Role of astrocytes in the central nervous system

The billions of cells in a mammalian nervous system can be classified into 2 distinct categories; The first being neurons, the primary communicating cell within the nervous system that is responsible for relaying messages within the central nervous system (CNS) and for transferring messages to cells in the periphery (Knott and Molnar 2001). The complex network of neurons needs to be regulated and the cells must be maintained, this is done by glial cells, the second category, a diverse group of cells that play an extremely important role in the functioning of the nervous system by providing both chemical and structural support (Knott and Molnar 2001). Glial cells can be separated into to sub-categories: Microglia, the immune cells of the nervous system and macroglia. Astrocytes fall into the category of macroglial cells, along with oligodendrocytes and are intimately involved in the activity of neurons and in the CNS and their actions at synapses (Panatier and Robitaill 2007).

Astrocytes are the most abundant type of glia (Panatier and Robitaill 2007). They are a highly branched cell found in almost all regions and having some type of association with vitually all processes occurring within the CNS (Reichenbach and Derouiche 2010). Evidence has implicated an involvement of these cells in neurovascular coupling, neurogenesis, synapse formation, neuronal excitability and synaptic transmission. They are also play a part in inflammatory responses and are known to supply metabolites essential for neurons (Panatier and Robitaill, 2007).

Fig 1: One astrocyte enwraps several neuronal somata (top-view reconstructions) A- an astrocyte labelled with enhanced green fluorescent protein. B- immunofluorescence labelling of neuronal somata, the cell bodies

within the astrocytic territory shown in red (yellow arrows). C- image shows how the astrocyte ensheaths multiple somas(at least 50% of the surface area of a neuron had to make contact with the astrocyte to be considered as having sufficient interaction.) Any one astrocyte interacts with an average of 4 cortical neuron cell bodies, with an upper limit of eight and 300-600 neuronal dendrites are in contact with a single astrocyte. (Adapted from Halassa et al 2007).

An astrocyte cell consists of a small cell body surrounded by a complexity of processes that have close affiliations to both neuronal and vascular elements. Towards the periphery of the cell the processes become increasingly finer and they surround neuronal cell bodies, dendrites and synapses (Theodosis et al 2008). Halassa et al (2007) proposed a concept of functional islands of synapses. Astrocytes from both in-situ and in-vivo were labelled with enhanced green fluorescent protein and a three dimensional reconstruction was created (Fig 1). This study suggests that clusters of synapses confined within the domain of a specific astrocyte are modulated by the environment that is controlled by that astrocyte , forming synaptic islands(Halassa et al 2007). Oberheim et al (2006) describes an astrocyte domain as defining a close group of synapses that interacts solely with an individual astrocyte so synapses within a particularly territory are linked via a shared astrocyte (Oberheim et al 2006). This can be backed up by the fact that astrocytes appear to be evenly distributed with very little prominant area of overlap (Ogata and Kosaka 2002)(Fig. 2).. Each astrocyte occupies a discrete area with a limited overlap only at its periphery (Ogata and Kosaka 2002). Astrocytic domains are most clearly deï¬ ned in areas of high

synaptic density, including hippocampus and cortex, this could suggests that the domain organization might be important for astrocytes as modulators of synaptic transmission. Oberheim et al (2006). This is important functionally as it means that astrocytes are capable of interacting with neurons in a restricted microenvironment (Theodosis et al 2008). They are also are highly mobile cells and convey remarkable structural plasticity at the level of their distal processes. These processes can undergo morphological changes that adjust both the shape and diffusion properties of the extracellular space varying the cells relationships with adjacent neuronal elements (Theodosis et al 2008).

Fig 2: Two astrocytes intracellularly labelled with two different tracers LY (green) and CB(red) in the mouse hippocampus. Overlap occurs only at the peripheral rims of the cells whereas its inner core portion is not penetrated by processes form the adjacent cell A – In this projection image the border between two labeled astrocytes appears to overlap. B – The side view of the trace image of A. Shared volume is seen as area occupied with yellow lines. The overlap between two astrocytes is limited. (Adapted from Ogata and Kosaka 2002).

Astrocytes regulate the ionic environment in the brain, upholding a stable environment that allows neurons and chemical synapses to function normally (Panatier and Robitaill 2007). This role of regulating extracelltrlar space and transport of ions, metabolites and micromolectdes. for astrocytes was first proposed in the 1950’s and is now well covered in scientific literature (Vernadaki 1996). It is now established belief that neurons transmit signals to glial cells during an action potential by releasing K+ as well as a chemical

mediator into the extracellular space. This rise in the extracellular K+ concentration triggers the release of acetylcholine from the astrocyte which then acts on receptors on the cell surface of the astrocyte to decrease the condacnce of Cl- subsequently leading to hyperpolarisation of the cell (Vernadaki 1996). The uptake of the excess K+ by astrocytes raises the intracellular level of K+ in. This rise in K+ will then be distributed to other parts of the astrocyte or even to different astrocytes through gap junctions. Astrocytes regulate K+ concentration by rapidly removing K+ to redistribute away from the intitial area for example in regions where neuronal activity is not so high (Panatier and Robitaill 2007). There is a close relationship between extracellular K+ concentration, extracellular pH and extracellular volume (Vernadaki 1996). A significant change in pH can be detrimental to regular neuronal function, having a great effect on neuronal excitability by altering ion-channel gating and conductance along with synaptic transmission, intercellular communication via gap junctions and metabolite exchange. (Panatier and Robitaill 2007). Astrocytes play a part in controlling the pH by transporting protons(H+) and HCO3- using the Cl- /HCO3- exchanger, the Na+ /H+ exchanger and the carbonic anhydrase enzyme, which converts carbon dioxide into HCO3- (Panatier and Robitaill 2007). Other important environmental regulatory functions of astrocytes include the ellimination from the extracellular space of various harmful metabolites, through the intricate and interconnected processes of the astrocytic network these metabolites can be redirected through gap junctions and ultimately released into the blood stream(Panatier and Robitaill 2007).

Over the past decade more and more evidence has been presented to suggest that astrocytes are intimately associated with the control of neuronal activity and synaptic neurotransmission (Araque et al 1999). Astrocytes not only respond to signals form neurons but also actively regulate the neuronal and synaptic action. Perea et al (2009) reviewed the fact that astrocytes must be considered as fundamental parts of synapse, along with the presynaptic and postsynaptic terminals, and play an important role in synaptic physiology. This is the idea that synapses in the CNS are tripartite, based on the notion of the occurrence of reciprocal communication between astrocytes and neurons (Perea et al 2009). Our understanding of the mechanisms resulting in its formation, maintenance and turnover is still limited (Reichenbach and Derouiche 2010).

Astrocytes can sense neuronal activity through a wide variety of neurotransmitter receptors and ion channels that are expressed on the surface of their ï¬ ne processes (Theodosis et al 2008). Activation of these receptors evokes a rich repertoire of responses including an increase in their intracellular Ca2+ concentration and the release of gliotransmitters. (Newman 2003). When a presynaptic terminal is depolarised by an action potential it releases neutransmitters into the synaptic cleft, the neurotransmitter then binds to specific receptors on the postsynaptic terminal triggering a range of different mechanisms that overall result in depolarisation of the postsynaptic element and the occurrence of an action potential (Fig 3 B). In order to maintain efficient synaptic transmission the neurotransmitter must be effectively cleared from the synaptic cleft (Panatier and Robitaill 2007). Astrocytes have a neurotransmitter specific

transporters for the uptake of neuro transmitters, glutamate in particular, this means they are likely to be involved in the termination of the effect of the transmitters on the synapse (Fig 3 A) (Panatier and Robitaill 2007).

Astrocytes are excitable cells, their membrane depolarises as a result of an elevation in intracellular Ca2= concentration (Perea and Araque 2006). This increase in cytosolic Ca2= can be a result of mechanical stimulation or neurotransmitters released by synaptic terminals but can also occur spontaneously. Perea and Araque (2006) emphasise the importance of the synpatically evoked Ca2+ signal because it reveals a key aspect of the signalling pathway between astrocytes and neurons. The majority of neurotransmitter recptors expressed by the astrocyte are metatrobic G-protein coupled receptors which when activated stimulate hospholipase C and the formation of inositol(1, 4, 5)-triphosphate (IP3) which increases the intracellular Ca2+ by triggering its release from intracellular stores in the endoplasmic reticulum (Perea et al 2009) (Fig 3 B). The Ca2+ increase is initiated in subcellular microdomains, restricted areas of the astrocyte processes, and can remain in these regions. Intracellular extension of the astrocyte Ca 2+ signal occurs if the frequency of synaptic activity is relatively high, whereas at low synaptic activity the signal remains confined (Perea and Araque 2005). Early studies using cultured cells such as Charles et al (1991) and Cornell – Bell et al (1990), also showed that the astrocyte Ca 2+ signal can propagate to neighboring astrocytes as an intercellular Ca 2+ wave involving dozens of cells. This Implies that networks of astrocytes could constitute a long-range signaling system within the brain (Cornell – Bell et al 1990). This research can be backed up by a recent study conducted by Kuga

et al (2011) in which simultaneous regenerative calcium waves occurred in hundreds of mouse hippocampal astrocytes in vivo and propagated from cell to cell.

Three different models have been proposed for the propagation of Ca2+ waves through the astrocytic network of the CNS (Perea and Araque 2005). The first is the diffusion of IP3 through gap junctions to neighbouring astrocytes (Perea and Araque 2005) (Fig 3 E). IP3 then stimulates the release of Ca2+ from the intracellular calcium stores. When an astrocyte is stimulated the Ca2+ increase triggers the release of adenosine triphosphate (ATP) through calcium dependent exocytosis or through connexin hemichannels. Another proposed model suggests the ATP molecules then act as extracellular messengers activating purinergic receptors in neighboring cells and instigating a sequence of events involving the activation of phospholipase C, IP3 production and Ca 2+ elevations, the subsequent ATP release will then regeneratively propel the wave. The third model suggests that it is the extracellular diffusion of ATP released exclusively from the stimulated cell that is responsible for the entire wave (Perea and Araque 2005). In a review of the subject Perea and Araque (2005) indicate the possibility that all three coexist under different conditions are different areas of the CNS. Calcium waves are means in which astrocytes can transmit messages to away from the synapse but he increase in Ca2+ concentration in the astrocyte initiates additional glial responses.

The increase in intracellular Ca2+ concentration results in a release of gliotransmitters. (Newman 2003) This a means in which astrocytes modulate synaptic transmission. A single gliotransmitter can wield numerous

consequences depending on the sites of action and the activated receptor subtypes, providing a substantial degree of complexity to astrocyte-neuron communication (Perea et al 2009). Glutamate released from astrocytes plays a role in modulating the activity of both the pre and post synaptic terminals (Fig 3 C) (Newman 2003). As mentioned before ATP is released by a stimulated astrocyte, not only does this aid the propagation of the calcium wave but it also has an inhibitory effect on the post synaptic neuron (Fig 3 D) D-serine is synthesized and released by astrocytes, it acts as a coagonist with glutamate at NMDA receptors (NMDARs) and has an role in -dependent long-term potentiation (LTP) in the Schaffer collateral pathway of the hippocampus (Paixão and Klein 2010). Glial cells are also the source of the cytokine tumor-necrosis factor-a (TNF-a). This gliatransmitter is involved in adjusting the strength of a synapse globally in response to prolonged changes in activity and is also required for experience-dependent plasticity in the developing visual cortex (Paixão and Klein 2010).

Fig 3: Examples of some of he Proposed Mechanisms of Astrosyte Regulation of the Synapse. A: Astrocytes modulate synaptic transmission by uptake of glutamate and by regulating extracellular K+ and H+ levels . B: Release of neurotransmitter (in this case glutamate(Glu)) from the presynaptic terminal activates receptors on astrocytes leading to an increase in IP3 levels and a release of Ca2+ from intracellular stores. C: the increase in Inracellular Ca2+ triggers the release of astrocytic glutamate. Glutamate activation of presynaptic receptors regulates transmitter release, while activation of postsynaptic receptors directly depolarizes neurons. D: Stimulation of the astrocyte also elicits the release of ATP, which inhibits postsynaptic neurons

by activating A1 receptors. E: A calcium wave may also in induced Activation which propagates between aastrocytes by diffusion of IP3 through gap junctions and by release of ATP , and results in the modulation of distant synapses. (adapted from: Newman 2003)

Astrocyte action is not exclusive to synapses, they are alo known to promote the myelinating activity of oligodendrocytes(Ishabishi 2006). A myelin sheath is essential for the conductance of a typical impulse in a neuron (Ishabishi 2006) It has recently been uncovered that astrocytes promote oligodendrocyte progenitor migration, proliferation, and differentiation thereby functioning as mediators of CNS myelination (Moore et al 2011). Aswell as that they have a key involvement in the blood-brain barrier releasing chemical factors that modulate endothelial permeability and controlling the long term inductionand maintenance of the barrier (Abbott 2002). Astrocytes as a network of cells couple synapses and capillaries modulating local blood flow to control cognitive function (Paixão and Klein 2010).

The discovery that astrocytes are active partners of neurons in brain communication is key to understanding brain processes not just in normal conditions but also in diseases of the CNS. The astrocytic Ca2+ signal has been shown to be altered in areas of lesions in many brain pathologies including traumatic injury and Alzheimer’s disease in turn this leads to alterations in the Ca 2+ -dependent glutamate release. These events may lead to important pathological changes in surrounding areas due to effects of changed modulatory control of neighbouring synapses or excitotoxic damage to nearby neurons(Rossi and Volterra 2009). Growing evidence also indicates

that under certain pathological circumstances, astrocytes become vulnerable to non-toxic stimuli, so a slight rise in the glutamate concentration in the external environment may cause progressive degeneration of the cell. This means surrounding neurons can be deprived of their optimal microenvironment having detrimental consequences on the function and survival of neurons (Rossi and Volterra 2009). Evidence can also be presented to show their involvement in epilepsy although it is still unclear as to whether the glial abnormalities are the cause of the condition or a consequence, (Seifert et al 2010) this can also be said for many other neurological disorders. It is clear however, that astrocyte malfunctioning cannot be simply considered as insignificant events or simple reactions to neuronal injury, but as intrinsic machinery of the neurodegenerative processes (Rossi and Volterra 2009).

The classically accepted paradigm that brain function results exclusively from neuronal activity can now be rejected. The development of neurophysiological research over the past decade has shown that brain function actually results from the coordinated activity of a network of both neurons and glial cells (Perea et al 2009). It is only recently that the essential role of astrocytes in the CNS has come under critical investigation and we have only jut touched the surface when it comes to knowing and understanding the mechanisms involved in astrocytic synaptic modulation and the many other crucial functions credited the extrodinary glial cells, I have mentioned only a few in detail. Indeed it is also possible that there are yet still many more regulatory responsibilities that have not yet been uncovered. Understanding the mechanisms involved in the functioning of

astrocytes has the potential to in the development of novel treatments where malfunctioning astrocytes can be targeted, for disorders of the CNS and help understand what triggers the different pathological states.