubMed: 11589127]

Neumann ID. Involvement of the brain oxytocin system in stress coping: interactions with the hypothalamo-pituitary-adrenal axis. Prog Brain Res. 2002; 139:147–162. [PubMed: 12436933]

Neumann ID. Brain mechanisms underlying emotional alterations in the peripartum period in rats. Depress Anxiety. 2003; 17:111–121. [PubMed: 12768645]

Neumann ID. Brain oxytocin: a key regulator of emotional and social behaviours in both females and males. J Neuroendocrinol. 2008; 20:858–865. [PubMed: 18601710]

Neville MC. Lactation and Its Hormonal Control. In: Neill JD, editorPhysiology of Reproduction. Academic Press; Amsterdam: 2006. 2993–3054.

Numan M. The role of the medial preoptic area in the regulation of maternal behavior in the rat. Ann N Y Acad Sci. 1986; 474:226–233. [PubMed: 3555225]

Numan M, Insel TR. The Neurobiology of Parental Behavior. Springer; New York: 2003.

Numan M, Numan MJ. Importance of pup-related sensory inputs and maternal performance for the expression of Fos-like immunoreactivity in the preoptic area and ventral bed nucleus of the stria terminalis of postpartum rats. Behav Neurosci. 1995; 109:135–149. [PubMed: 7734069]

Numan M, Numan MJ, Schwarz JM, Neuner CM, Flood TF, Smith CD. Medial preoptic area interactions with the nucleus accumbens-ventral pallidum circuit and maternal behavior in rats. Behav Brain Res. 2005; 158:53–68. [PubMed: 15680194]

Numan M, Woodside B. Maternity: neural mechanisms, motivational processes, and physiological adaptations. Behav Neurosci. 2010; 124:715–741. [PubMed: 21133530]

Numan M, Young LJ. Neural mechanisms of mother-infant bonding and pair bonding: Similarities, differences, and broader implications. Horm Behav. 2016; 77:98–112. [PubMed: 26062432]

Okabe S, Tsuneoka Y, Takahashi A, Ooyama R, Watarai A, Maeda S, Honda Y, Nagasawa M, Mogi K, Nishimori K, Kuroda M, Koide T, Kikusui T. Pup exposure facilitates retrieving behavior via the oxytocin neural system in female mice. Psychoneuroendocrinology. 2017; 79:20–30. [PubMed: 28246032]

Onaka T. Neural pathways controlling central and peripheral oxytocin release during stress. J Neuroendocrinol. 2004; 16:308–312. [PubMed: 15089967]

Palkovits M, Dobolyi A, Helfferich F, Usdin TB. Acute loud noise activates TIP39-immunoreactive neurons in the rat brain. Brain Structure and Function. 2009a Submitted.

Palkovits M, Usdin T, Dobolyi A. TIP39-immunoreactive input to the hypothalamic nuclei in rats. Neuroscience. 2009b In preparation.

Paxinos G, Watson C. The rat brain in stereotaxic coordinates. Academic Press; San Diego: 2007.

Pereira M, Morrell JI. The changing role of the medial preoptic area in the regulation of maternal behavior across the postpartum period: facilitation followed by inhibition. Behav Brain Res. 2009; 205:238–248. [PubMed: 19549547]

Pereira M, Morrell JI. The medial preoptic area is necessary for motivated choice of pup- over cocaine-associated environments by early postpartum rats. Neuroscience. 2010; 167:216–231. [PubMed: 20156528]

Pereira M, Morrell JI. Functional mapping of the neural circuitry of rat maternal motivation: effects of site-specific transient neural inactivation. J Neuroendocrinol. 2011; 23:1020–1035. [PubMed: 21815954]

Pfaus JG. Neurobiology of sexual behavior. Curr Opin Neurobiol. 1999; 9:751–758. [PubMed: 10607643]

Pfaus JG, Heeb MM. Implications of immediate-early gene induction in the brain following sexual stimulation of female and male rodents. Brain Res Bull. 1997; 44:397–407. [PubMed: 9370204]

Rich ME, deCardenas EJ, Lee HJ, Caldwell HK. Impairments in the initiation of maternal behavior in oxytocin receptor knockout mice. PLoS One. 2014; 9:e98839. [PubMed: 24892749]

Rilling JK, Young LJ. The biology of mammalian parenting and its effect on offspring social development. Science. 2014; 345:771–776. [PubMed: 25124431]

Romanov RA, Zeisel A, Bakker J, Girach F, Hellysaz A, Tomer R, Alpar A, Mulder J, Clotman F, Keimpema E, Hsueh B, Crow AK, Martens H, Schwindling C, Calvigioni D, Bains JS, Mate Z, Szabo G, Yanagawa Y, Zhang MD, Rendeiro A, Farlik M, Uhlen M, Wulff P, Bock C, Broberger C, Deisseroth K, Hokfelt T, Linnarsson S, Horvath TL, Harkany T. Molecular interrogation of hypothalamic organization reveals distinct dopamine neuronal subtypes. Nat Neurosci. 2017; 20:176–188. [PubMed: 27991900]

Rosenblatt JS. Nonhormonal basis of maternal behavior in the rat. Science. 1967; 156:1512–1514. [PubMed: 5611028]

Ross HE, Cole CD, Smith Y, Neumann ID, Landgraf R, Murphy AZ, Young LJ. Characterization of the oxytocin system regulating affiliative behavior in female prairie voles. Neuroscience. 2009; 162:892–903. [PubMed: 19482070]

Ross HE, Young LJ. Oxytocin and the neural mechanisms regulating social cognition and affiliative behavior. Front Neuroendocrinol. 2009; 30:534–547. [PubMed: 19481567]

Royle NJ, Russell AF, Wilson AJ. The evolution of flexible parenting. Science. 2014; 345:776–781. [PubMed: 25124432]

Russell JA, Douglas AJ, Brunton PJ. Reduced hypothalamo-pituitary-adrenal axis stress responses in late pregnancy: central opioid inhibition and noradrenergic mechanisms. Ann N Y Acad Sci. 2008; 1148:428–438. [PubMed: 19120138]

Russell JA, Leng G, Douglas AJ. The magnocellular oxytocin system, the fount of maternity: adaptations in pregnancy. Front Neuroendocrinol. 2003; 24:27–61. [PubMed: 12609499]

Sawchenko PE, Swanson LW. The organization of noradrenergic pathways from the brainstem to the paraventricular and supraoptic nuclei in the rat. Brain Res. 1982; 257:275–325. [PubMed: 6756545]

Schober JM, Pfaff D. The neurophysiology of sexual arousal. Best Pract Res Clin Endocrinol Metab. 2007; 21:445–461. [PubMed: 17875491]

Schwarz JM, Bilbo SD. Adolescent morphine exposure affects long-term microglial function and later-life relapse liability in a model of addiction. J Neurosci. 2013; 33:961–971. [PubMed: 23325235]

Seip KM, Morrell JI. Transient inactivation of the ventral tegmental area selectively disrupts the expression of conditioned place preference for pup- but not cocaine-paired contexts. Behav Neurosci. 2009; 123:1325–1338. [PubMed: 20001116]

Shamay-Tsoory S, Young LJ. Understanding the Oxytocin System and Its Relevance to Psychiatry. Biol Psychiatry. 2016; 79:150–152. [PubMed: 26723107]

Sheehan TP, Cirrito J, Numan MJ, Numan M. Using c-Fos immunocytochemistry to identify forebrain regions that may inhibit maternal behavior in rats. Behav Neurosci. 2000; 114:337–352. [PubMed: 10832795]

Siegel HI. Hormonal basis of maternal behavior in the rat. Ann N Y Acad Sci. 1986; 474:202–215. [PubMed: 3555222]

Silva MR, Bernardi MM, Nasello AG, Felicio LF. Influence of lactation on motor activity and elevated plus maze behavior. Braz J Med Biol Res. 1997; 30:241–244. [PubMed: 9239311]

Simerly RB, Swanson LW. The organization of neural inputs to the medial preoptic nucleus of the rat. J Comp Neurol. 1986; 246:312–342. [PubMed: 3517086]

Smith MS, True C, Grove KL. The neuroendocrine basis of lactation-induced suppression of GnRH: role of kisspeptin and leptin. Brain Res. 2010; 1364:139–152. [PubMed: 20727862]

Stack EC, Numan M. The temporal course of expression of c-Fos and Fos B within the medial preoptic area and other brain regions of postpartum female rats during prolonged mother--young interactions. Behav Neurosci. 2000; 114:609–622. [PubMed: 10883811]

Stern JM. Maternal Behavior: Sensory, Hormonal and Neural Determinants. In: Brush FR, Levine AS, editorsPsychoendocrinology. Academic Press; San Diego: 1989. 103–226.

Stern JM, Kolunie JM. Maternal aggression of rats is impaired by cutaneous anesthesia of the ventral trunk, but not by nipple removal. Physiol Behav. 1993; 54:861–868. [PubMed: 8248374]

Stock S, Uvnas-Moberg K. Increased plasma levels of oxytocin in response to afferent electrical stimulation of the sciatic and vagal nerves and in response to touch and pinch in anaesthetized rats. Acta Physiol Scand. 1988; 132:29–34. [PubMed: 3223304]

Stoop R. Sniffing and Oxytocin: Effects on Olfactory Memories. Neuron. 2016; 90:431–433. [PubMed: 27151635]

Szabo FK, Snyder N, Usdin TB, Hoffman GE. A direct neuronal connection between the subparafascicular and ventrolateral arcuate nuclei in non-lactating female rats. Could this pathway play a role in the suckling-induced prolactin release? Endocrine. 2010; 37:62–70. [PubMed: 20963557]

Terkel J, Damassa DA, Sawyer CH. Ultrasonic cries from infant rats stimulate prolactin release in lactating mothers. Horm Behav. 1979; 12:95–102. [PubMed: 478446]

Tindal JS, Knaggs GS. Determination of the detailed hypothalamic route of the milk-ejection reflex in the guinea-pig. J Endocrinol. 1971; 50:135–152. [PubMed: 5580822]

Tindal JS, Knaggs GS. Further studies on the afferent path of the milk-ejection reflex in the brain stem of the rabbit. J Endocrinol. 1975; 66:107–113. [PubMed: 1165431]

Tindal JS, Knaggs GS, Turvey A. The afferent path of the milk-ejection reflex in the brain of the guinea-pig. J Endocrinol. 1967; 38:337–349. [PubMed: 6067503]

Topaloglu AK, Kotan LD, Yuksel B. Neurokinin B signalling in human puberty. J Neuroendocrinol. 2010; 22:765–770. [PubMed: 20456599]

Tribollet E, Armstrong WE, Dubois-Dauphin M, Dreifuss JJ. Extra-hypothalamic afferent inputs to the supraoptic nucleus area of the rat as determined by retrograde and anterograde tracing techniques. Neuroscience. 1985; 15:135–148. [PubMed: 4010932]

Trueta C, De-Miguel FF. Extrasynaptic exocytosis and its mechanisms: a source of molecules mediating volume transmission in the nervous system. Front Physiol. 2012; 3:319. [PubMed: 22969726]

Tsukamura H, Maeda K. Non-metabolic and metabolic factors causing lactational anestrus: rat models uncovering the neuroendocrine mechanism underlying the suckling-induced changes in the mother. Prog Brain Res. 2001; 133:187–205. [PubMed: 11589130]

Tsuneoka Y, Maruyama T, Yoshida S, Nishimori K, Kato T, Numan M, Kuroda KO. Functional, anatomical, and neurochemical differentiation of medial preoptic area subregions in relation to maternal behavior in the mouse. J Comp Neurol. 2013; 521:1633–1663. [PubMed: 23124836]

Uenoyama Y, Pheng V, Tsukamura H, Maeda KI. The roles of kisspeptin revisited: inside and outside the hypothalamus. J Reprod Dev. 2016; 62:537–545. [PubMed: 27478063]

Usdin TB, Dobolyi A. TIP39 (Tuberoinfundibular peptide 39). In: Squire LR, editorEncyclopedia of Neuroscience. Vol. 9. Academic Press; Oxford: 2009. 1009–1017.

Usdin TB, Hoare SR, Wang T, Mezey E, Kowalak JA. TIP39: a new neuropeptide and PTH2-receptor agonist from hypothalamus. Nat Neurosci. 1999; 2:941–943. [PubMed: 10526330]

Uvnas-Moberg K. Oxytocin may mediate the benefits of positive social interaction and emotions. Psychoneuroendocrinology. 1998; 23:819–835. [PubMed: 9924739]

Varga T, Mogyorodi B, Bago AG, Cservenak M, Domokos D, Renner E, Gallatz K, Usdin TB, Palkovits M, Dobolyi A. Paralemniscal TIP39 is induced in rat dams and may participate in maternal functions. Brain Struct Funct. 2012; 217:323–335. [PubMed: 22081168]

Varga T, Palkovits M, Usdin TB, Dobolyi A. The medial paralemniscal nucleus and its afferent neuronal connections in rat. J Comp Neurol. 2008; 511:221–237. [PubMed: 18770870]

Veening JG, Coolen LM, Gerrits PO. Neural mechanisms of female sexual behavior in the rat; comparison with male ejaculatory control. Pharmacol Biochem Behav. 121:16–30.

Waldherr M, Neumann ID. Centrally released oxytocin mediates mating-induced anxiolysis in male rats. Proc Natl Acad Sci U S A. 2007; 104:16681–16684. [PubMed: 17925443]

Walsh CJ, Fleming AS, Lee A, Magnusson JE. The effects of olfactory and somatosensory desensitization on Fos-like immunoreactivity in the brains of pup-exposed postpartum rats. Behav Neurosci. 1996; 110:134–153. [PubMed: 8652063]

Wang J, Coolen LM, Brown JL, Usdin TB. Neurons containing tuberoinfundibular peptide of 39 residues are activated following male sexual behavior. Neuropeptides. 2006

Wang T, Palkovits M, Rusnak M, Mezey E, Usdin TB. Distribution of parathyroid hormone-2 receptor-like immunoreactivity and messenger RNA n the rat nervous system. Neuroscience. 2000; 100:629–649. [PubMed: 11098126]

Wang YF, Negoro H, Honda K. Effects of hemitransection of the midbrain on milk-ejection burst of oxytocin neurones in lactating rat. J Endocrinol. 1995; 144:463–470. [PubMed: 7738471]

Wu Z, Autry AE, Bergan JF, Watabe-Uchida M, Dulac CG. Galanin neurons in the medial preoptic area govern parental behaviour. Nature. 2014; 509:325–330. [PubMed: 24828191]

Yasui Y, Kayahara T, Nakano K, Mizuno N. The subparafascicular thalamic nucleus of the rat receives projection fibers from the inferior colliculus and auditory cortex. Brain Res. 1990; 537:323–327. [PubMed: 1707732]

Young LJ. Being human: love: neuroscience reveals all. Nature. 2009; 457:148. [PubMed: 19129828]

Young LJ, Alexander B. Current. New York: 2012. The Chemistry Between us: Love, Sex and the Science of Attraction.

Young LJ, Barrett CE. Neuroscience. Can oxytocin treat autism? Science. 2015; 347:825–826. [PubMed: 25700501]

Highlights

- The posterior intralaminar complex of the thalamus (PIL) conveys suckling information to the forebrain
- Tuberoinfundibular peptide 39 (TIP39) is induced in the PIL of lactating mother rats
- TIP39-containing terminals innervate oxytocin neurons and galanin neurons in the preoptic area
- The PIL may correspond to the lateral subparafascicular area activated by sexual activity
- PIL neurons are activated by social stimuli and may be involved in social cue evoked oxytocin release

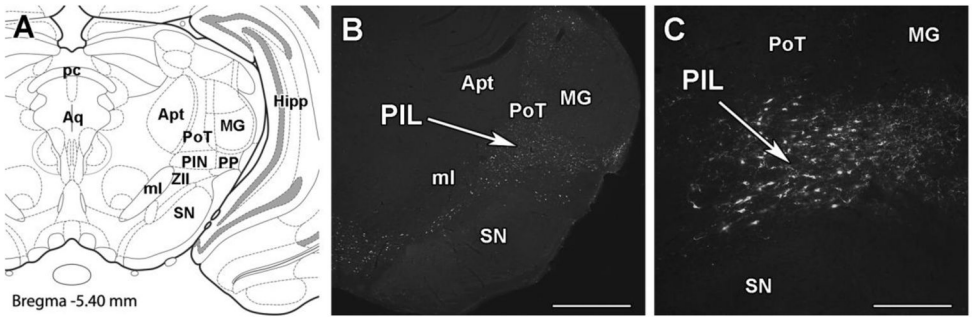

Fig. 1.

The posterior intralaminar complex of the thalamus (PIL). A: A schematic drawing from the Paxinos rat atlas demonstrates the nuclei in the region (Paxinos and Watson, 2007). B: Calbindin immunolabeling shows the distribution of calbindin-positive cell bodies in the PIL as well as in some of the surrounding nuclei including the triangular subdivision of the posterior thalamic nucleus (PoT), and the peripeduncular area (PP). However, the substantia nigra (SN), the medial geniculate body (MG) and the anterior pretectal area (Apt) are mostly devoid of calbindin immunoreactivity. C: TIP39 immunoreactivity is present in the PIL of a mother rat. TIP39-ir cell bodies are mostly located in the medial part of the PIL while TIP39-ir fibers are also visible in the lateral PIL. Additional abbreviations: Aq–cerebral aqueduct, Hipp–hippocampus, ml–medial lemniscus, pc–posterior commissure, PIN–posterior thalamic nucleus, ZIl–zona incerta pars lateralis. Scale bar = 1 mm for B and 400 μm for C. The figure was created from the material presented in our previous paper (Cservenak et al., 2017a).

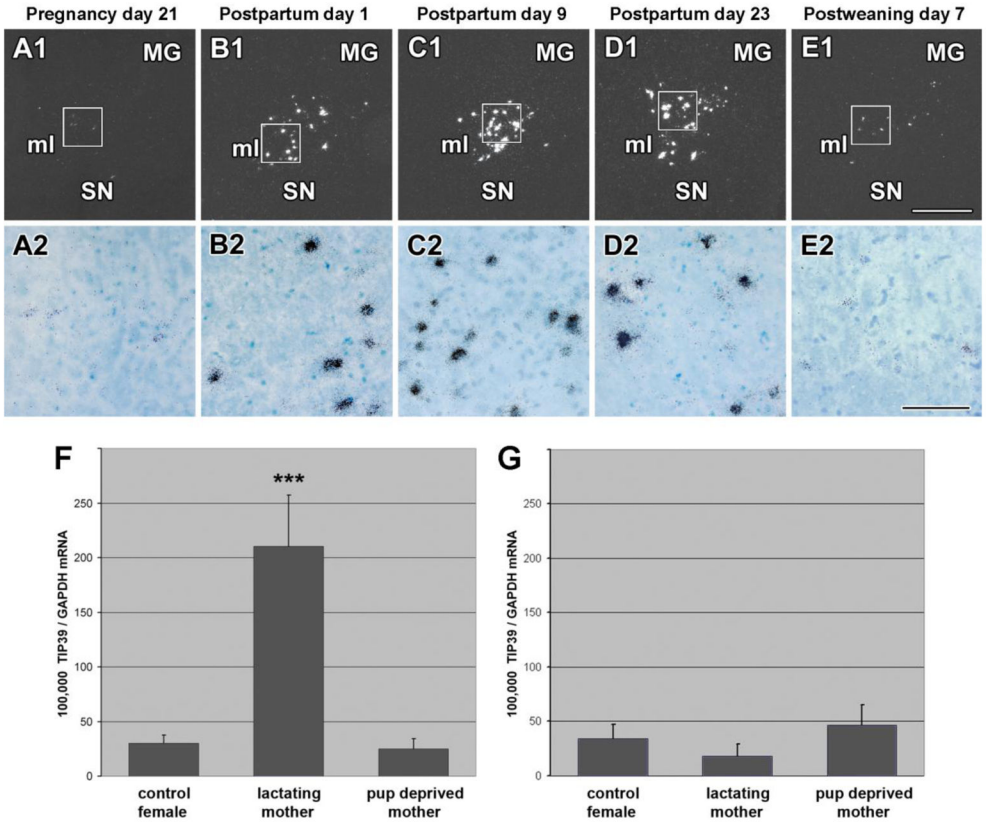

Fig. 2.

Expression level of TIP39. A–E: Low magnification dark- and high magnification bright-field images of sections are shown at the level of the PIL visualized with in situ hybridization histochemistry for TIP39. The framed areas in upper panels are shown in the lower panels. F: RT-PCR data confirm the induction of TIP39 in the PIL. G: TIP39 mRNA level is not elevated in the periventricular gray of the thalamus during lactation. Abbreviations: MG–medial geniculate body, ml–medial lemniscus, SN–substantia nigra. Scale bar = 500 μm for E1 and 100 μm for E2. The figure was adapted from our previous papers (Cservenak et al., 2010; Cservenák et al., 2013).

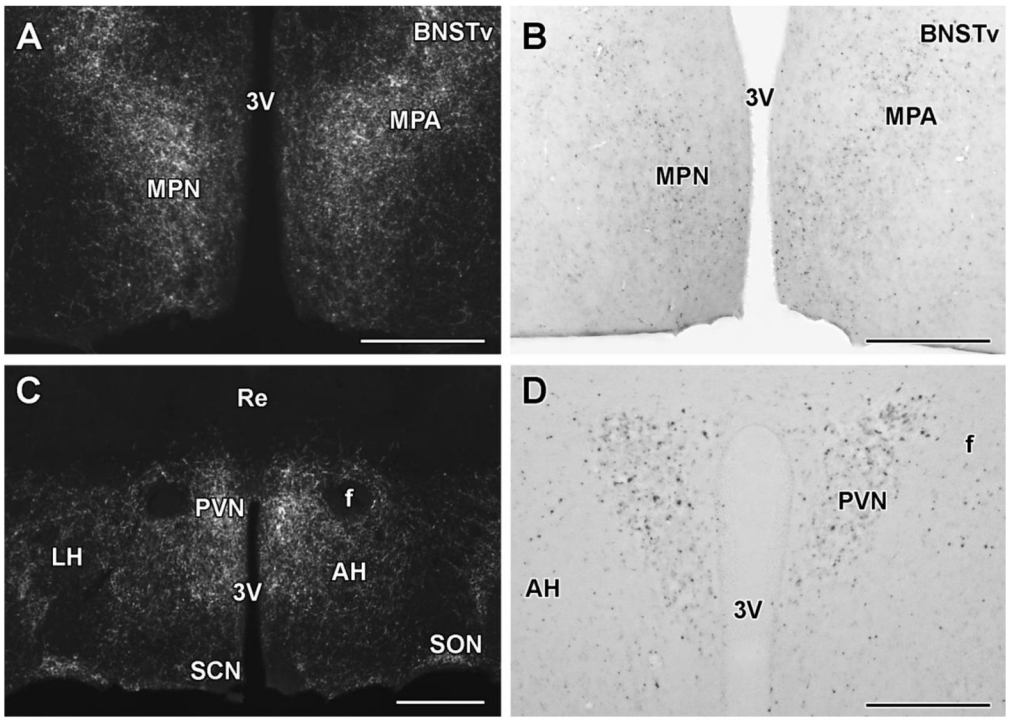

Fig. 3.

TIP39-ir fibers and parathyroid hormone 2 receptor (PTH2 receptor)-expressing neurons in the preoptic and anterior hypothalamus of mice. A: TIP39-ir fibers are abundant in the medial preoptic nucleus (MPN) as well as dorsolateral to it in the medial preoptic area (MPA) and ventral subdivision of the bed nucleus of the stria terminalis (BNSTv). B: X-gal histochemistry in a mouse expressing LacZ driven by the promoter of the PTH2 receptor. The PTH2 receptor-expressing neurons are distributed similarly to TIP39 fibers. C: TIP39-ir fibers have particularly high density in the paraventricular hypothalamic nucleus (PVN). They are also present in the anterior and lateral hypothalamic areas (AH and LH, respectively) albeit with only a low density in the LH. TIP39 fibers are present in the supraoptic (SON) but absent in the suprachiasmatic nucleus (SCN). D: PTH2 receptor-expressing neurons are abundant in the PVN. Scale bar = 400 μm for A and B, 500 μm for C, and 300 μm for D. The figure is created from the material presented previously (Faber et al., 2007).

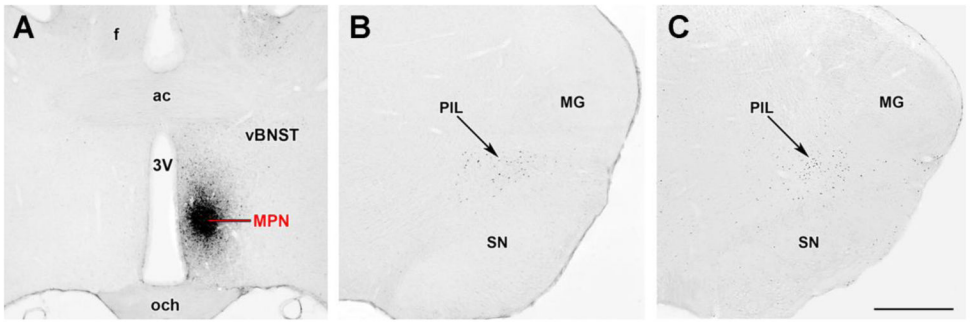

Fig. 4.

Comparison of neurons in the PIL retrogradely labeled from the medial preoptic nucleus and those that express c-Fos in response to pup exposure in mothers. A: Injection site of the retrograde tracer, cholera toxin beta subunit, in the medial preoptic nucleus (MPN). B: Retrogradely labeled neurons in the posterior intralaminar complex of the thalamus (PIL). C: Fos-immunoreactive neurons in the PIL following suckling in mother rats. Additional abbreviations: ac–anterior commissure, f–fornix, och–optic chiasm, MG–medial geniculate body, SN–substantia nigra, vBNST – ventral subdivision of the bed nucleus of the stria terminalis. Scale bar = 1 mm. The figure is created from the material of our previous paper (Cservenak et al., 2017b).

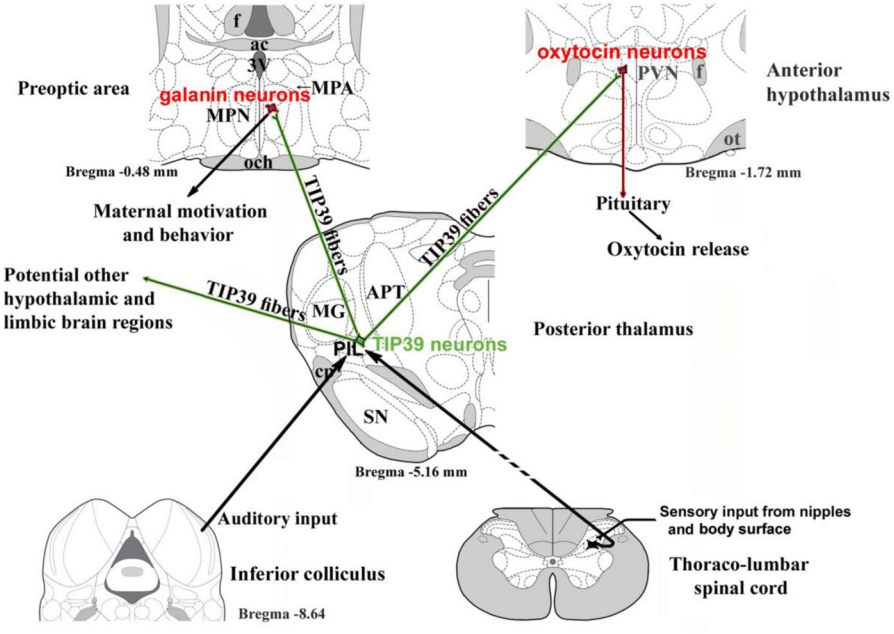

Fig. 5.

Schematic illustration of the major inputs and projections of TIP39 neurons in the PIL. TIP39 neurons (green) receive auditory input from the external cortex of the inferior colliculus as well as somatosensory input from the spinal cord (both direct and indirect inputs), and project to the medial preoptic area to innervate galanin neurons and the paraventricular hypothalamic nucleus to innervate oxytocin neurons.

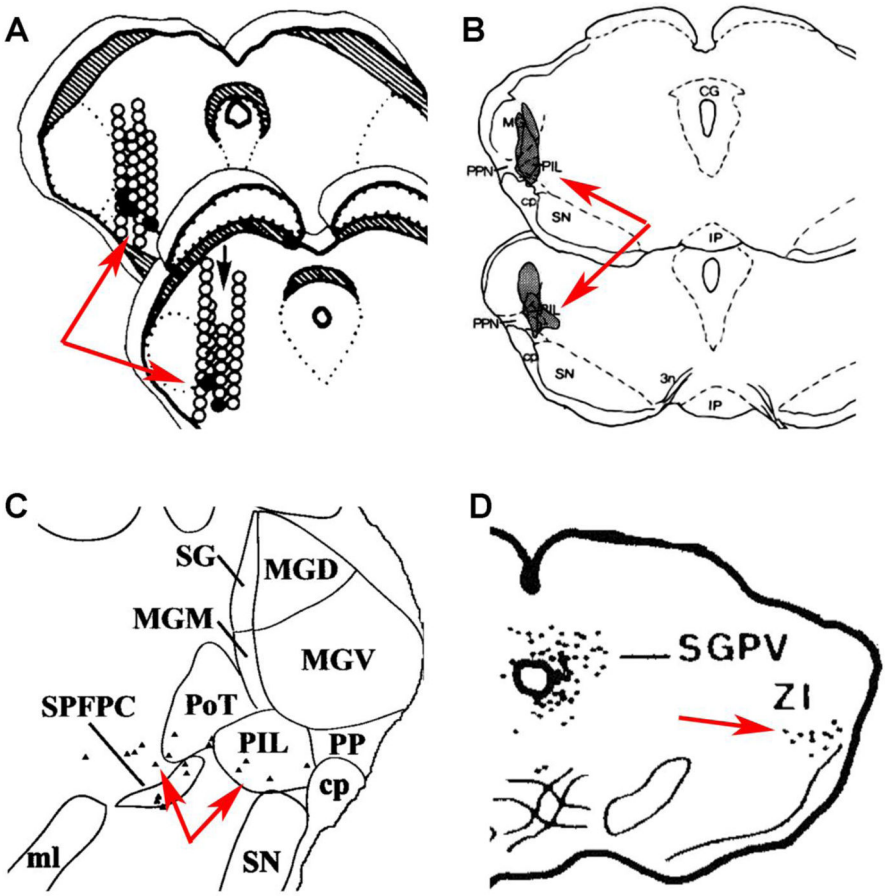

Fig. 6.

Presumed diencephalic relay center of the milk-ejection reflex. The panels are modifications from the reference papers. The red arrows point to the presumed relay station of suckling information. A: Black circles represent the position where microstimulations evoked, and empty circles where could not evoke milk ejection (Tindal and Knaggs, 1975). B: Lesion of the shaded areas with NMDA injections reduced milk ejection (Factor et al., 1993). C: Black triangles correspond to neurons retrogradely labeled following injection of tracer into the PVN (Campeau and Watson, 2000). D: Black dots represent neurons retrogradely labeled following injection of tracer into the supraoptic nucleus (Tribollet et al., 1985).
Abbreviations: CG–central gray (or substantia grisea, or periaqueductal gray), cp–cerebral peduncle, IP–interpeduncular nucleus, MG–medial geniculate body, MGD, medial geniculate body, dorsal subdivision, MGM - medial geniculate body, medial subdivision, MGV - medial geniculate body, ventral subdivision, ml–medial lemniscus, PP (or PPN)–peripeduncular nucleus, PIL–posterior intralaminar thalamic nucleus, PoT, Posterior thalamic nucleus, triangular subdivision, SG–suprageniculate nucleus, SGPV–substantia grisea periventricularis, SN–substantia nigra, SPFPC–subparafascicular nucleus, parvocellular subdivision, ZI–zona incerta, 3n–oculomotor nerve.