

## Chapter 2

# Probing Astrocyte Function in Fragile X Syndrome

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**Abstract** Astrocytes have been recognized as a class of cells that fill the space between neurons for more than a century. From their humble beginnings in the literature as merely space filling cells, an ever expanding list of functions in the CNS now exceeds the list of functions performed by neurons. In virtually all developmental and pathological conditions in the brain, astrocytes are involved in some capacity that directly affects neuronal function. Today we recognize that astrocytes are involved in the development and function of synaptic communication. Increasing evidence suggests that abnormal synaptic function may be a prominent contributing factor to the learning disability phenotype. With the discovery of FMRP in astrocytes, coupled with a role of astrocytes in synaptic function, research directed to glial neurobiology has never been more important. This chapter highlights the current knowledge of astrocyte function with a focus on their involvement in Fragile X syndrome.

### 2.1 Historical Synopsis of Astrocytes

The term astrocyte is first mentioned in 1891 by Michael von Lenhossek in the German journal “Verhandlungen der Anatomischen Gesellschaft” (Transactions of the Anatomical Society). He indicated in his writings that glial cells should be considered to consist of more than one cell type. Lenhossek wrote “I would suggest that all supporting cells be named spongiocytes. And the most common form in vertebrates be named spider cells or astrocytes, and use the term neuroglia *only cum grano salis* (with a grain of salt), at least until we have a clearer view” (von Lenhossek 1891).

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Today, we use the term neuroglia as a broad inclusive term for all cells in the nervous system that are not neurons. Most articles cite Rudolph Virchow (1821–1902) as introducing the term neuroglia (often translated as nerve glue, cement or putty) to the scientific community. In 1856, Virchow used the term neuroglia or “nervenkitt” to describe the connective or interstitial tissue substance in the brain, recognizing that it differed in appearance and consistency from other organs. Kettenman and Ransom (2005) point out that (although not highlighted in most historical accounts) Virchow only used the term neuroglia to refer to the interstitial substance and not to the cellular elements contained within the substance. The brain tissue that Virchow was likely referring to was the neuropil or the astrocyte processes that we readily identify today. As an interesting side note, it was a student of Rudolph Virchow who stenographed a lecture series given by Virchow at Berlin University. It was this stenographing that placed the neuroglia concept into print for the first time with subsequent dissemination around the world (Kettenmann and Verkhratsky 2008). Somjen (1988) provides further insight into the historical evolution of the broad separation of glial cells from neurons by scientists including Santiago Ramon y Cajal, Camillo Golgi, and Otto Deiters.

## 2.2 Developmental Origin of the Astrocyte

Research on the glial lineage has expanded dramatically in recent years. With advances in microscopic technology and improved methods of cellular identification, the complexity of astrocyte differentiation and function becomes increasingly apparent each year.

Astrocytes develop from precursor cells in at least three different regions of the brain (Goldman 2003). In the developing cerebrum, these include precursor cells in the subventricular zone (SVZ), the radial glia of the ventricular zone (VZ), and from glial precursors not necessarily confined to the SVZ or the VZ layer.

The SVZ, located just beneath the ventricular walls, is a principal source of neural stem cells in the adult mammalian brain. Stem cells in this zone generate thousands of progenitors that form neurons and glial cells each day during development (Alvarez-Buylla et al. 2001; Doetsch et al. 1999). In the presence of exogenous mitogens like fibroblast growth factor, SVZ-derived neural stem cells grown *in vitro* self-renew and differentiate into all three lineages including astrocytes (Reynolds and Weiss 1992; Chiasson et al. 1999; Gritti et al. 2002).

In addition to the stem cells of the SVZ, another distinct group of cells referred to as radial glia give rise to astrocytes. Radial glia were repeatedly identified at the end of the nineteenth century (Magini 1888; Retzius 1893; von Lenhossek 1895; Ramon y Cajal 1899). Consistent with what is known today, the illustrations in these early papers accurately showed these cells as having their cell bodies in the VZ with processes spanning the complete thickness of the developing cerebral cortex.

Differentiated astrocytes that reenter the cell cycle can also serve as precursors to astrocytes and other cell types (Ganat et al. 2006). These astrocytes located throughout all regions of the brain represent a form of plasticity in the brain and they respond in cases of injury or dysfunction.

Freeman (2010) reviews various intrinsic epigenetic mechanisms that converge with extrinsic signals to generate astrocyte differentiation from neural precursor cells. Signaling through the Wnt and JAK-STAT pathways are prominent in driving precursor cells to an astrocyte fate.

Our initial concept of just one or two different types of astrocytes is gradually being redefined. For example, many subtypes of astrocytes are now being identified according to their location in the brain and on the spatial domain or microniche of the astrocyte environment. Three subpopulations of astrocytes in the white matter of the spinal cord have been identified on the basis of a combinatorial expression of the guidance molecules Reelin and Slit1. The positional identities of these astrocyte subtypes are specified by the homeodomain transcription factors Pax6 and Nkx6.1 (Hochstim et al. 2008). With a transcriptome database now available (Cahoy et al. 2008), insight into new astrocyte subtypes from developmental and functional perspectives will continue to emerge.

## 2.3 Astrocytes Link Developmental Form with Function

Studies from recent years have revealed that astrocytes perform a significantly wider range of functions than previously appreciated. Technological advances in molecular approaches continue to reveal an ever expanding list of functions for the astrocyte in all ages of the nervous system. Beyond the more commonly described functions of modulating neurovascular blood flow (Attwell et al. 2010) and the regulation of the extracellular ionic milieu (homeostasis) (Walz 1989), research has shown that astrocytes shape the synaptic environment (Ullian et al. 2004) and generate signaling mechanisms within neural networks via calcium waves (Volterra and Meldolesi 2005). Table 2.1 outlines several astrocyte functions and corresponding review papers. The most recent comprehensive reviews of astrocyte function include Wang and Bordey (2008) and Kimelberg (2010).

### 2.3.1 Astrocyte Cytoarchitecture

The classical Golgi impregnation techniques and immunocytochemical methods used to identify glial fibrillary acidic protein (GFAP) reveal protoplasmic astrocytes with a relatively simple stellate appearance. In contrast to the classical descriptions of astrocyte shape, the work of Bushong et al. (2002), Halassa et al. (2007), Ogata and Kosaka (2002), and Oberheim et al. (2006) reveal astrocytes with exceedingly dense arrays of processes that radiate in a symmetrical fashion from the cell body.

**Table 2.1** Listing of various astrocyte functions in the CNS

Astrocyte function	Sub-function	Description	Suggested papers/ reviews
Homeostatic regulation of the neural microenvironment	Extracellular ion buffering	Clearance by uptake of excess extracellular $K^+$ ions; distribution of the ions through the astrocytic syncytium	Walz (2000)
	Neurotransmitter reuptake and release	High-affinity uptake of glutamate and GABA mediated by plasma membrane transporters	Kimelberg (2007)
		Release of glutamate or ATP in a vesicular, $Ca^{2+}$ -dependent manner	Schousboe and Waagepetersen (2004)
	Metabolic support	Uptake and metabolism of glutamate into glutamine for re-distribution to neurons	Schousboe and Waagepetersen (2004)
		Uptake of glucose via GLUT1 transporter found in astrocyte endfeet surrounding capillaries	Porras et al. (2008)
		Regulate neuronal metabolic responses to activity via: (1) astrocytic glycogen (short term repository for glucose in the brain) and (2) lactate (released to neurons as energy substrate)	Pellerin et al. (2007)
	Blood brain barrier (BBB)	Regulate induction, maintenance and permeability of BBB (tight junction formation, expression of various transport systems and secretion of molecules)	Abbott (2000), Abbott et al. (2006), Haseloff et al. (2005)
Neural development	Neurogenesis	GFAP-expressing cells in the SVZ or SGZ can contribute to cell genesis both as stem cells and as neural components of the neurogenic niche	Barkho et al. (2006), Lie et al. (2005)
Synaptic regulation	Modulate synaptic transmission and neural activity	Astrocytic glutamate release modulates synaptic transmission by activating presynaptic and postsynaptic glutamate receptors	Paixao and Klein (2010)
		Generate signaling mechanisms within neural networks via calcium waves	Volterra and Meldolesi (2005)

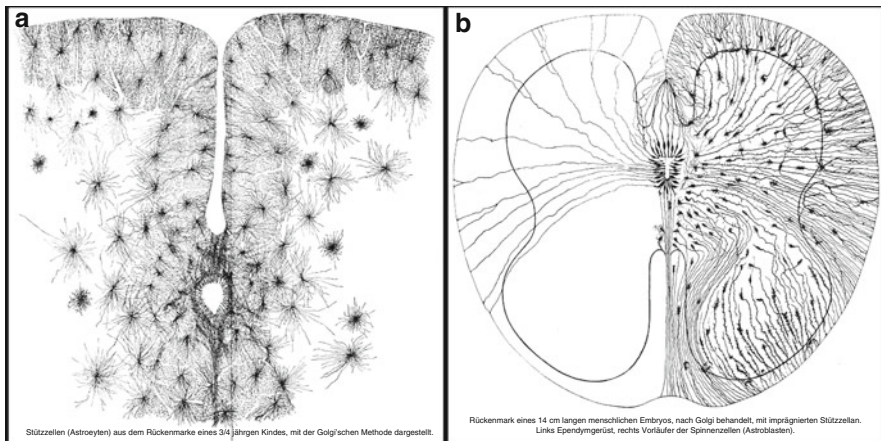
(continued)

**Table 2.1** (continued)

Astrocyte function	Sub-function	Description	Suggested papers/ reviews
Other	Synaptogenesis	Promote synaptogenesis between CNS neurons by release of diffusible molecules	Christopherson et al. (2005), Ethell and Pasquale (2005), Ullian et al. (2004)
	Synaptic plasticity	Modulate synaptic function through their role in glutamate re-uptake at the synapse by action of excitatory amino acid transporters (EAATs)	Paixao and Klein (2010)
		Modulate intensity and duration of postsynaptic activation (eg. release of glutamate prompting LTP, preservation of synaptic strength by release of TNF- $\alpha$ , etc)	Barker and Ullian (2010), Beattie et al. (2002), Bergami et al. (2008)
	Vasomodulation	Coordinate blood flow to the brain (functional hyperaemia)	Iadecola (2004)
		Control of blood glucose and O <sub>2</sub> by neurotransmitter mediated signaling (predominantly by glutamate)	Attwell et al. (2010), Iadecola and Nedergaard (2007)
		Secrete vasoactive agents to induce vasoconstriction or vasodilation (correlated with increased intracellular Ca <sup>2+</sup> )	Zonta et al. (2003)
	Detoxification	Prevent excitotoxic neuronal death by capturing excess ammonia and glutamate (converting them to glutamine)	Chung et al. (2008), Struzynska et al. (2001)
		Uptake of toxic or heavy metals	
	Immune activation	Bridges CNS and immune system:	
		(1) Express MHC II and costimulatory molecules important for T-cell activation and antigen presentation	Dong and Benveniste (2001)
		(2) Express receptors involved innate immunity	Farina et al. (2007)
		(3) Secrete a wide variety of chemokines and cytokines that act as immune mediators	

The complexity of astrocyte morphology is further highlighted by the facts that a single astrocyte (in the rodent) can contact 300–600 dendrites (Halassa et al. 2007), and each astrocyte oversees in excess of 100,000 synapses (Bushong et al. 2002). In the human, these values are further increased due to the larger size of the protoplasmic astrocytes. Oberheim et al. (2006) estimate that a single astrocyte in the human brain contacts on the order of two million synapses. Clearly, while difficult to conceptualize the numerical value of astrocyte contacts with neurons, the morphological arrangement of astrocyte processes at the synaptic level is critical to proper function.

Specialized anatomical tracing techniques have revealed that mature astrocytes occupy distinct, nonoverlapping domains in the brain (Bushong et al. 2002; Halassa et al. 2007). During development, the astrocyte processes appear quite ragged and display overlapping zones with adjacent astrocytes. By the 3rd to 4th week after birth, neighboring astrocytes occupy very distinct spatial domains with no overlapping processes. Remarkably, there is a striking similarity of these modern images to a figure published by von Lenhossek in 1893 (see Fig. 2.1). It is believed that astrocytes “tile” with one another through a mechanism that is similar to dendritic tiling (reviewed by Freeman 2010). This anatomical arrangement has been taken one step further in theory, with the suggestion that the defined domains of astrocytes function as synaptic islands (Halassa et al. 2007). This concept proposes that all the synapses confined within the boundaries of an individual astrocyte are modulated by the gliotransmitter environment of the same astrocyte.



**Fig. 2.1** Reproduction of the diagram from the 1893 article by Michael von Lenhossek. (a) Golgi impregnation of astrocytes in the spinal cord of a 9 month old child. Note the exquisite pattern of astrocyte “tiling” that is observed by modern day methods of cell filling. (b) Spinal cord preparation of a 14 cm human embryo reveals patterns of radial glial spanning the entire thickness of the cord. Golgi impregnation

### 2.3.2 *Gliotransmitters in Astrocytes*

Astrocytes are now recognized as “excitable” cells. When astrocytes are activated by internal or external signals, they communicate with neighboring cells in the form of gliotransmission. Astrocytes release various transmitters and factors such as glutamate, GABA, acetylcholine, noradrenaline, D-serine, ATP, nitric oxide, and brain-derived neurotrophic factor (BDNF) (reviewed by Volterra and Meldolesi 2005). In concert with the release of transmitters, many different receptors for neurotransmitters are expressed on the astrocyte cell membrane. These receptors respond with a particular form of excitability involving  $\text{Ca}^{2+}$  oscillations (Porter and McCarthy 1997).

Modulation of neuronal excitability and synaptic transmission by astrocytes was first shown to be mediated by glutamate release (Haydon 2001). With astrocytes providing local neuronal excitation via glutamate, they provide a source of neuronal activation that may be critical in controlling the synchronous depolarization of neurons (Fellin et al. 2006). At the same time, astrocytes can also suppress synaptic transmission by releasing purines. Through these coordinated actions, the astrocyte is thought to provide balanced excitation and inhibition mediated by two distinct transmitter systems.

Astrocyte excitation, which is chemically encoded, can be detected experimentally by assays of  $\text{Ca}^{2+}$  transients and oscillations. Two main forms of astrocyte excitation are well-documented: one that is generated by chemical signals in neuronal circuits (neuron-dependent excitation) and one that occurs independently of neuronal input (spontaneous excitation). Numerous studies highlight the release of glutamate from astrocytes in response to neuronal activity. In the case of glutamate, synaptic-like glutamatergic microvesicles have been identified in astrocytes and these vesicles are released via  $\text{Ca}^{2+}$ -dependent exocytosis (Bezzi et al. 2004).

### 2.3.3 *Astrocytes Modulate Synapse Development and Function*

Various insect and vertebrate animal models indicate that glial cells and neurons function together to guide axons during development (Chotard and Salecker 2004). When axons reach their target, glial cells contribute to the specification of the appropriate synaptic connections. The importance of the neuron–astrocyte interaction in synaptic development and function has been highlighted in several papers (Haydon 2001; Ullian et al. 2001; Slezak and Pfrieger 2003; Schipke and Kettenmann 2004). Astrocytes secrete diffusible factors, such as cholesterol (Mauch et al. 2001), tumor necrosis factor- $\alpha$  (Beattie et al. 2002), activity-dependent neurotrophic factor (Blondel et al. 2000), and thrombospondins–extracellular matrix glycoproteins (Ullian et al. 2004; Christopherson et al. 2005) to promote synapse formation. Other classes of cell adhesion molecules such as the  $\gamma$ -protocadherins, a family of neuronal adhesion molecules that are critical for

synaptogenesis, are expressed by astrocytes (Garrett and Weiner 2009). Direct astrocytic contacts also upregulate synapse formation in a protein kinase C-dependent manner (Hama et al. 2004).

Astrocyte contacts may induce local structural and functional modifications of dendritic segments or individual synapses. Membrane-bound ligands on astrocytes, such as ephrin-A3, have been shown to regulate spine morphology in the hippocampus (Murai et al. 2003), suggesting local activation of EphA receptors on spines by astrocytic ephrin-A3. Using organotypic hippocampal slice preparations, Haber et al. (2006) showed that astrocytes can rapidly extend and retract fine processes to engage and disengage from postsynaptic dendritic spines. These dynamic structural changes in astrocytes possibly control the degree of neuron–glia communication at the synapse. With two-photon time-lapse imaging methodology (Nishida and Okabe 2007), they revealed that astrocyte motility in the form of protrusive activity acts as a key local regulator for stabilization of individual dendritic protrusions and subsequent maturation into spines.

### **2.3.4 The Neurovascular Unit**

Considering the contacts made between astrocytes and blood vessels, it has been estimated that in excess of 99% of the brain vasculature is ensheathed by astrocytic processes (Takano et al. 2006). This active interaction between the neuron, astrocyte, and blood vessel has been termed the neurovascular unit and is essential for the regulation of blood flow (Takano et al. 2006; Koehler et al. 2009). The importance of regulating blood volume in the brain is highlighted by the fact that the brain consumes approximately 20% of the energy produced by the body at rest. The control of blood glucose and O<sub>2</sub> are tightly controlled by neurotransmitter mediated signaling (predominantly by glutamate) and this control is modulated by astrocytes (see review by Attwell et al. 2010). The increase in glia research and evolution of the importance of astrocytes to normal neuronal and vasculature function is also highlighted by numerous reviews (Attwell et al. 2010; Freeman 2010; Pfeiffer and Huber 2010; Eroglu and Barres 2010; Barker and Ullian 2010).

## **2.4 Astrocytes in Neurological Disorders**

With an evident role of astrocytes in normal neural function at all cellular and molecular levels, it is not surprising that astrocytes have been implicated in virtually all pathological conditions in the nervous system. Dysregulated astrocyte function has been linked with the progressive pathology of stroke and to a number of neurodegenerative diseases including Alzheimer's disease, Huntington's disease, and Parkinson's disease (Maragakis and Rothstein 2006). While a comprehensive review of astrocytes in the various pathologies is beyond the scope of this chapter, the involvement of astrocytes in the development of Rett syndrome (RTT) is very



applicable. Recently, Ballas and colleagues (2009) demonstrated that astrocytes and astrocyte-conditioned media from the RTT mouse model failed to support normal dendritic morphology. Taken together with our findings in Fragile X (discussed in the next section), and the consistent synaptic alterations seen in Fragile X, learning impairments and autism spectrum disorders, the possibility of an astrocyte involvement in multiple childhood neurodevelopmental disorders certainly becomes evident.

## 2.5 The Fragile X Astrocyte

With overall synaptic function standing as a prominent link to the expression of the disease phenotype in a number of neurodevelopmental disorders, and knowing that astrocytes influence synapse development and function, our lab initiated experiments to evaluate the role of astrocytes in Fragile X neurobiology. These experiments were preceded by the observation that astrocytes, in addition to neurons, also express the Fragile X Mental retardation Protein (FMRP) (Pacey and Doering 2007). At the time of this finding, FMRP expression in the brain was considered to be primarily neuronal. FMRP had been reported in oligodendrocyte precursor cells, but not mature oligodendrocytes by Wang et al. (2004). When studying stem and progenitor cells from the brains of wildtype and knockout Fragile X mice, approximately 50% of the cells in culture coexpressed FMRP and GFAP. Parallel immunocytochemical studies *in vivo* also showed the coexpression of FMRP and GFAP in the embryonic and adult developing hippocampus.

With the identification of FMRP in astrocytes and knowledge of their role in synaptogenesis, we initiated experiments to explore neuronal development and synapse formation in the Fragile X mouse. A coculture design was used to selectively combine cells from the *Fmr1* KO mouse and its wild-type (WT) counterpart (Jacobs and Doering 2009). With this tissue culture approach, neurons and astrocytes were independently isolated to explore four different combinations of neuronal-astrocyte cultures (WT neurons + WT astrocytes, WT neurons + *Fmr1* KO astrocytes, *Fmr1* KO neurons + WT astrocytes and *Fmr1* KO neurons + *Fmr1* KO astrocytes). The cells were grown for 7, 14, or 21 days and then processed for immunocytochemistry to analyze the morphological and synaptic profiles.

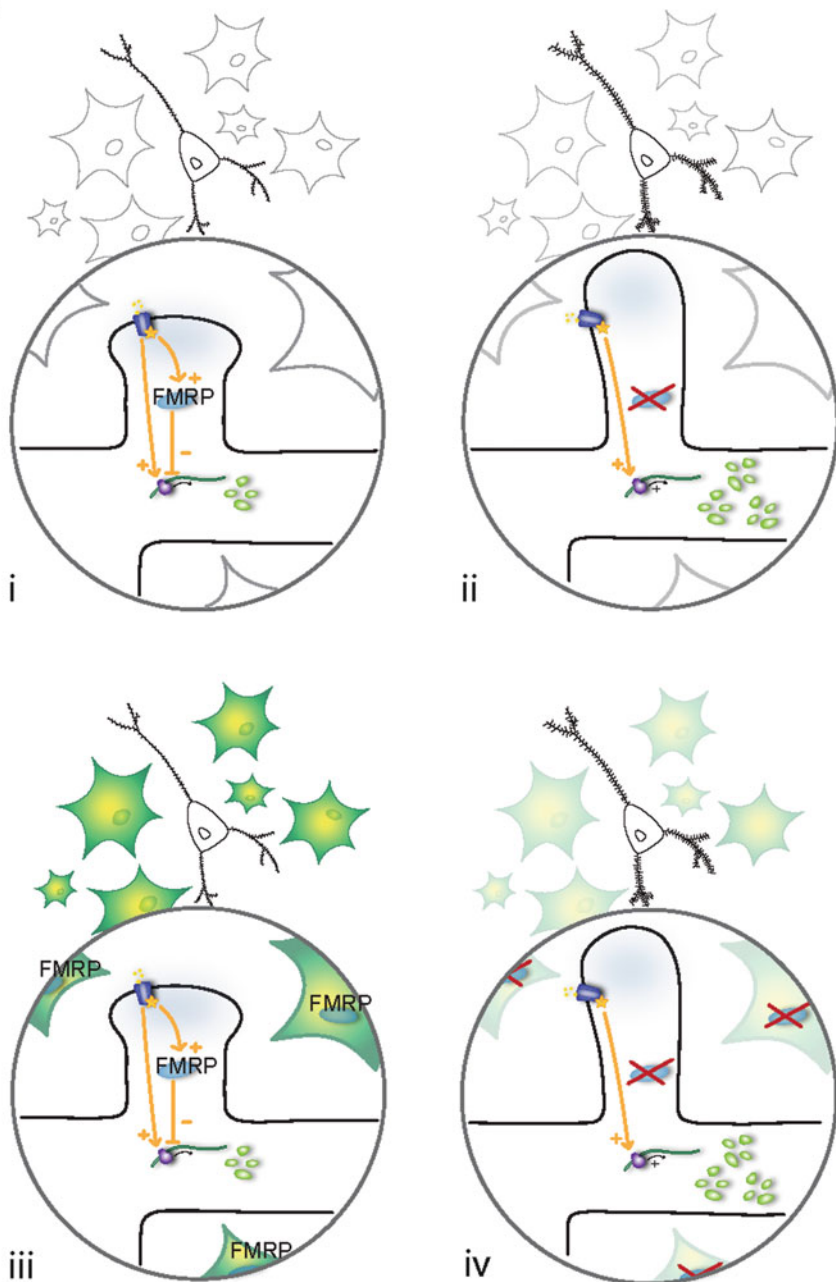
The first set of experiments focused on neurons in each of the four combinations, cultured for 7 days (Jacobs and Doering 2010). The neurons were studied with an antibody directed against microtubule-associated protein-2, (MAP2; a dendritic marker) and the pre- and postsynaptic proteins, synaptophysin and postsynaptic density protein-95 (PSD-95), respectively. The WT neurons grown on the *Fmr1* KO astrocytes had significantly altered dendritic arbor morphologies, with a shift toward a more compact and highly branched dendritic tree. These neurons also displayed a significant reduction in the number of pre- and postsynaptic protein aggregates. However, when the *Fmr1* KO neurons were cultured with the WT astrocytes, the alterations in dendritic morphology and synaptic protein expression were prevented. In fact, their morphological characteristics and synaptic protein

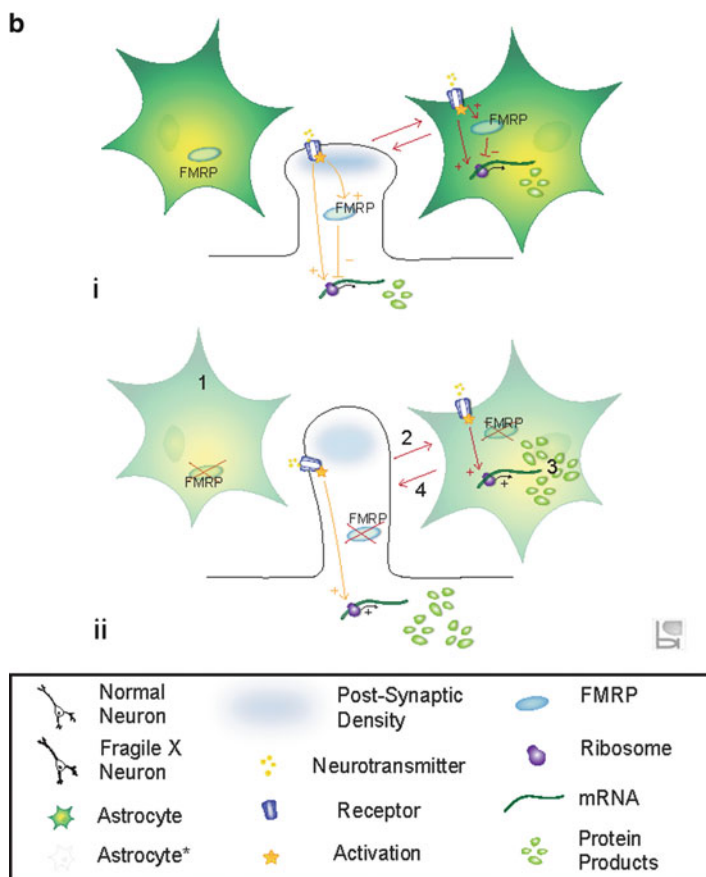
expression approached the appearance of the normal neurons grown with WT astrocytes. These experiments were the first to suggest that astrocytes contribute to the abnormal dendritic morphology and the dysregulated synapse development seen in Fragile X syndrome.

In the next phase of this research, we wanted to determine if these altered characteristics represented a developmental delay imparted by the *Fmr1* KO astrocytes (Jacobs et al. 2010). Focusing on WT neurons grown in the presence of WT or *Fmr1* KO astrocytes, we evaluated the dendritic arbor morphology and synaptic protein expression at 7, 14, and 21 days in culture. If we considered the developmental pattern of the WT neurons on the WT astrocytes to reflect a normal pattern of dendrite and synaptic protein development, we found a significant alteration to these patterns when WT neurons were grown with *Fmr1* KO astrocytes. Our results revealed that the WT neurons grown with *Fmr1* KO astrocytes displayed significantly altered morphological and synaptic protein profiles at 7 days (when compared to the WT condition); however, by 21 days in culture these differences were no longer significantly different from normal. On the basis of this research at this time, it appears that the astrocytes in the Fragile X mouse may contribute to the altered characteristics of neurons seen in Fragile X syndrome, in a developmentally regulated manner.

In preliminary studies to examine if neuronal subsets are preferentially affected, we performed Sholl analyses on the morphology of the neurons in the experiments described above. Our findings suggest that there is a bias in the extent of the morphological alterations imparted by the astrocytes to a subset of neurons with a stellate dendritic arbor morphology (unpublished results). However, it should be noted that in these experiments, the astrocyte involvement was assessed independently of the alterations that would be observed due to a lack of *Fmr1* (and therefore, FMRP) in the Fragile X neurons themselves. Therefore, the situation in vivo, having both neurons and astrocytes affected by a lack of FMRP may not truly reflect the experimental results in vitro. Additional experiments with a rigorous method of identifying subtypes of neurons (e.g., excitatory versus inhibitory neuronal markers) should be performed to specifically address this possibility.

These studies create numerous new avenues to identify and detail the role of astrocytes in the morphological alterations of neurons seen in Fragile X. Establishing key aspects to altered molecular relationships between astrocytes and neurons in Fragile X will lead to new therapeutic possibilities (Fig. 2.2). Are the alterations due to a lack of FMRP in the astrocytes or are the astrocytes abnormal because they develop and function in a diseased microenvironment? If the absence of FMRP in the astrocytes is the primary source of dysfunction, how are these effects translated to the neurons? For example, is the astrocyte–neuron signaling disrupted due to a lack of astrocyte-FMRP? How, where, and when do these signals act? Is the abnormal astrocyte–neuron communication mitigated by a membrane associated or a soluble factor? Finally, can these abnormalities observed in vitro be studied in vivo? These, and many other questions about the Fragile X astrocyte are now important targets for Fragile X research – the answers important in gaining a full understanding of the underlying neurobiology that contributes to

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**Fig. 2.2** The role of FMRP in astrocytes in Fragile X syndrome. (a) Historically, FMRP has only been associated with neurons. (i) With FMRP present there is regulated protein synthesis, normal dendritic spine morphology and no abnormalities associated with Fragile X syndrome (FXS). (ii) In Fragile X (in humans and in mouse models) there is a lack of FMRP in neurons leading to the dysregulation of synaptic protein synthesis, abnormal dendritic spine morphologies and features associated with FXS. (iii) Recent studies indicate that FMRP is present in both neurons AND astrocytes. (iv) In the *Fmr1* KO mouse (and presumably in FXS) FMRP is absent from both neurons AND astrocytes, and the astrocyte FMRP plays an important role in shaping the neuron morphology and synaptic protein profiles. (b) It is now important to investigate the role of astrocytes in Fragile X. (i) FMRP may play a similar role in astrocytes as in neurons, functioning as a regulator of protein translation. (ii) There are a number of possibilities for how the lack of FMRP in astrocytes may contribute to the abnormal neurobiology of FXS. (1) The astrocytes may be abnormal as a consequence of developing in an abnormal environment (and therefore not due to a direct effect of astrocyte-FMRP). (2) The neuron–glia signaling may be altered as a result of dysregulated FMRP-dependent protein synthesis, which in turn could alter astrocyte function (again, not due directly to astrocyte FMRP). (3) The translation of a subset of glial proteins may be dysregulated in the absence of astrocyte-FMRP. (4) The glia–neuron signaling may be disrupted due to an abnormal glial signaling protein profile (membrane bound or secreted) as a result of a lack of astrocyte-FMRP. \*Presence of astrocyte but not a key player. Figure © Biomedical Illustrations, 2011

the morphological phenotype seen in Fragile X, and in the potential of a future treatment for individuals with Fragile X syndrome.

## 2.6 Astrocyte Research in the Future

With each year passing, neuroscience research continues to unfold aspects of astrocyte involvement in health and disease. Each new molecular and cellular finding builds into the extensive functioning of how glial cells control and modify neuronal structure and communication.

Subtle changes in the connectivity patterns within subsets of neurons may significantly alter the output of the neuronal circuitry. Interestingly, mutations in the synaptic proteins neurexin 1 and neuroligins 3 and 4 are associated with autism spectrum disorders and mental impairment (Sudhof 2008). The postsynaptic scaffolding molecule and interacting protein of neuroligin SHANK3 (ProSAP2) is also associated with autism (Durand et al. 2007). Accumulating evidence illustrates roles for FMRP in synapse development and corresponding alterations in synaptic molecules in Fragile X (Pfeiffer and Huber 2009). In fact, synaptic function and structure may be the converging point of malfunction in many neurodevelopmental disorders such as Fragile X, RTT, and autism (Walsh et al. 2008; Geshwind 2008).

Together, the last three decades have created a more complete image of synaptic development and function both in health and in diseases of neurological dysfunction – one that is highly dependent on the glial cells of the CNS. Keystone papers by Pfrieger and Barres (1997), Ullian et al. (2001), Christopherson et al. (2005), and others revealed that astrocytes play a major role in the modulation of the development and functioning of synapses. Given the recent findings of astrocyte involvement in neurodevelopmental disorders such as RTT and FXS, it is realistic to now consider astrocytes as holding the key to avenues of intervention for learning disabilities that we previously did not appreciate.

Since many aspects of CNS development involve a neuron–glial interaction, solving neurological dysfunction will require solutions that include glial cells as part of the picture. To maintain a healthy microenvironment for neurons, it will be important to continue research efforts that target our understanding of how astrocytes interface with neuronal circuitry at the cellular and molecular levels. Modes of pharmacological therapy should indeed concentrate on the health of the astrocyte. With astrocytes as “gatekeepers” of neuronal health and function, if we can target astrocytes, then they may in turn take care of the neurons.

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Modeling Fragile X Syndrome

Denman, R.B. (Ed.)

2012, XII, 392 p., Hardcover

ISBN: 978-3-642-21648-0