Module:
Biological Foundations of Mental Health

Week 2
Building blocks of the brain

Topic 1
Neuron-glial interactions and mental health – part 1b

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Lecture transcript

Slide 2

What are the consequences of the gliotransmission - that is the release of gliotransmitter by astrocytes? And what are the consequences of astrocytic modulation at the tripartite synapse for brain function and behaviour? The simple answer is, we don't know for sure. But there is some evidence for a possible role in memory and in sleep regulation.

For what concerns their role in memory, evidence include the finding that, in brains slices, astrocyte activity can modulate long term potentiation LTP - as I mentioned before, a strengthening of synaptic connectivity, a mechanism, which is thought to underlie memory information as you have seen in the reading that you have just performed. Other experiments in vivo also support the idea of an involvement of astrocytes in cognition. We are now going to look at an example of a study on astrocyte and cognition.

Slide 3

This is a diagram from an article by Han and colleagues, published in 2012. They perform some experiments in mice. They were exploring the mechanisms underlying working memory impairment, which is observed after cannabinoid exposure. In humans, one of the most significant consequence of marijuana intoxication is in fact, an impairment in working memory. But the mechanism was so far unknown.

In this study, they examined conditional mutant mice - that is mice that lack type 1 cannabinoid receptor, CB1R in this slide, selectively either in brain astroglial cells or lacking CB1R in either glutamatergic or GABAergic neuron. Glutamatergic neuron release the excitatory neurotransmitter glutamate, and GABAergic neuron release the inhibitory neurotransmitter GABA.

They exposed these different types of mice lacking the cannabinoid receptor either on astrocytes or the two different type of excitator and inhibitor neurons acutely to cannabinoids. They found an impairment of spatial working memory in mice that lacked the CB1 receptor on glutamatergic or GABAergic neuron. But they found that preservation of this spatial working memory in mice that lack the astrocytic CB1 receptor. They also found that LTD - long term depression of synaptic strength - at these hippocampal synapses was preserved in mice lacking the astrocytic CB1 receptor, and was impaired in mice lacking the CB1 receptor in neurons.

Han and his colleagues explained their results assuming that cannabinoid exposure in vivo

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sequentially activates astroglial cannabinoid 1 receptor. This leads to a glutamate release from astrocytes, which then will lead to activation of post-synaptic NR2B an MDA receptor, here in three, which then elicits AMPA receptor, endocytosis. This would result in working memory impairment. It has to be noticed that other authors has shown that CB1 receptor exists in astrocytes at this location in the hippocampus, and they also show that they exist in the neurons in the presynaptic membranes of glutamatergic and GABAergic neuron.

They also observed that the density of this receptor is 10 to 20-fold higher in GABAergic neurons versus glutamatergic neurons. They found that GABAergic and glutamatergic terminals containing these cannabinoid receptors do synapse with dendrites and spines of pyramidal cells as indicated in this diagram. Activation of this presynaptic cannabinoid receptor reduces the release of glutamate and GABA from glutamatergic and GABAergic neurons respectively. However, since in the study presented here by Hahn et al., they showed that cannabinoid could exert their actual working memory also in the absence of the receptors neuron, they could conclude that astrocytes were mediating their action. The finding, presented here, supports the idea that astrocytes can play an active role in cognition, and a role in its impairment in pathological state.

Slide 4

Another behaviour that astrocytes might have a role in controlling is sleep. For some time it has been known that adenosine plays a role in controlling sleep homeostasis. In particular, accumulation of adenosine during wakefulness promotes sleep. On the contrary, adenosine antagonist, such as caffeine, notoriously promote wakefulness.

A number of studies have shown that the source of adenosine is astrocytes, and these regulate sleep homeostasis. Actually, as shown in this slide, astrocytes actually release ATP, and this is converted to adenosine extracellular. As we've seen, astrocytes can release gliotransmitter by different pathways, including exocytosis.

The exocytotic release of chemical transmitter depends on the formation of a complex, which is dependent on a protein called SNARE between vesicle and the target membrane. It is possible to genetically modify mice so that this SNARE dependent release of gliotransmitter is abolished. These are mice with the conditional astrocyte selective expression of the SNARE domain of the protein synaptobrevin-2, the so-called dominant negative SNARE. This genetic modification prevents both tonic and activity dependent extracellular accumulation of adenosine, which acts on A1 receptor, as shown here.

Studies in these transgenic mice incapable of exocytosis in astrocytes have demonstrated the role for gliotransmission in the control of sleep. In the words of Halassa and his coworkers, which made this discovery, taken together these studies provide the first demonstration that the non-neuronal cell type of the brain, the astrocyte, modulate behaviour and provide strong evidence of the important role of A1 receptor in the regulation of sleep homeostasis and the cognitive decline associated with sleep loss.

Slide 5

The previous slide we've seen how astrocytes may affect memory and controlled sleep. Does this indicate that they may contribute to mental health pathology, considering that many mental health disorders affect cognition and exhibit sleep co-morbidities?

We're going to explore these issues in part two. But for the moment, let's look at the other feature of astrocytes, which may be important in determining their influence on behaviour - that is their organisation in astrocytic networks.

Slide 6

Astrocytes can be directly coupled with neighbouring astrocytes via gap junction, which form

aqueous channels between cells. These gap junctions allow the passage of ions and small molecules therefore they allow direct intercellular communication. In astrocytes, gap junction are formed by two proteins: connexin-30 and connexin-43. It is possible to study the coupling of astrocytes into networks injecting a soluable fluorescent dye in astrocytes, such as biocytin.

In this micrograph, this dye was injected in the astrocyte labelled with a white star, and diffused to all astrocytes labelled in red in this figure, which the four are connected to the injected one in a network. In green are astrocytes outside the network. Gap junctions display selective permeability, and this permeability can be regulated.

Furthermore, permeability is age-specific and region-specific. Gap junction can also be studied in transgenic animals in which both connexin-30 and connexin-43 have been knocked out. These animals are unable to form functional gap junction.

Slide 7

What do astrocytic networks do? Well, one important consequence of the coupling of astrocytes in networks is the way in which this type of organisation allows for calcium rises, which are induced by a neurotransmitter acting on to metabotropic receptor on the membrane of an astrocyte to spread to connect the astrocyte, generating the so-called calcium waves, as shown here in the left panel. Combining these with the concept of gliotransmission, spreading calcium waves may cause gliotransmitter release at remote synapses from the astrocytes which was originally activated. In the panel on the right, the role that astrocytic processes in blue could have at nearby glutamatergic synapses in red is shown.

In A, only neuroglial interaction occurring at the three part of synapses are taken into consideration - so just an astrocyte and a synapse. The different steps involved in these dynamic interaction are initially the first step, the release of neurotransmitter by the presynaptic neuron. This neurotransmitter will act on receptor and transporters in the astrocyte. These will lead to the release of gliotransmitter, which in turn can influence neuronal activity.

In addition to these three steps, glutamate that has been taken up by a neighbouring astrocyte, and also the glutamate derivative glutamine, can diffuse and permeate through gap junction channels of astrocytic networks, represented here by yellow stars. This trafficking may result in the subsequent release of gliotransmitter at the remote synapse, or even at the extrasynaptic sites, and hence, affect the activity on the underlying neuronal network.

Slide 8

What can astrocytic networks do? Evidence is available that they can regulate the generation of a rhythmic firing pattern in neuron. This is necessary for several vital functions, such as respiration and mastication.

It is intriguing to note that respiratory rhythm is disrupted in Rhett Syndrome, which is an autism spectrum disorder that is a neurodevelopmental disorder. Active astroglial networks have been also proposed to function as a master hub, which integrates the result of distributed processing from several brain areas and support conscious states. Indeed, Pereira and Furlan in 2010, proposed that astrocytic network are essential for voluntary behaviour. Only automatic behaviour could be executed purely by neuronal network.

Dysfunction of these astrocytic networks, therefore, could lead to cognitive impairment. It is however, not clear if changes to the astrocytic network are cause or consequence of neuronal dysfunction. In part two, the potential involvement of astrocytic network dysfunction and depression will be illustrated.