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Role of Glia In Reproduction and Consequent Human Therapeutic Potentials-A Systematic Review

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Abstract

Background: Recent evidence suggests that astrocytes have important neuroregulatory functions besides classic functions of support and segregation of neurons which includes regulation of neuron communication,neurosecretion and synaptic plasticity.The aim of this review was to focus on astrocyte-neuron interactions in the hypothalamus ,specially with respect to their potential contributions to the regulation of gonadotropin hormone(GnRH) secretion,and their role in initiation of puberty.

Methods: A systemic review of international literature by a search of PUBMED and authors files was done for glia in sexual maturation/puberty, reproduction/in control of GnRH secretion with reference to mostly animal studies and occasional human MRI studies and cases of precocious puberty which are currently getting available with advent of MRI. .

Results: Both from animal studies as well as occasional human MRI data it is clear that tanycyte plasticity varies with the state of ovarian steroids and that how precocious puberty in humans occurs in hamartomas lacking GnRH neurons and that role of glial growth factors(TGFα /erbB1,neuregulins/erbB4)signaling is important besides prostaglandin E2 (PGE2) production for GnRH secretion.

Conclusions: Glial-neuronal interactions are important for neuroendocrine control of female puberty,regulation of GnRH secretion.Growth factors of the epidermal growth factor(EGF) family activating via erbB receptors(with tyrosine kinase activity) play a major role in glia-neuron communication.In turn,neurons facilitate astrocytic erbB signaling via glutamate dependent cleavage of erbB ligand precursors.Genetic disruption of erbB receptors delays sexual development due to impaired erbB ligand –induced glial PGE2 release.Besides the production of growth factors,glial cells contribute to initiation of puberty by plastic rearrangement of glia-GnRH neuron adhesiveness.

Introduction

It is increasingly clear that astrocytes play an important role in maintaining central nervous system(CNS)function(1-3)and controlling key bodily processes such as breathing(4),sleep(5)and reproduction(6).Because of their perivascular and interneuronal localization astrocytes are well positioned to sense afferent neuronal and blood borne signals and ideally suited for the temporal and spatial propagation of these signals(7-9).The activation of astrocytes leads to the release of gliotransmitters(8,10)that trigger rapid responses in neighbouring cells and thus contribute to the region specific homeostatic regulation of neuronal function.

As the most abundant cell type in the brain ,glial cells outnumber neurons by a 9:1ratio.The majority of them being astrocytes which are so named because of their starlike shape. Traditionally astrocytes have been relegated primarily to a supportive or structural role in brain.However ,there is a growing literature that suggests astrocytes are also an important source of neuroactive substances,such as growth factors,eicosanoids,and neurosteroids which may subsequently affect neuronal development,survival ,and neurosecretion. In the hypothalamus astrocytes regulate the secretory activity of neuroendocrine neurons(11-14).Asubset of such neurons secretes the decapeptide gonadotropin releasing hormone(GnRH),which controls both the initiation of puberty and adult reproductive function.In rodents GnRH neurons are mostly located in the preoptic region of the ventral forebrain.The importance of studying the rodent model has been highlighted earlier(15).These GnRH neurons project to the median eminence of the hypothalamus where GnRH is released into the pituitary portal blood for delivery to the anterior pituitary.As the projection field of neuroendocrine GnRH neurons ,the median eminence (ME) of the hypothalamus is poised to play a crucial role in the precise regulation of GnRH release and therefore central to the control of the reproductive axis

The Role of Glial cells in the maturation of neuronal circuits regulating GnRH neurons

The glial cells are important mediators of the sexual differentiation of neuronal connectivity induced by gonadal hormones.This is substantiated by findings of several laboratories indicating that the morphology ,immunoreactivity,enzymatic activity,and gene expression of astroglia are sexually dimorphic in several brain areas and can be modified by the postnatal actions of sexhormones.Furthermore ,the glial cells express receptors for gonadal hormonesii)metabolize gonadal steroids,iii)and participate in the synthesis of endogenous steroids by the nervous system(16).Sex differences in the differentiation of astroglia may impact on the organization of neuronal network that regulates the activity and secretion of GnRH neurons Exposure of Gn RH neuronal network in female animals(guineapigs,mice,sheep,rhesus monkeys)to testosterone results in modification in number and function of synaptic inputs to GnRH neurons and animals that have been exposed in utero to testosterone have an impaired ,male like response to the E2 –stimulated surge.

Neuroglia plasticity in the arcuate nucleus may integrate the action of different hormonal signals ,including estradiol (E2) and leptin,which may coordinate GnRH release with other physiological changes at the onset of puberty.Consequently, the role of glial cells in maturation of neuronal circuits regulating GnRH neurons has been studied in detail in the arcuate nucleus of the rat hypothalamus.In this nucleus ,parallel maturation of neuronal membranes,glial cells and synaptic inputs during the juvenile and prepubertal maturation period(17)generates a sexually dimorphic organization of synapses and c glia such that ,after puberty females ,but not males respond to neuroplastic actions of E2(18).These sex differences are induced by the perinatal secretion of testosterone(Tn) in male rats.Perinatal Tn increases in astrocytes the expression of a cytoskeletal protein that regulates astroglia cells morphology,glia fibrillary acidic protein(GFAP),increasing the growth of astrocytic processes and the extent of neuronal membranes covered by these processes .Coincident with these changes in astrocytic morphology there is a strong reduction in the density of dendritic spines and axo-somatic synapses on arcuate neurons in male(19).

Role of Glial-Neuronal Interactions in Initiation of Puberty

Pubertal activation of GnRH secretion requires information from glial cells,besides transsynaptic inputs(20-reviewed in ojeda2010).Both astrocytes and ependomyoglial cells lining the ventral surface of the third ventricle(tanycytes)produce cell to cell signaling molecules that stimulate GnRH release ,and that are necessary for timing of puberty(21)Glial cells contribute to the pubertal activation of GnRH secretion via two complementary mechanisms.i)One involves growth factors of at least four different families a)Transforming growth factorbeta(TGFβ) ,of the TGFβ superfamily,is recognized by the cellmembrane receptors endowed with serine threonine kinase activityand that are located within Gn RH neurons (22).Upon binding TGFβ enhances GnRH gene expression and Gn RH secretion(23).Growth factors of the other three families ,including theb)epidermal growth factor(EGF),family,c)basic fibroblast growth factor (bFGF) and d)insulin like growth factor 1(IGF1)are recognized by receptors with tyrosine kinase activity.Some of these receptors (FGFR,IGF-1R)are expressed in GnRH neurons,but erbB receptors (which recognize EGF and EGF –like peptides)are mostly expressed on glial cells themselves.Genetic disruption of erbB receptors delays female sexual development due, at least in part,to impaired erbB ligand induced glial prostaglandin E2(PGE2) release(21)While growth factors of glial origin set in motion glia-to neuron signaling pathways ,atleast one neuron-to glia regulatory pathway initiated by glutamatergic neurons ,has been shown to facilitate astrocytic signaling mediated by erbB receptors(24).

The second mechanism involves plastic rearrangement of cell adhesiveness. Molecules Mediating glial-GnRH neuron adhesiveness Although reviewed in detail by ojeda et al the main molecules postulated to mediate glia-GnRH neuron adhesive communications in the hypothalamus are

1. Neural cell adhesion molecule(PSA-NCAM)-with GnRH –glial adhesiveness mediated by hemophilic interaction with NCAM 140(25)
2. GnRH neurons adhere to astrocytes by hemophilic interactions mediated by synaptic cell adhesion molecule 1(SynCAM 1) and 3)by heterophilic interactions mediated by the binding of contactin present in GnRH neurons to the receptor Receptor –like Protein Tyrosine Phosphataseβ(RPTPβ)-that uses its carbonic anhydrase(CAH) extracellular subdomain to interact with contactin.Immunoreactive contactin found to be abundant in OVLT and ME,suggesting GnRH axons are an important site of contactin dependent cell adhesiveness.

Additionally three multigene familes of adhesion/signaling molecules with complementary functions has been reported in both the prepubertal female monkey hypothalamus and the GnRH secreting cell linesGT1-7.One of these families is composed of a large number of synaptic specifiers termed i)neurexins ;another is formed by ii)protocadherins,a group of membrane-anchored proteins that function as a synaptic adhesion molecules.iii)The third family consists of members of the contactin associated protein(Caspr)gene family(26)Despite the unmistakable presence of these molecules in the neuroendocrine brain,the contributions they have to adhesiveness of GnRH neurons and glial cells remain to be established,however contactin has been shown to interact in cis with Caspr 1 whose cytoplasmic domain contains a proline –rich sequence with a canonical SH3 domain that associates with atleast four SH domains –containing proteins C,including Src,Fyn,p85and PLCγ.(27)Altogether these results indicate that GnRH neurons adhere to astrocytes using both heterophilic(contactin/RPTPβand homophilic (SynCAM/SynCAM)interactions .Because both systems have signaling capabilities it would appear that in addition to providing an adhesive interaction ,these molecules can activate intracellular signaling cascades in both Gn RH neurons and astrocytes(21).(fig1)

The pubertal process can be set in motion prematurely by the pathological activation of discrete subsets of astrocytes fuctionally connected to the GnRH network.For instance ,puberty inducing lesions of of the anterior hypothalamic area in rats ,results in activation of TGFα and erbB1 receptor expression in astrocytes surrounding the lesion site(28,29).ii)Some hypothalamic hamartomas associated with sexual precocity in humans are endowed with a rich network of astrocytes containing TGFα and erbB1 receptors (30),suggesting that foci of glial activation in the proximity of GnRH neurons such as these ,may be a cause of idopathic sexual precocity of central origin in human females.

Role of Glia in Control of GnRH secretion

The ME ,which is located ventral to the third ventricle in the tuberal region of the hypothalamus ,is one of the seven circumventricular organs and primarily contains neurosecretory axon terminals(31).It constitutes a window of exchanges between the hypothalamus and periphery that is facilitated by the presence of permeable brain capillaries feauturing fenestrated endothelium(32,33).Thus it appears that the most important function associated with the lack of blood brain barrier in this region is that it permits the release of neurohormones produced by neuroendocrine cells from terminals into the pituitary portal circulation.It is also important to acknowledge that the cellular processes through which neuroendocrine terminals release their neuropeptides into the circulation could be subjected to the direct modulatory influence of the blood borne factors acting on this region.

As the projection field of neuroendocrine GnRH neurons ,the ME of the hypothalamus is poised to play a crucial role in the precise regulation of GnRH reClease ,and is therefore central to the control of reproductive axis .The ME ,which is located ventral to the third ventricle in the tuberal region of the hypothalamus ,is one of the seven circumventricular organs and primarily contains neurosecretory axon terminals(31).It constitutes awindow of exchanges between the hypothalacmus and the peripherythat is facilitated by the presence of permeable brain capillaries feauturing fenestrated endothelium(32,33).Thus it appears that the most important function associated with the lack of a blood brain barrier in this region is that it permits the release of neurohormones produced by neuroendocrine cells from terminals into the pituitary portal circulation.It is also important to know that the cellular processes through which neuroendocrine terminals release their neuropeptides into the circulation could be subjected to the direct modulatory influences of b lood borne factors acting on this region.The peculiar cytoarchitecture of the ME is mainly conferred by tanycytes ,which are specialized ependymoglial cells that form a belt lining the floor of the third ventricle(31).One dominant feature of tanycytes is their marked polarization ;although tanycyte cellbodies line the border of the third ventricle,they also send processes to the vascular walls,where they make contact through endfeet specialization.In addition tanycytes were recently shown to express efficient tight junction complexes at their apex that bestow them with properties of the blood brain barrier(BBB)(33). Although tanycytes are the dominant celltype,astrocytes also reside within the internal zone of the ME.

While in primates,including humans GnRH neuronal cell bodies are diffusely distributed in the forebrain and are particularly abundant in the preoptic region and in the tuberal region of the hypothalamus;in rats they are not present in the latter region.Deafferentation studies in rodents together with work showing that release of

GnRH from hypothalamic explants is pulsatile(34,35),thus led to the concept that atleast part of the mechanisms synchronizing GnRH secretion may reside within the tuberal region of the hypothalamus.These synchronizing events could even occur directly within the ME as ME explants were also shown to release GnRH in a pulsatile mode in vitro(36,37).Intriguingly plastic events taking place within the ME modulate the direct access of GnRH neurons to the pituitary pcortal blood vessels and that these structural changes are directly correlated to the endocrine status of the individual,e.g.in rats direct neurohaemal junctions are visualized at the onset of the preovulatory surge of GnRH when E2levels are highest(38).

Ovarian cycle-related morphological plasticity at the neurohaemal interface for GnRH neurons.

ME dynamics involve coordination of neuroendocrine axons,tanycytes,and the parenchymatous basal lamina ,the last structure secreted neurohormones must cross to enter the blood((39-41).Over the past decade ,it has been established that fluctuating physiological conditions during the ovarian cycle have the power to reversibly alter structural relationships among the various cell types of the ME that specifically interact with nerve terminals containing GnRH terminals(42-45).During the ovarian cycle ,under conditions of low gonadotropin output ,GnRH neuroendocrine terminals are completely enwrapped by tanycyte endfeet,which prevent direct access to the pericapillary space and thus create a diffusion barrier hampering GnRH entry into the pituitary portal circulation(38).Astructural rearrangement of tanycytes occurs during the preovulatory surge resulting in the release of the engulfed neuroendocrine terminals and the establishment of direct neurohaemal contacts between GnRH neurons and the pituitary portal blood(38).In parallel to tanycytic endfeet retraction ,GnRH axon terminals are frequently seen to sprout new terminals towards the pericapillary space and thus appear to be attracted by the endothelial wall which they eventually contact(38).Similarly ,electron microscopy studies performed in gonadectomized rats ,an experimental condition that results in increased GnRH release ,showed that the distance of GnRH axon terminal from the pericapillary space was positively correlated to plasma LH levels(46).

Human Studies

With the advancement of magnetic resonance imaging(MRI)techniques such as diffusion MRI(measurement of water diffusion coefficient that provides information about the cellular structure of tissue)and proton MR spectroscopy(measurement of a range of cerebral metabolites including N-acetyl aspartate,choline and creatine that providesinformation about tissue metabolism) tissue structure can now be probed and imaged on microscopic scale in vivo(47,48). Recently Baroncini et al showed that Gn RH axon fibers were abundantly apposed to tanycytic processes in the human ME raising the possibility that as in rodents,putative physiological condition-induced plastic changes involving morphological interaction could play a role in the neuroendocrine control of GnRH secretion in humans(49). A noninvasive longitudinal study monitoring sexsteroid hormone controlled plasticity in women recently evidenced that structural changes actually occur within the hypothalamus during an artificial menstrual cycle(50).In this study ,female volunteers were subjected to diffusion and spectroscopy MRI at two stages of their artificial menstrual cycle. Thirteen days after initiating oral contraception i.e.,when the hypothalamic-pituituitary-gonadal(HPG)axis is fully inhibited(51)and at the end of pill free interval,i.e when most of the steroidogenic negative effects wear off and normal early follicular phase LH pulse pattern is found(51).Results showed that removal of oral contraceptive-mediated gonadal steroid negative feedback on the reproductive axis dramatically and selectively favours diffusion in the hypothalamus and is associated with variations in the release of choline(the precursor of phosphadityl choline,the corephospholipid in the cell membrane),which is a metabolite mainly released by glial cells(52,53)when changes in cell membrane turnover occur(54).ii)Similar to studies conducted in brain slices showing that changes in the astrocytic coverage of neurons modify extracellular space geometry and diffusion parameters(55),these human data raise the possibility that the microstructural changes monitored during the pillfree period (increased diffusivity of water molecules)in the female hypothalamus could be due to the retraction of the glial cell processes(50).

Role for Glia in the release of GnRH and ME functional plasticity

Initial studies showed that transforming growth factor α (TGFα),an epidermalgrowth factor (EGF)related peptide expressed by tanycytes and astrocytes of the ME(56)was able to stimulate GnRH release from ME explants(57).TGFα does not stimulate GnRH release directly ;instead it does so via a paracrine mechanism that involves PGE2 release which subsequently acts

on GnRH neurons to induce GnRH secretion(58,59)but also triggers acute tanycytes retraction both in cultured tanycytes and in hypothalamic explants(60).Both invitro and in situ studies showed that the TGFα receptor erbB1,was expressed in tanycytes(61-63)Blockade of erbB1 receptor tyrosine kinase activity in the ME delays puberty(56)whereas TGFα overexpression induced via either transgenic approach(64) or by grafting cells genetically engineered to secrete TGFα into the ME accelerates the onset of puberty in female rats(59). Injection of E2 and progesterone(Pg)was shown to increase TGFα Mrna expression in premature rats and blockade of TGFαaction with tyrphostins ,erbB1 inhibitors,delayed the occurrence of the first GnRH/LH preovulatory surge at puberty(56).Because tanycytes of the ME express E2 receptors (60,65)E2 may act directly on these cells to promote both TGFα expression and release on the day of prooestrus.In vitro studies conducted in primary culture of tanycytes showed that12hr TGFα treatment promotes the release of PGE2 ,and a PGE2 dependent release of TGFβ1(63),a growth factor also known to be involved in the glial control of Gn RH secretion(66-68).Morphometric studies in vitro showed that both TGFα and TGFβ1 had dramatic but opposite effects on tanycyte morphology(63).When tanycytes monolayers are treated with TGFα,during the first 16hrs of treatment ,TGFα-erbB1 signaling acts on tanycytes to first promote outgrowthof their processes and then to elicit a PGE2 dependent production ofTGF β1(63).Subsequently TGFα induced TGFβ1 release induces retraction of the tanycytic processes during the following 6-8h(63). This sequence of events appears to recapitulate the E2 dependent changes in growth factor expression and morphology displayed by tanycytes during the preovulatory surge of GnRH.TGF β1 mediated cellretraction in tanycytes ,which were shown to express TGFβ receptors in vivo(22,68) requires the activity of matrix matalloproteinases(63)that were alsoshown to be expressed in the ME(69).In contrast to the aforementioned effect of PGE2 that promotes tanycyte endfeet retractionby promoting actin cytoskeleton remodeling (within30min) (60)TGFβ1-mediated tanycyte retraction involves digestion of extracellular matrix that causes substrate adhesion loss for tanycytes as shown by timelapse experiments(63)Thus these two mechanisms mediating tanycyte retraction appear highly complementary.

Role of Glial Neuregulin-erb2/4 signaling complex in modulating GnRH Release/tanycyte plasticity

Cultured hypothalamic astrocytes express NRG1,NRG3 as well as erbB2 and erbB4 receptors.When the cells are exposed to NRG1β or TGFα there is phosphorylation of erbB4 and erbB1 receptors ,respectively,in addition to erbB2 receptor crossphosphorylation.As a result ,production of PGE2 increases(61)erbB2 receptors plays an important role in amplifying intracellular signals initiated by TGFα and NRGs ;in vitro blockade of astrocytic erbB2 synthesis prevents both the stimulatory effects of NRG1 on PGE2 release and the increase in GnRH secretion elicited by NRG1–conditioned astrocyte culture medium(61).Consistent with the presence of erbB2 and erbB4 receptors in cultured astrocytes immunohistochemistry and in situ hybridization studies demonstrated the presence of erbB2 Mrna and protein in hypothalamic asrocytes and tanycytes of the third ventricle/ME,cand erbB4 in astrocytes,but not in tanycytes(61).The key involvement of ME astrocytes in the control of GnRH release was demonstrated using transgenic mice in which a dominant negative form of the erbB4 receptor ,lacking the intracellular domain ,was specifically targeted to astrocytes(70,71).The mutant astrocytes exhibited a blunted PGE2 response to neuregulin stmulation,ii)a reduced GnRH response to neuregulin treatment in ME explants ,iii)diminished plasma gonadotrophin levels andiv)delayed onset of the first preovulatory surge at puberty,all of these on the face of normal erbB1 dependent function(70)PGE2) PGE2 originating from ME astrocytes following erbB receptor activation could,in addition to stimulating GnRH neurons themselves ,also modulate ME plasticity either by promoting actin cytoskeleton remodeling(60)and/orTGFβ1 expression(63)in tanycytes. erbB4 expression within the hypothalamus is regulated by E2 and its expression levels are maximal at the time of proestrus(61). In addition the expression of SynCAM1,a synaptic adhesion molecule which is expressed in astrocytes as well as GnRH neurons and is a mediator of adhesion between hypothalamic astrocytes and GnRH neurons(72) ;isregulated by erbB4 signaling(73).

Role of vascular endothelial celss-NO

PGE2 synthesis in tanycytes of the ME could be prompted by two indepen dent but complimentary cell-based mechanisms,one involving glial-glial interactions set in motion by the paracrine activation of TGFβ/erbB1 signaling pathway in tanycytes(fig2a) and another involving endothelial-tanycyte interaction and the release of nitric oxide(NO)by vascular endothelial cells ,which in turn directly modulates COX activity in tanycytes(60).Both pathways could

be subject to the modulatory influence of Gonadal steroids ,as estrogen are known to upregulate both TGFα expression in astroglial cells (56) and COX expression in tanycytes.(60) (fig2b)

Other Glial Derived Factors

Although glial PGE2 is a major mediator of the stimulatory actions that TGFα and NRG's exert on GnRH release astrocytes release additional substances capable of stimulating GnRH release(74). Among these substances ,calcium,glutamate and ATP are the most conspicuous(75). Calcium reaches adjacent astrocytes via gap junctions(76)and stimulates the release of ATP and glutamate ,which then affect neuronal function upon binding to specific receptors(75).In the primate hypothalamus ,GnRH neurons respond to extracellular ATP ,via P2X2 and P2X4 receptors with an immediate increase in intracellular calcium and release of GnRH(77,78).ATP and glutamate can also activate Ca mobilization in astrocytes (75);Ca release more glutamate,which in turn stimulates PGE2 formation (79),PGE2 elicits further release of arachidonic acid .In turn arachidonic acid inhibits glutamate uptake into astrocytes(80)thereby increasing the halflife of the neurotransmitter in the synapses.

Neuron to Glia and Glia To Glia interactions in control of PGE2 release

In vitro experiments suggest that erbB signaling in hypothalamic astrocytes is functionally connected to the neuronal glutamatergic system,the primary mode of excitatory transsynaptic communication used by hypothalamic neuons(81).and one that is known to increase GnRH secretion.Neuronally released glutamate (Glu)coactivates metabotrobic glutamatergic(mGlur) and AMPA glutamatergic(Glut) receptors in astrocytes, stimulating the activity of zinc dependent matrix metalloproteinases(MMPs)of the ADAM(a disintegrin and metalloproteinase)family. TheMMPs catalyze ectodomain shedding of the proEGF ligands i)proTGFαand ii)proNRG(neuregulin).In particular the processing of proTGFα has been shown to involve the metalloproteinase ADAM17 also known as tumour necrosis alpha converting enzyme(TACE)(82).The subsequent release of matrix TGFαand NRG activate erbB1/erbB2 and erbB4/erbB2 heterodimers respectively(24).The coactivation of glutamatergic receptors,caused extracellular Ca2+ influx ,a Ca2+/protein kinase C dependent increase in TACE like activityand enhanced release of TGFα(83) and induces recruitment of erbB1 and erbB4 and their proligandcs to the cell membranes ,where MMP complexes form as demonstrated by the direct physical association of erbB and glutamatergiuc receptors.TACE is abundant in astrocytes of the ME and becomes more active in this region at the time of the first preovulatory surge of gonadotrophins.Inhibition of TACE activity in the ME decreases GnRH secretion and delays puberty indicating that an increased TACE activity in this region is necessary for the pubertal activation of GnRH secretion to take place(83). The activation of erbB receptors in hypothalamic astrocytes induces profound morphological changes including the retraction of cytoplasmii)stellation of cellsandiii)the elongation of processes. 2)The activation of erbB also promotes release of PGE2(24),stimulates a cyclic AMP /PKA pathway in GnRH neurons through the mobilization of EP2 receptors(84).Activation of this signaling pathway induces a reversible membrane depolarization ,initiation of spike firing via a post synaptic effect involving the activation of a nonselective cation current (84)(fig3).

Role for astroglial PGE2 in dendritic plasticity in GnRH neurons

GnRH neurons exhibit a simple bipolar morphology with one or two very long dendritic processes that can extend upto 1mm(85,86)Intriguingly ,recent studies have demonstrated that the density of spines along these dendrites is subject to robust increases not only during sexual development in immature animals ,but also at the onset of the GnRH/LH surge induced by gonadal steroids in ovariectomized adult mice(87).Although sexual maturation and the surge mechanisms have been shown to require the neuronal expression of sex steroid receptors(88),studies suggesting that astrocytic mechanisms might control the stabilization of individual dendritic processes and their subsequent maturation into spines(89),together with the demonstration that specific juxtacrine signaling pathways are involved in sculpting astrocyte-dendritic interactions(90),raises the possibility that astrocytes play a role in the physiological changes of synaptic structure underlying GnRH neuronal maturation and function.PGE2 has in fact been shown to mediate the dramatic neuronal spastic plasticity induced by estrogens in the developing preoptic region(91).This effect involves the activation of AMPA and metabotrobic Glut receptors (92), as well as the EP2/PKA signaling pathway(91), recently found to be functional in neuronal spine plasticity in the adult hippocampus, have also been

shown to promote comparable changes in the immature hippocampus(91).However ,in the hippocampus ,the underlying mechanisms do not appear to require PGE2 synthesis (91),suggesting that increases in PGE2 synthesis are selectively used by E2 to promote dendritic spine plasticity in the developincg preoptic region .Further studies are required to determine whether estrogenic effects on the plasticity of hypothalamic neurons such as those seen in newborn rodents can also occur later in postnatal life and/or in adulthood.

Glia as the Metabolic sensing Unit

Astrocytes are essential for both neuronal metabolism and metabolism sensing and are a critical component of the so called tripartite synapse,which also includes the pre and post synaptic processes of neurons(93).Astrocytes take up glutamate released by neurons,use it for thir own cellular metabolism ,and recycle the resultant glutamine for neuronal metabolism(94).In addition to producing glutamate ,astrocytes also regulate glutamate synthesis.This function changes according to the reproductive stage of the animals.For instance ,glutamate metabolism changes in the adult mouse hypothalamus in response to preovulatory levels of E2(95) and in female rat s during the normal onset of puberty(96).They also take up glucose,metabolize,and release it as lactate or store it as glycogen (94).Although the exact degree to which neuronal metabolism is dependent on astrocyte derived lactate is controversial,it is clear that neurons can take up lactate via monocarboxylate transporters(97) and convert it to pyruvate for oxidative production of ATP(94). Because lactate bypasses most glucosensing pathways alteration in astrocyte lactate production by neurotransmitters such as norepinephrine,dopamine,serotoinin,glutamine,and γ -amino butyric acid(98) can override the effects of glucose on neuronal glucosensing((99).Perhaps the most important function of astrocyte lactate production from glycogen is to provide an energy reserve toc support neuronal function during hypoglycemia.Finally ,the majority of fatty acid oxidation in the brain occurs in astrocytes.Astrocytes can also produce ketone bodies,which are exported and traken up by MCTs to serve as an alternate source for neuronal metabolism.AMPK is a major regulator of astrocyte ketone production(100)so that studies in which AMPK activity or other fatty acid metabolic pathways are altered may produce physiological effects primarily by altering astrocyte rather than neuronal metabolism.

Role of Tanycytes

Little is known about the function of tanycytes in supporting neuronal metabolism. However, processes of tanycytes(vimentin expressing)lining the third ventricle divide theARC and VMN into compartments and effectively prevent diffusion of substances such as glucose and larger molecules from ME,which lacks a BBB,into theARC(33).Presumptive GK expressing glucosensing neurons line up along these processes suggesting asupportive role of tanycytes in metabolic sensing.Also tanycytes express both Glut2 and GK ,which make them potentially glucosensing themselves(101). Transient destruction of third ventricular tanycytes markedly impairs counterregulatory responses to glucoprivation ,and this is reversed when they regenerate.However much more work is required to further elucidate the role of these intriguing cellsas members of a metabolic sensing unit.

Other Molecular Mechanisms involved in neuron-glia interaction associated with GnRH regulation

Genomic and proteomic analysis carried out in laboratories of ojeda et al have identified several genes that may potentially be involved in the initiation of the structural and functional neuro-glia remodeling of the ME at puberty and duting estrus cyclicity although its functional significance is still uncertain.Some of these genes may act as master genes or upper echelon genes ,which coordinate the expression of a network of other regulatory genes and maintain the hierarchical structure of the network.Among these three are of particular interest i)Oct2(octamer binding protein 2)ii)TTF1(thyroid transcription factor1)iii)EAP1(enhanced at puberty1)i)Oct2 is a transcriptional regulator of the POU domain family of homeobox –containing genes ,which may regulate TGFα and SynCAM transcription.The expression of Oct2 increases in the hypothalamus during juvenile development and the blockade of the Oct 2 synthesis delays the age at first ovulation.In contrast sexual precocity is associated with increased expression of Oct2(102).ii)TTF1 like Oct 2,a homeobox gene enhances the transcriptional activity of genes that facilitate puberty,such as GnRH,erbB2(erythroblastic leukemia viral oncogene homolog 2) and KISS1(human melanoma metastasis suppressor),and suppresses the expression of genes inhibitory to the pubertal process,such as the preproenkephalin gene ,TTF1 is expressed by GnRH neurons and tanycytes and its expression increases

at puberty in the hypothalamus .TTF1 disruption is associated with delayed puberty ,disruption of initial cyclicity and decreased reproductive capacity(102),and recently TTF1 has also been found to be a component of the molecular machinery which controls circadian oscillations in GnRH gene transcription.(103).iii)The third candidate EAP1 encodes a nuclear protein expressed in GnRH neurons and in neuronal subpopulations involved in the control of GnRH neurons ,such as glutamatergic ,GABAergic ,proenkephalinergic ,and KiSS1neurons .Hypothalamic EAP1 Mrna levels increase in both monkeys and rats during female puberty .Similar to TTF1 ,EAP 1 enhances the transcriptional activity of genes that inhibit the pubertal process and its knocking down in the hypothalamus delays puberty and disrupts estrus cyclicity(102).Recent studies in nonhuman primates confirms the requirement of EAP1 for menstrual cyclicity (104)and single nucleotide polymorphisms in the EAP1 gene has been associated with amenorrhea/oligomenorhea in non human primates(105) which raises the possibility that polymorphisms in EAP1 may increase the risk of functional amenorrhea in humans.Also recently Lomniczi et al showed that epigenetic mechanisms of transcriptional repression time the initiation of puberty in rats.Silencers of the Polycombgroup(PcG)were principal contributors with hypothalamic expression of 2 key PcG genes ,EeD and Cbx7 decreased and methylation of their promoters increased before puberty ,Pubertal increase in Kiss1 expression was accompanied by EED loos from Kiss1 promoter and enrichment of histone 3 modificatio associated with gene activation.Pulsatile GnRH release was disrupted by preventing evictin of EED from the Kiss1 promoter.Hence epigenetic silencingis a mechanism underlying neuroendocrine control of female puberty (106).

Conclusions

Since GnRH lacks estrogen receptors (categorically estrogen receptor α),it is generally believed that estrogenic control of GnRH release occurs in an indirect manner.In addition to a role for inhibitory and excitatory transmitter containing neurons ,the hypothalamic astrocytes have been documented to release a variety of neuroactive factors ,including TGF α &TGFβ,IGF1,PGE2,and the neurosteroid 3-α -5-pregnane-20-one,each of which have been shown to stimulate GnRH release ,and receptors for each factor have been documented on Gn RH neurons.

Astrocytes have also been implicated in the regulation of synaptic plasticity in key areas of the hypothalamus that control GnRH release,an effect achieved by extension and retraction of glial processes(i.e glial ensheathment).Through this mechanism ,the number of synapses on GnRH neurons and GnRH regulatory neurons can be potentially modulated ,thereby influencing the activation state of GnRH neurons .The steroid hormone 17-β-estradiol ,which triggers the GnRH sand LH surge has been shown to induce the astrocyte regulated changes in hypothalamic synapticplasticity as well as enhance formation and release of the astrocytic neuroactive factors ,thereby providing another potential mechanistic layer for astrocytic regulation of Gn RH release.

With advent of MRI one can correlate in humans the plasticity changes in tanycytes during the menstrual cycle and try to find the aetiology of precocious puberty with further studies on upper echelon regulatory genes such as Oct2 TTF1,and EAP1 would be helpful in determining their role in coordination of hormonal signals with the plasticity of tanycytes and GnRH axons in the median eminence ,the uptake of IGF1 by tanycytes ,the neuroglial plasticity of the hypothalamic neuronal circuits regulating GnRH neurons,and the plasticity and the neurosecretoryactivity of GnRH neurons at puberty and during reproductive cycles in adult brain.Finally both astrocytes and tanycytes(33,107) may act as metabolic sensors and may contribute to metabolic regulation of reproduction besides dire ct glucosensing by GnRH neurons(108)through AMPK ,and astrocytes can protect GnRH neurons besides other neurons by the release of TGFβ and activation of a c-Jun /AP1 protective pathway(23).

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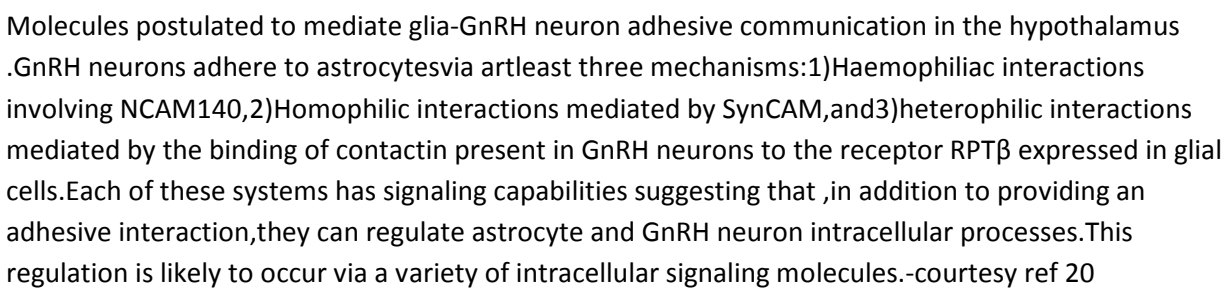
Illustrations

Illustration 1

Fig 1



Molecules postulated to mediate glia-GnRH neuron adhesive communication in the hypothalamus .GnRH neurons adhere to astrocytesvia artleast three mechanisms:1)Haemophiliac interactions involving NCAM140,2)Homophilic interactions mediated by SynCAM,and3)heterophilic interactions mediated by the binding of contactin present in GnRH neurons to the receptor RPTβ expressed in glial cells.Each of these systems has signaling capabilities suggesting that ,in addition to providing an adhesive interaction,they can regulate astrocyte and GnRH neuron intracellular processes.This regulation is likely to occur via a variety of intracellular signaling molecules.-courtesy ref 20

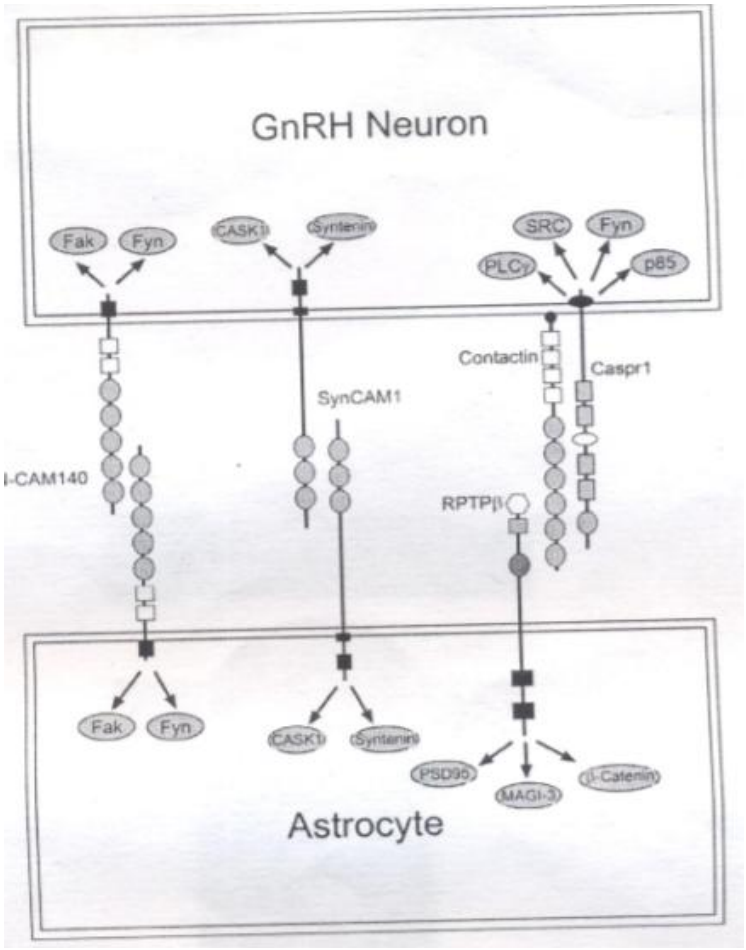


Illustration 2

Fig 2

SCHEMATIC REPRESENTATION OF NEURAL-GLIAL-ENDOTHELIAL INTERACTIONS INVOLVED IN THE CONTROL OF GnRH neurosecretion in the ME

A)Glial-neuronal interactions in the MEinvolve the production of epidermal growth factor(EGF)-related peptides by glial cells .Activation of erbB1/erbB2 and erbB4/erbB2 heterodimers by TGFα and NRG,respectively,promotes the release of PGE2 from astrocytes .The binding of TGFα to tanycytic erbB1 receptors results in the recruitment of erbB2 coreceptors and signal transduction.The ligand dependent activation of erbB1 receptors in tanycytes results in biphasic plastic changes characterized by an initial phase of tanycyte outgrowth(1)and secondary phase of retraction(5).Although the initial outgrowth(1) is independent of TGFβ1 system ,the subsequent retraction requires PGE2 synthesis (2),a PGE2 –dependent increase in the production of TGFβ1(3')and matrix metalloproteinase(MMP)activity(4).In addition to promoting TGFβ1 synthesis by tanycytes(3')PGE2 released by tanycytes(2)and astrocytes is able to directly stimulate GnRH release at nerve endings through the EP1 receptor(EP1)-mediated mobilization of intracellular calcium stores(3).

B)Endothelial-neuronal interactionsat the level of ME involve the production of nitric oxide(NO)by the endothelial cells of fenestrated capillaries of the portal blood vessels.Upon its secretion ,NO diffuses from its source and production of PGE2 from tanycytes.PGE2 promotes the release of GnRH into the blood stream by the direct stimulation of nerve endings (3)and by promoting their access to the pericapillary spaceby inducing cytoarchitectural changes in tanycyte end feet(1-3').Estrogens(Og) are likely tobe the key humoral factors involved in the orchestration of endothelia-glia communication that that allows GnRH neurons to directly contact the piruitary portal blood vessels on the day of prooestrus.Og treatment upregulates COX expression in tanycytes and stimulates endothelial nitric oxide synthase(Enos)expression in ME endothelial cells.-courtesy ref10 –with permission

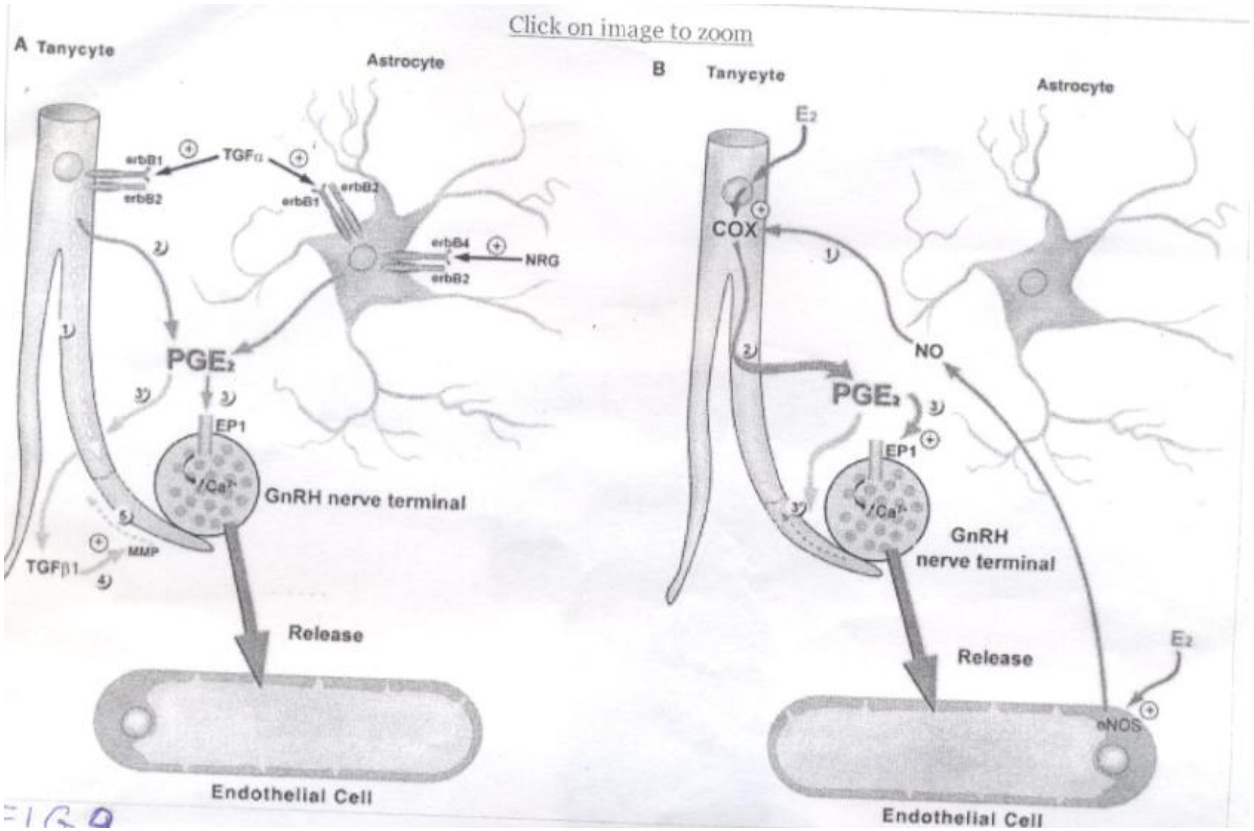
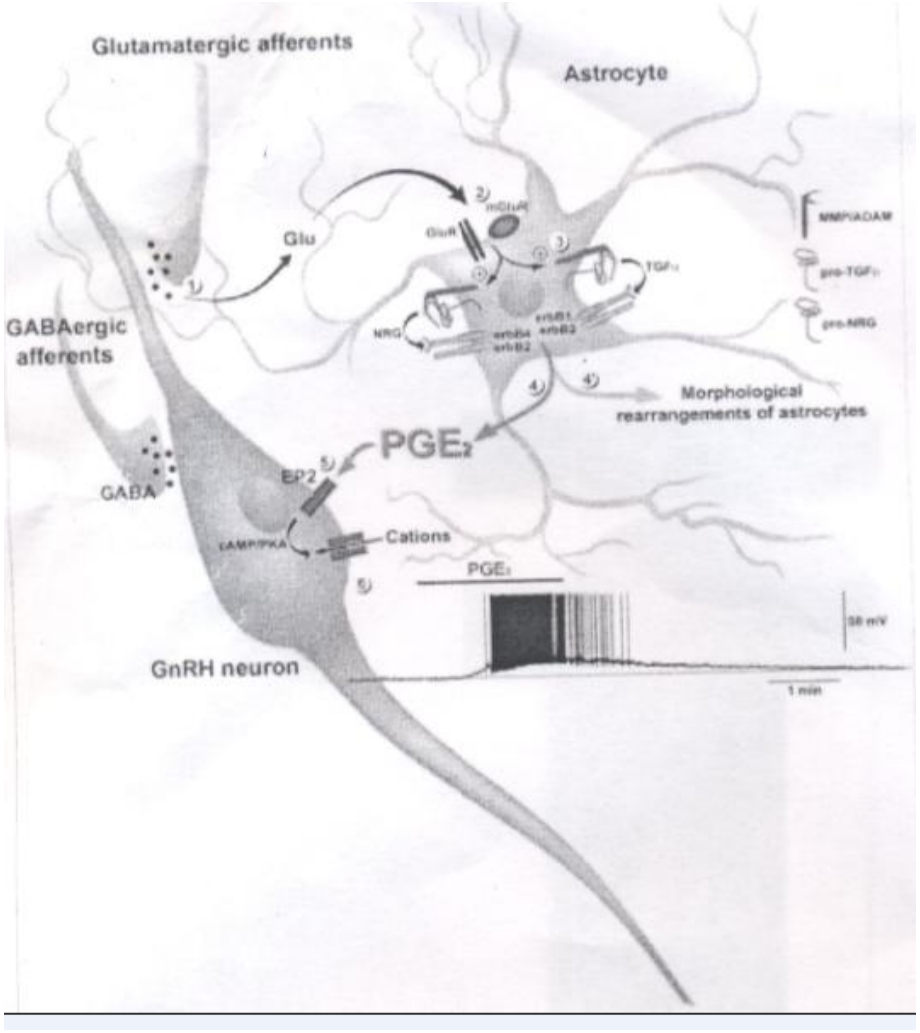


Illustration 3

Fig 3

PGE2 acts as a gliotransmitter to stimulate GnRH neurn electrical activity.-Neuronally released glutamate(Glu)(1)co-activates metabotropic glutamatergic(mGlur)and AMPA glutamatergic receptors(GluR)in astrcytes(2),stimulating the activity of zinc-dependent-matrix metalloproteinases(MMP)of the ADAM(adisintegrin and metalloproteinase)family(3).The MMP's catalyze ectodomain shedding of the pro-EGF ligands pro-TGFα and pro NRG(pr-neuregulin).In particular ,the processing of peo-TGFα has been shown to involve the metalloproteinase ADAM 17,also known as tumour necrosis factorα converting enzyme(TACE).The subsequently released mature TGFα and NRG activate erbB1/erbB2 and erbB4/erbB2heterodimers respectively.The coactivation of glutamatergic receptors induce the recruitment of erbB1 ,erbB4,and their pro-ligands to the cell membrane,where multiprotein complexes form,as demonstrated by direct the direct physical association of glutamatergic and erbB receptors.The activation of erbB receptors in hypothalamic astrocytes promotes profound morphological changes ,including thev retraction of cytoplasm,stellation of cells and elongatin of processes.The activation of erbB receptors also prpmotes release of PGE2(4)which stimulates Camp /proteinkinase A(PKA)pathway in GnRH neurons through the mobilization of EP2 receptors(5).Activation f this signaling pathway induces a reversible membrane depolarization of GnRH neurons leading t the initiation of spike firing via a postsynaptic effect involving the activation of non selective cation current.-courtesy ref 10 with permission.



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