Hormones, Brain Plasticity and Reproductive Functions

Dionysia T. Theodosis[1]

Summary

The magnocellular oxytocin system of the hypothalamus illustrates remarkably well activity-dependent structural plasticity in the adult brain. Its neurons secrete the neurohormone oxytocin, which plays a key role in the initiation of parturition and maintenance of lactation. The somata and dendrites of oxytocin neurons accumulate in the supraoptic and paraventricular nuclei of the hypothalamus whereas their axons project to the neurohypophysis. There, oxytocin is secreted into the bloodstream from neurosecretory terminals upon electrical and biosynthetic activation of the neurons driven by afferent stimulation from the periphery. Oxytocin is released centrally as well, including within the hypothalamic nuclei, where it facilitates the electrical, biosynthetic and secretory activities of its own neurons. During conditions that stimulate peripheral and central oxytocin release, like parturition and lactation, there is a significant reduction in ensheathing of oxytocin neurons and their synapses by fine processes of astrocytes. As a consequence, the geometry and diffusion properties of the extracellular space surrounding the cells are significantly modified. In addition, there is a concomitant formation of new functional synapses on oxytocin neurons, which, in the main, are inhibitory. The anatomical changes are rapid, occuring within an hour, and reversible with arrest of stimulation. In vivo and in vitro evidence shows that oxytocin, in synergy with estrogen, mediates this neuronal, glial and synaptic remodeling. It is mediated specifically by oxytocin receptors, requires de novo protein synthesis, ongoing neuronal activity and expression of cell adhesion molecules that are permissive for plasticity. Similar neuro-glial changes occur in other hypothalamic nuclei whose neurons intervene in estrogen-dependent reproductive behaviors, like ovarian cyclicity and puberty. The functional consequences of such structural plasticity are important since the plasticity modifies neurotransmission, gliotransmission, neurohormone secretion and, ultimately, behaviors associated with reproduction.

Introduction

Parturition and lactation are neuroendocrine events vital for reproduction in mammals, and, therefore, of utmost import to the survival of the species. Like all physiological phenomena, their regulation involves numerous and diverse molecules that

[1] Inserm Research Center U862, Bordeaux F33077, France; University Victor Segalen-Bordeaux 2, Bordeaux F33077, France, e-mail: dionysia.theodosis@bordeaux.inserm.fr

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intervene in signaling, genomic and biosynthetic mechanisms. Of these, the nonapeptide oxytocin (OT) is particularly important. OT is synthetized in magnocellular neurons that accumulate in well-delineated regions of the hypothalamus, the paired supraoptic (SON) and paraventricular (PVN) nuclei. In these structures, oxytocinergic neurons occur intermingled with their close relatives, neurons secreting vasopressin (VP), a neurohormone important in cardiovascular and osmotic regulation. After synthesis, the hormones, packaged in secretory granules, follow the regulated secretory pathway to be released from axon terminals in the posterior lobe of the pituitary or neurohypophysis (for a recent review, see Burbach et al. 2001). Synthesis and release of OT, like VP, and ultimately circulating levels of the neurohormones, are in large part determined by the electrical activity of the neurons, which in turn is regulated by afferent inputs. The latter utilize neurotransmitters common to all central systems, including GABA, glutamate, the monoamines and acetylcholine (reviewed in Poulain and Wakerley 1982; Armstrong and Stern 1998). In addition, OT is released in many areas of the central and peripheral nervous systems, where it participates in different neurovegetative and limbic functions (see Landgraf and Neumann 2004). It is secreted in the SON and PVN. mainly via a somato-dendritic exocytotic mechanism, and exerts a positive feedback action, ultimately facilitating the electrical and secretory activities of its own system (reviewed in Ludwig and Pittman 2003).

It is now generally acknowledged that many adult neurons, as well as the synapses controlling their activities, are not static anatomical entities since they can undergo dynamic structural transformations that alter their morphologies and interrelationships. This alteration occurs under normal physiological conditions of heightened neuronal activity and highlights the brain's remarkable capacity for restructuring to meet particular functional requirements. Together with morphological changes in neurons and synapses, there is remodeling of the other major cellular elements in the nervous system, glia and, in particular, astrocytes. This neuronal-glial plasticity not only has direct consequences on the respective functions of each type of cell but also may affect neuronal and glial behavior by modifying the immediate extracellular environment, with consequences on synaptic and volume transmission.

The OT system is an excellent model illustrating this kind of activity-dependent structural plasticity. Whenever it is strongly or persistently stimulated, as at parturition and lactation, its neurons respond by significantly increased electrophysiological and secretory activities (Poulain and Wakerley 1982; Armstrong and Stern 1998; Burbach et al. 2001). At the same time, their overall morphology is modified since they progressively hypertrophy, their dendrites change in size and branching and their axons in the neurohypophysis enlarge and ramify. In the hypothalamus, there is a concomitant remodeling of their afferent inputs as well as of their associated astrocytes. Several recent reviews describe this physiological structural plasticity in detail (see, for example, Theodosis 2002; Miyata and Hatton 2002; Theodosis et al. 2008), and only its most salient features will be presented here. I will then briefly show that this kind of neuronal-glial plasticity is not limited to the hypothalamo-neurohypophysial system (HNS) since it occurs in other central systems, including in hypothalamic neuroendocrine centers involved in reproductive functions like ovarian cyclicity and puberty (reviewed in Theodosis et al. 2008). In the latter, plasticity takes place in concert with fluctuations in circulating levels of sexual steroids. I will then discuss the functional consequences of such plasticity at the cellular and systems levels. Finally, I shall present

molecular mechanisms that may shed some light on how such plasticity takes place in the adult nervous system, whose structure, until now, has been considered to be relatively unchangeable, except in response to aging, trauma or degeneration.

Morphological Plasticity of the OT System

Like most other central neurons, oxytocinergic neurons are normally ensheathed by processes of astrocytes, the most abundant glial cells in the magnocellular nuclei. Astrocytes in the SON and PVN have a variable, complex morphology (Bonfanti et al. 1993; Bobak and Salm 1996; Israel et al. 2003b), consisting of relatively small cell bodies, several thick processes extending into the neuronal network, and numerous thin processes, at times consisting merely of two membranes enclosing little cytoplasm. It is these lamellipodia that ensheath the somata, dendrites and axons of the neurons, as well as their synapses driving the activity. As has been illustrated in the hippocampus, their tips probably surround several synapses (Halassa et al. 2007), thereby creating glial microdomains enabling neuron-glia interactions in a restricted microenvironment (Grosche et al. 1999). Astrocytes respond to physiological stimuli by increases in intracellular calcium (Perea and Araque 2005), which consequently affect glial structure and function via different intracellular signaling mechanisms and gene activation.

Numerous observations obtained over the past two decades have made it clear that neurons, synapses and astrocytes of the HNS undergo significant morphological transformations under different physiological conditions. In particular, as clearly seen with electron microscopy coupled to morphometric analyses of immunoidentified profiles, this system's OT somata and dendrites, as well as their neighboring astrocytic processes, are surprisingly dynamic, continually changing their morphology in relation to neuronal activity. OT neurons usually occur in tightly packed clusters, yet, under basal conditions of neurosecretion, they remain separated by astrocytic processes. In contrast, during parturition, lactation, chronic dehydration, or in response to elevated ambient levels of OT, there is a significant reduction in astrocytic coverage of all portions of OT neurons. Thus, in the rat SON under basal conditions, astrocytic processes cover about 90% of any OT soma, a proportion that is reduced to 70% during lactation or chronic dehydration (Chapman et al. 1986; Theodosis et al. 1986a; Theodosis and Poulain 1987). This reduction in glial coverage leaves soma and dendritic surfaces directly and extensively juxtaposed. Astrocytic coverage of synapses contacting OT neurons is also significantly reduced (Oliet et al. 2001). It is important to note that this plasticity is not limited to one particular hypothalamic center but occurs throughout the hypothalamus, in all nuclei containing OT neurons (Theodosis and Poulain 1989). In contrast, in response to most stimuli for VP secretion, including severe chronic salt loading (Chapman et al. 1986), astrocytic coverage of VP neurons is not altered and remains around 90%. While VP neurons display some juxtapositions, their incidence and extent are low and show no variation with changing conditions of VP secretion (Chapman et al. 1986; Theodosis et al. 1986a).

Activity-dependent restructuring is visible not only in the magnocellular nuclei in the hypothalamus but also in the neurohypophysis (reviewed in Hatton et al. 1984; Theodosis and MacVicar 1996; Miyata and Hatton 2002). The gland is composed essentially of axons of SON and PVN neurons and astrocyte-like glial cells, the pituicytes.

The gland is highly vascularized and its capillaries are fenestrated, which permits passage of the secreted neurohormones into the circulation. Under basal conditions of neurosecretion, about 40% of the perivascular basal lamina is covered by neurosecretory terminals and about 60% by pituicyte processes. During stimulated conditions, as in the neurohypophyses of parturient and lactating animals (Tweedle and Hatton 1987; Luckman and Bicknell 1991) or when the glands are exposed in vitro to media that enhance secretion (Perlmutter et al. 1984; Smithson et al. 1990; Monlezun et al. 2005), pituicyte processes retract from the basal lamina and these proportions are reversed. Moreover, there is multiplication of terminals (Monlezun et al. 2005), and the end result is a significantly enlarged neurovascular contact zone. In addition, under stimulated conditions, throughout the gland, there is a reduction in the extent to which neurosecretory axons are engulfed or ensheated by pituicytes (Tweedle and Hatton 1982).

The structural transformations in the hypothalamic nuclei and neurohypophysis occur rapidly. This is evident in vivo, where ultrastructural changes can be detected within a few hours of the onset of parturition (Montagnese et al. 1987). It is even more apparent in vitro, in acute slices of adult hypothalamus that include the SON treated with OT (Langle et al. 2003; Theodosis et al. 2006) and in hemi-neurohypophyses exposed to hypertonic media or beta-adrenergic stimulation (Perlmutter et al. 1984; Monlezun et al. 2005). In both preparations, changes can be detected within one hour of treatment. When ambient levels of OT are again reduced (for example, after weaning the young, or in slices exposed to normal media), astrocytic processes reappear between neuronal profiles. Similarly, the extent of neurovascular contact in the neurohypophysis returns to baseline, non-stimulated levels upon cessation of stimulation of neurohypophysial secretion (Tweedle and Hatton 1987; Monlezun et al. 2005).

In the magnocellular nuclei, variations in astrocytic coverage of neuronal somata and dendrites are invariably accompanied by synapse turnover (reviewed in Theodosis 2002; Theodosis et al. 2005). This is represented by a changing number of boutons making synaptic contact onto more than one postsynaptic element simultaneously ("multiple" synapses) and boutons making single synaptic contacts on OT somata and dendrites (Theodosis et al. 1986c; Gies and Theodosis, 1994; El Majdoubi et al. 1997). Moreover, analyses of immunoidentified elements have allowed identification of the circuits undergoing plasticity as inhibitory (GABAergic) and excitatory (glutamatergic and noradrenergic ; reviewed in Theodosis et al. 2005). The most important increases affect GABAergic inputs, so that in the SON of lactating rats, about 50% of all axo-somatic and axo-dendritic synapses are GABAergic, compared to about 35% under basal conditions (El Majdoubi et al. 1997). Once stimulation is over, synaptic numbers revert to control levels. This synaptic remodeling can be reproduced in vitro in acute hypothalamic slices of adult SON. Electron microscopy and patch clamp electrophysiology of such preparations showed without ambiguity that synapse formation is extremely rapid, occurring within an hour, and is reversible within hours as well and results in the formation of inhibitory synapses that are functional (Theodosis et al. 2006).

How neuronal surfaces become extensively juxtaposed remains to be determined. The suggestion that juxtaposed neuronal surfaces are due simply to glial retraction is debatable. On the other hand, it is highly unlikely that astrocytic processes are passively squeezed away by hypertrophied neuronal profiles. For example, this mechanism does not explain the significant reduction in astrocytic ensheathing of dendrites or the numerous juxtaposed elements in tissues where hypertrophy of neuronal elements has

yet to take place (Langle et al. 2003). It is noteworthy that VP neurons significantly hypertrophy during chronic dehydration, yet their surfaces do not become increasingly juxtaposed (Chapman et al. 1986). A more likely scenario is that neuronal juxtapositions result from both active retraction and elongation of glial processes over neuronal surfaces whose morphology is constantly changing. In the neurohypophysis, glial process retraction from the perivascular zone could explain reduction in glio-vascular contact associated with stimulation,whereas the return to baseline conditions could be associated with a reinsertion of pituicyte processes between the neurosecretory terminals. The modified expression of several cytoskeletal proteins (Nothias et al. 1996; Hawrylak et al. 1999; Miyata et al. 1999) probably reflects this remodeling. In comparison to other systems (Bailey and Kandel 1993), one expects that these cell transformations are accompanied by differential gene expression and de novo protein synthesis. In the SON, new macromolecular synthesis is essential since there is no glial or neuronal remodeling when protein synthesis is blocked by agents like anisomycin (Langle et al. 2003).

Neuronal-glial Plasticity in Other Neuroendocrine Centers

Rapid, activity-dependent morphological changes similar to those visible in the magnocellular nuclei are detectable in other areas of the basal hypothalamus. In the rat arcuate nucleus, for example, which includes neurons secreting reproductive hormones like gonadotropin releasing hormone (GnRH), the proportion of neuronal somatic surface covered by astrocytic processes fluctuates with changing sexual steroid levels, being high when plasma estrogen is elevated (afternoon of proestrus and morning of estrus) and low 24 hours later at metestrus, when estrogen levels have diminished (reviewed in Garcia-Segura et al. 1994). Administration of estradiol to ovariectomized animals mimics the effects of the estrous cycle and shows clearly that the astro-neuronal changes are rapid, occurring within 2 hours of steroid injection. Similar phenomena have been described in the infundibulum and preoptic area of primates, like the Rhesus and African green monkey (Witkin et al. 1991; Garcia-Segura et al. 1994).

Synaptic changes accompany astrocytic remodeling in these areas of the hypothalamus, as they do in the magnocellular nuclei. In adult females, there is a natural phasic synaptic remodeling that is linked to variations of the ovarian cycle and is reflected in a changing number of inhibitory GABAergic synapses on somata of arcuate neurons (see Garcia-Segura et al. 1994a). A negative correlation between the level of glial ensheathment and number of synaptic inputs in relation to fluctuations in steroid levels has also been detected in primates (Witkin et al. 1991; Garcia-Segura et al. 1994a). In sheep, seasonal variations in glial ensheathment of GnRH neurons, together with changes in the number of synaptic inputs to GnRH neurons, occur in the preoptic area. Thus, the number of synapses decreases between the breeding and non-breeding seasons in conjunction with a decreased pulsatile GnRH secretion that leads to anestrous (Viguié et al. 2001), a decline accompanied by a significantly increased coverage of the neurons by astrocytic processes. Interestingly, in the rodent arcuate, rewiring of inhibitory inputs also occurs on POMC neurons, in response to enhanced circulating levels of the gut hormone ghrelin, which intervenes in the control of energy balance and growth hormone release (Pinto et al. 2004). It is not unlikely that these latter synaptic

changes are accompanied by astrocytic changes similar to those seen in response to estrogen, but this remains to be demonstrated.

The axons of GnRH neurons project to the external layer of the median eminence where, as in the neurohypophysis, they release the hormone from neurosecretory terminals in close proximity to fenestrated capillaries. In this neurohemal structure, it is fluctuations in sexual steroid levels that lead to axo-glial changes similar to those of the stimulated neurohypophysis. They result in retraction of end feet of tanycytes (modified ependymoglial cells) from the perivascular zone and exposure of GnRH terminals to fenestrated capillaries (King and Rubin 1995; De Serrano et al. 2004). In neurohemal structures, therefore, glial rearrangements ultimately permit direct access of neurosecretory axons to perivascular zones.

Consequences of Neuronal-glial Plasticity at the Cellular Level

In addition to supportive and nutritive functions (Magistretti et al. 1999), astrocytic processes, by their mere presence, act as a physical barrier to restrict spillover and diffusion of neuroactive substances in the extracellular space surrounding neurons and synapses. Therefore, a major consequence of astrocytic remodeling during stimulated conditions of neuronal activity is to reduce the extent to which astrocytic processes fill the extracellular space surrounding all neuronal elements, including synapses. As recent studies have demonstrated, this retraction has several important consequences on neuronal functions.

First, the ionic homeostasis of the extracellular space will be modified. A major function of astrocytic processes is to remove ions that can potentially influence neuronal activity. When absent during enhanced neuronal activity, there will be accumulation of ions like K+, which can facilitate further neuronal excitability. Such increases have been recorded in the SON (Coles and Poulain 1991) and neurohypophysis (Leng and Shibuki 1986) of lactating animals.

Secondly, the matrix (ECM) of all extracellular spaces is composed of many glycoproteins secreted by astrocytes, including cell adhesion molecules, proteoglycans and tenascins. While several of these molecules may act as permissive molecular factors to allow glial and neuronal remodeling (Theodosis et al. 2004a), they can also intervene more directly in neuron-glia interactions. They are large, complex, often charged molecules that can hinder access to receptors and transporters. In addition, they can interact homo- and heterophilically, between each other and/or with other ECM components, interactions that can affect neuronal activity (see for example, Dityatev and Schachner, 2003). Where astrocytic processes are withdrawn, therefore, the expression of such molecules will be absent or reduced (Theodosis et al. 1999), which will modify further intercellular communication and dynamic cell interactions.

Thirdly, since astrocytic processes possess many neurotransmitter receptors, transporters and ion channels (Danbolt 2001; Verkhratsky et al. 1998), they can sense activity in neighboring neurons. Indeed, as shown by numerous recent studies, astrocytes intervene actively in neuronal communication (Araque et al. 1999) and are considered integral parts of the synapse, which is now termed "tripartite" and seen to consist of pre- and post-synaptic neuronal elements and a glial component (Haydon 2001). In this context, then, a modified ensheathment of synapses will have important consequences

on neurotransmission, especially that due to the excitatory amino acid, glutamate. This is because astrocytic processes in the vicinity of glutamatergic synapses, because of their high content of glutamate transporters, limit glutamate spillover and are therefore critical for the maintenance of point-to-point synaptic transmission (Oliet et al. 2001). As clearly shown by the SON of lactating animals, a reduction of astrocytic coverage will enhance levels of ambient glutamate (Oliet et al. 2001). Glutamate then stimulates inhibitory metabotropic receptors at presynaptic sites of glutamate and even neighboring GABA synapses and results in homo- and heterosynaptic depression of neurotransmitter release (see Oliet et al. 2004). A reduced synaptic efficacy at glutamatergic synapses will also give rise to a decrease in background synaptic noise, which renders the neuron more electrically compact, increasing input resistance and the gain of the input-output neuronal response (Oliet et al. 2004). Such changes may be critical for tuning the responsiveness of neurons to pertinent synaptic information. In addition, astrocytes can potentiate inhibitory neurotransmission by activating presynaptic GABA-B receptors, an effect that is also potentiated by glutamate (Kang et al. 1998).

Fourth, the extracellular space is a kind of communication channel for molecules implicated in extrasynaptic or volume transmission (reviewed in Sykova 2004). A physical lack of astrocytic processes, therefore, could potentially facilitate diffusion of neurotransmitters like glutamate, GABA, and catecholamines to sites distant from their release (Piet et al. 2004), which could then allow crosstalk between neighboring synapses and neurons. In the same vein, facilitated diffusion of neureptides like OT and VP could contribute to their autocrine and paracrine actions (Moos et al. 1998; Ludwig and Pittman 2003).

Fifth, retraction of astrocytic processes will have further direct effects on neuronal function by affecting gliotransmission. It is now generally admitted that astrocytes themselves release different signalling molecules, or gliotransmitters, such as glutamate (Kang et al. 1998), D-serine (Wolosker et al. 1999; Panatier et al. 2006), taurine (Hussy 2002), and ATP (Gordon et al. 2005; Neumann 2003; Fields and Burnstock 2006) and these can mediate astrocyte-neuron cross-talk (Oliet and Mothet 2006) and affect further neuronal excitability (Volterra and Meldolesi 2005). Thus, glutamate (Kang et al. 1998) and D-serine (Miller 2004; Panatier et al. 2006), acting as gliotransmitters, activate NMDA receptors. The degree of astrocytic coverage of neurons will then govern the level of glycine site occupancy of these receptors, thereby affecting their availability for activation. Besides the direct effects on glutamatergic transmission, this means that the activity dependence of long-term synaptic changes, whose direction and magnitude depend on the number of NMDA receptors activated during afferent input stimulation, is also affected. This effect is clearly illustrated in the SON. Its astrocytes are enriched in D-serine, the endogenous coagonist of NMDA receptors in this hypothalamic area (Panatier et al. 2006), where the levels of D-serine and therefore the occupancy of NMDA receptors are controlled by astrocytic coverage. In this nucleus, then, NMDA-dependent phenomena like LTP and LTD are modified by its glial remodeling so that, on withdrawal of astrocytic processes, the number of activated NMDA receptors is reduced and the activity dependence of long-term synaptic changes is shifted towards higher activity values.

Finally, besides direct effects, astrocytic withdrawal can have indirect consequences on neuronal function by favoring synapse formation. As noted earlier, changes in astrocytic coverage in hypothalamic neuroendocrine centers like the SON and arcuate

nuclei are, invariably, accompanied by changes in synaptic connectivity, especially of inhibitory GABA circuits (reviewed in Garcia-Segura et al. 1994; Theodosis et al. 2005). Nevertheless, we still do not know how astrocytic processes actually participate in structural synaptic plasticity. What is clear is that their mere presence between pre- and postsynaptic partners will prevent synapse formation whereas their reinsertion may contribute to detachment of synaptic terminals from post-synaptic sites (see also Garcia-Segura et al. 1994; Aldskogius et al. 1999; Hirrlinger et al. 2004; Theodosis et al. 2005).

Consequences on Neuroendocrine Regulations

Parturition and Lactation

The magnocellular system of the hypothalamus constitutes a physiologically controlled system that intervenes in the regulation of several vital neuroendocrine processes. Its morphological reorganization is now a well-established phenomenon. Since it is easily accessible in vivo and in vitro, it serves as a ready model to analyze the importance of neuronal-glial remodeling not only at the level of synaptic function, as discussed above, but also in the more general context of system physiology. This is particularly clear in the case of the OT system, during its highly characteristic activity at lactation.

Peripheral information during suckling is transmitted to OT neurons through proximal glutamatergic afferents. During the milk ejection reflex, for example, OT neurons display high-frequency bursts of action potentials (Poulain and Wakerley 1982) that are triggered by bursts of glutamatergic possynaptic potentials (Jourdain et al. 1998; Israel et al. 2003a). As discussed above, patch clamp recordings provided convincing evidence that excitatory information transmitted by glutamatergic inputs is affected by glial remodeling (Oliet et al. 2004). Thus, reduced astrocytic coverage of OT elements and their synapses during lactation gives rise to increased levels of glutamate in the extracellular space, which, via its action on metabotropic receptors, will in turn inhibit synaptic glutamate release (Oliet et al. 2001). On first sight, it seems paradoxical that these inputs exhibit a lower probability of release at a time when OT neurons are strongly activated. However, presynaptic inhibition depends on presynaptic activity. A tonic presynaptic inhibition mediated by metabotropic glutamate receptor activation is likely to be overcome when the probability of release associated with Ca^{2+} accumulation in the terminals strongly increases during high-frequency trains of action potentials in glutamatergic terminals at the time of milk ejection. Information transmitted via high frequency excitatory synaptic activity, therefore, would be less affected by a negative glutamate feedback than information transmitted by low or moderate frequency activities. This may serve as a high-pass filter to increase signal-to-noise ratio for information carried by high frequency activities. On the other hand, accumulating glutamate in the extracellular environment, via its heterosynaptic actions, can inhibit GABAergic transmission in the vicinity of glutamatergic inputs (Piet et al. 2003, 2004), leading to a local disinhibition of the somatodendritic compartment (Mitchell and Silver 2000).

As also described in detail earlier, the presence or absence of astrocytic processes has important consequences on the concentration of gliotransmitters like D-serine,

which will affect NMDA receptor activation, intracellular Ca^{2+} concentrations and ultimately phenomena of synaptic plasticity like LTP and LTD (Panatier et al. 2006). During lactation, when fewer NMDA receptors are occupied by D-serine, the threshold for synapse potentiation is elevated, making it more difficult for synapses to become stronger. Making potentiation harder to achieve may favor very active synapses, like those communicating the suckling stimulus to OT neurons, whereas other, less active but potentially confounding inputs will be depressed.

It should be kept in mind that the increased number of synapses associated with reduced glial coverage in the magnocellular nuclei at lactation (El Majdoubi et al. 1997) will facilitate enhanced OT firing as well. It is obvious that an increased number of glutamatergic inputs will potentiate such firing. To this facilitation must be added that derived from additional noradrenergic synapses (Michaloudi et al. 1997) that provide an excitatory input to OT neurons, both on their own (Day et al. 1984) and through a central synergistic action with glutamate (Parker and Crowley 1993; Daftary et al. 1998). As for the highly significant increase in the number of inhibitory synapses (reviewed in Theodosis et al. 2005), their action, at first glance, might appear incongruous for neuronal excitability. A likely possibility is that the increased inhibitory input serves to prevent the neurons from being stimulated by factors other than those relevant to parturition and lactation, attenuating the response of OT neurons to stimuli other than suckling (Lightman and Young 1989; Fenelon et al. 1994). This kind of "filtering" action may also contribute to maintain OT neurons at a level of depolarization that would facilitate their subsequent synchronous activation just before milk ejection (Voisin et al. 1995; Moos 1995).

To these phenomena in the hypothalamus one must add the facilitatory action on neurosecretion provided by the glial-axonal changes in the neurohypophysis. In the gland, retraction of glial processes from around neurosecretory axons and from the perivascular space will promote paracrine actions of the secreted peptides. Moreover, as noted earlier, by removing a physical barrier from the perivascular spaces, such plasticity should greatly facilitate diffusion of the secreted hormones into fenestrated capillaries and thus into the general circulation.

Other Reproductive Functions

The functional consequences in neuroendocrine centers in the basal hypothalamus other than the magnocellular nuclei are also of high import. The neuropeptide is made in neuronal somata distributed in different centers of the basal forebrain (preoptic area, arcuate or infundibular nucleus, mediobasal hypothalamus) and is secreted from their terminals in the median eminence into the portal circulation to reach the pituitary, where it modulates the secretion of gonadotropins essential to gonadal function and reproduction. As described earlier, the astrocytic ensheathment/synapse relationship of GnRH neurons in the hypothalamic nuclei in various species varies in relation to changing levels of gonadal steroids, after gonadectomy, during the estrus cycle and at the preovulatory surge of gonadotropins (reviewed in Garcia-Segura and McCarthy 2004). While direct evidence is lacking, it is highly likely that astrocytes contribute actively to estrogen-dependent increases in arcuate neuronal firing that is correlated in time with the release of GnRH. Thus, the increased release of estrogen at estrus, like estrogen administration in castrated animals, augments astrocytic coverage, thereby

decreasing the number of inhibitory GABAergic inputs impinging on the neurons. In the median eminence, as in the neurohypophysis, concurrent retraction of glial processes and tanycyte end feet from the perivascular area exposes GnRH terminals directly to the portal capillaries (King and Rubin 1995; De Serrano et al. 2004), thereby facilitating diffusion of GnRH into the general circulation.

Cell Mechanisms Underlying Astro-neuronal Plasticity

Permissive Molecular Factors

The structural plasticity described in this review connotes interactions that will bring into play cell surface and ECM molecules, as well as soluble factors, many of which have been identified by molecular neurobiology in developing systems undergoing similar glial and neuronal transformations. In the developing brain, the effects of these molecules result from mutual interactions and via activation of intracellular signal transduction mechanisms through diverse cell surface receptors, ultimately determining the architecture of nervous tissue. It is not too surprising, then, that adult neural systems capable of remodeling continue to express many of these "juvenile" molecules. The list includes cell adhesion molecules like the cadherins, neurexins and those like NCAM that belong to the immunoglobulin superfamily. Complex ECM glycoproteins, like the chondroitin sulphate proteoglycans and tenascins, as well as their receptors, also contribute (Theodosis et al. 2004a; Kleene and Schachner 2004; Waites et al. 2005; Dalva et al. 2007). There are many excellent reviews describing these molecules and their contributions to cell interactions, especially in the context of axon outgrowth and synaptic plasticity (see, for example, Levinson and El-Husseini 2005; Dityatev and Schachner 2003). We will focus here on NCAM, and in particular, its highly sialylated isoform, PSA-NCAM, since we have strong evidence that this cell surface molecule does intervene in astro-neuronal remodeling.

While PSA-NCAM is abundant in developing tissues, most adult tissues contain NCAM with little PSA. However, PSA-NCAM continues to be strongly expressed in adult systems endowed with the capacity for morphological plasticity (Bonfanti et al. 1992; Seki and Arai 1993; Bonfanti 2006). Thus, in the HNS, PSA-NCAM is made by astrocytes and neurons throughout life (Theodosis et al. 1991; Kiss et al. 1993; Theodosis et al. 1999). In some systems, like the hippocampus, PSA-NCAM expression is linked to synaptic activity (Kiss and Muller 2001), but in the HNS (Pierre et al. 2001), its expression is constitutive and not markedly affected by neuronal activity. Nevertheless, it is a prerequisite for all dynamic phases of plasticity. Thus, specific enzymatic removal of PSA from NCAM in the SON in situ inhibited glial and neuronal remodeling associated with lactation and chronic dehydration; there was no effect if PSA was removed once morphological changes in the nuclei had already taken place (Theodosis et al. 1999). Likewise, PSA removal from cell surfaces in the neurohypophysis prevented stimulation-related induction and reversal of axonal and glial changes but had no effect once remodeling had occurred (Monlezun et al. 2005). A similar strong, quite constant expression characterizes PSA-NCAM in the GnRH system of rodents (Bonfanti et al. 1992; Hoyk et al. 2001), sheep (Viguié et al. 2001) and primates (Perera et al. 1994),

and in this system as well, removal of PSA inhibits the onset of astrocytic and synaptic changes associated with reproductive status (Hoyk et al. 2001). How PSA intervenes to permit morphological changes remains undetermined, but a possible mechanism is that large quantities of the carbohydrate on cell surfaces attenuate adhesion via physical impedance or charge repulsion (Rutishauser and Landmesser 1996). Cells can then detach from their neighbors or from the extracellular matrix and undergo changes in their conformation.

We consider that a molecule like NCAM to be permissive for morphological plasticity because its expression, while not tightly linked to neuronal activity in the neuroendocrine centers, appears obligatory for their morphological plasticity. This was clearly evident from enzyme perturbation experiments (Theodosis et al. 1999; Hoyk et al. 2001; Monlezun et al. 2005). Nonetheless, there can be compensatory replacement by other molecules, since remodeling occurs in lactating and salt-loaded mice genetically deficient in NCAM (Theodosis et al. 2004b), which reflects a redundancy in the molecular systems permitting such plasticity. Similar phenomena have been described in other neuronal systems in which NCAM is highly expressed and which continue to undergo plasticity in NCAM -/- mutants (Durbec and Cremer 2001). In a sense, the specific identity of molecules that are permissive for remodeling may not be important provided that they activate the same intracellular mechanism. On the other hand, the response of neurons and astrocytes implicated in remodeling would be invariant and independent of the identity of the factor, provided the proper stimulus intervenes.

Signaling Molecules

If molecules like PSA-NCAM act as primers, providing a permissive environment for remodeling, then there must be molecules whose expression is particular to each potentially plastic system that act as specific stimuli, triggering cascades of intracellular events that result in glial and neuronal transformations. Such molecules include those expressed at the onset of enhanced activity to bring on remodeling as well as molecules, not necessarily identical to the former, that signal the system to revert to its original condition. There are many candidates for such functions, including neuropeptides, neurotransmitters, steroids and trophic factors that are released by neighboring elements. Nevertheless, we still have little knowledge of how these signaling pathways consequently operate, through genomic and non-genomic pathways, to influence the morphology of the brain's cells and its synaptic wiring.

In the OT system, parturition and lactation, the conditions in which plasticity is most striking, are characterized by enhanced peripheral release of OT and by increased secretion within the hypothalamic nuclei. Central OT has a positive feedback action on the activity of its own system (Jourdain et al. 1998; Israel et al. 2003a; de Kock et al. 2003). It can also induce its morphological plasticity, since intracerebroventricular infusion of the peptide, presumably mimicking this central release, induced neuronal-glial and synaptic changes in the SON similar to those detected during lactation (Theodosis et al. 1986b). These effects can be reproduced in vitro, in acute slices of the adult hypothalamus, a preparation that allows pharmacological manipulation. We were thus able to determine that the neuropeptide acts specifically via its receptors since its action was mimicked by close analogues and inhibited with specific OT receptor antagonists (Langle et al. 2003). Addition of even structurally similar peptides like VP had no effect.

The receptor-mediated action of the neuropeptide may explain why morphological changes in the HNS are specific to its OT system. In the hypothalamic magnocellular nuclei, OT receptors occur on OT but not on VP neurons (Barberis and Tribollet 1996); they are present on astrocytes as well (Guenot-Di Scala and Strosser 1992).

Nevertheless, OT does not act alone but in synergy with sexual steroids, especially estrogens (Montagnese et al. 1990; Langle et al. 2003; Theodosis et al. 2006). In view of the rapidity of the effects of the steroid (Langle et al. 2003; Theodosis et al. 2006), it is probable that it acts via a plasmalemmal mechanism (Revankar et al. 2005), mobilizing intracellular Ca^{2+} and ultimately inducing remodeling. Such a mechanism is likely when one considers the extremely rapid beneficial effects of the steroid on the electrical activity of OT neurons (Israel and Poulain 2000), their gene expression (Crowley and Amico 1993) and central and peripheral release (Yamaguchi et al. 1979; Wang et al. 1995). It is noteworthy that estrogens affect OT gene regulation if treatment is accompanied by a progesterone withdrawal protocol (Amico et al. 1995), as in the endocrine conditions characterizing the end of gestation (Bridges 1984) when remodeling occurs under physiological conditions. Nevertheless, although OT, with or without steroids, appears essential for remodeling in the magnocellular nuclei, there are other candidates for such signaling and OT may act in a secondary fashion, by facilitating their expression.

Of these, glutamate is an excellent candidate since it can serve as a bi-directional signal to transfer information between activated neurons and adjacent astrocytes. In the cerebellum, activation of AMPA receptors on Bergmann glia is required for the maintenance of neuron-glia interrelationships (Iino et al. 2001). It is to be expected, then, that changes in glutamate transmission may lead to rapid and concerted modifications in the morphology of neurons and their astrocytes. In the SON, exposure to a combination of metabotropic and ionotropic glutamate receptor antagonists prevented OT/estrogen-mediated remodeling (Langle et al. 2003). Likewise, such a treatment inhibits the appearance of new GABA synapses (Trailin, Israel and Theodosis, unpublished observations). This finding strongly suggests that glutamate itself may be a more immediate signaling agent than OT. In the preoptic area of the hypothalamus, a mediator of astro-neuronal communication via glutamate appears to be prostaglandin-estrogen2 (PGE2). PGE2 induces astrocytic release of glutamate, which in turn activates glutamate receptors on adjacent neurons, an effect that can have important consequences on neuronal morphology and dendritic spine formation (Amateu and McCarthy, 2002).

Another neurotransmitter that may signal glial-neuronal changes is nitric oxide (NO). Electron microscopic observations of the external layer of the median eminence indicate that vascular endothelial cells use a signaling pathway mediated by NO to regulate neuronal-glial plasticity (De Serrano et al. 2004). Thus, activation of endogenous NO release induced a rapid structural remodeling resulting in the freeing of GnRH terminals from ensheathing astrocytic processes.

Other excellent signaling candidates are the purines, especially in the neurohypophysis. Neurohypophysial pituicytes possess purinergic receptors (Loesch and Burnstock 2001; Rosso et al. 2002), ATP can be released from neurosecretory granules in the terminals (Sperlagh et al. 1999), and adenosine, secondary to the metabolism of ATP, induces pituicyte stellation (Miyata et al. 1999; Rosso et al. 2002). Activated Rho A GT-Pase activation is a key event in coupling purine receptor activation and stellation (Rosso et al. 2002). In line with these results are preliminary observations of the SON

in the acute slice preparation, where adenosine can substitute for OT in inducing glial and neuronal changes similar to those visible under physiological conditions (Trailin, Oliet, Poulain and Theodosis, unpublished observations).

Finally, there is abundant evidence indicating that gonadal steroids on their own signal the onset of morphological changes. As noted earlier, estrogen can substitute for OT, at least in vitro, to induce neuronal-glial (Langle et al. 2003) and synaptic (Theodosis et al. 2006) changes in the SON. In the arcuate nucleus, administration of one single dose of 17ß-estradiol resulting in plasma levels similar to those at proestrus induced a change in synaptic numbers and astrocytic transformations similar to those detected at proestrus (Garcia-Segura et al. 1994). GnRH neurons themselves do not express estrogen receptors, so the effects of the steroid must be mediated through effects on presynaptic axons and/or astrocytes (Witkin et al. 1991). Indeed, in this area of the hypothalamus, not only are astrocytes targets for estrogen action, they themselves release factors that could affect neuron-glia interactions. Thus, gonadal steroids facilitate astrocytic expression of growth factors of the epidermal growth factor family and their tyrosine kinase receptors, thereby contributing to neuron-glia signaling intervening at the initiation of puberty (Ojeda and Ma 1999). Moreover, median eminence astrocytes and tanycytes release factors like PGE2 that contribute to estrogen-induced synaptic remodeling in the arcuate nucleus and to GnRH terminal remodeling in the external layer of the median eminence (Ojeda and Ma 1999; Garcia-Segura and McCarthy 2004).

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