Exploring the role of astroglia in Down syndrome

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In Down syndrome (DS), astrocytes are increased in number and size in the hippocampus and also exhibit higher levels of activity, which reduces neuronal activity[1]. Although astrocytes were considered to provide just structural and metabolic support to neurons in the brain, compelling evidence suggests that they are able to communicate with neurons and to influence their responses by the release of several neuroactive substances that can depress or potentiate neuronal responses [2]. We propose that astroglial alterations in DS have disruptive effects in the synaptic transmission of the hippocampus, a highly interconnected and specialized structure involved in learning and memory.

Background

Recently, the conception how brain works in normal and pathological conditions has changed and the astrocyte has gained importance. Astrocytes are star-shaped cells in the brain that participate in a wide range of processes. Astrocytes provide neurons with nutrients and structural support in the brain. Astrocytes also respond to inflammatory processes such as brain injury or infections. Traditionally, neuroscientists have focused their efforts in understanding how neurons communicate in the brain not only in normal conditions but also in cognitive disorders. However, during the last two decades, it has been demonstrated that astrocytes are able to sense and respond to neuronal communication influencing how neurons communicate with each other [3].

In DS, the triplication of the human chromosome 21 (HSA21) affects the astrocyte population at different levels. Astrocytes are increased in number and size in brain of individuals with DS[4]. Astrocytes in DS present higher levels of activity, which has been demonstrated to reduce the activity of neurons[1]. The communication between neurons and their synchronized activity in the brain is essential for learning and memory. In fact, recent evidences show that astrocytes are important for memory as inhibiting their activity resulted in memory deficits in mice[5]. On the contrary, astrocyte activation improved memory performance[2]. For this reason, it has been proposed that astrocytes could have a unique function in learning and memory processes.

Problem Statement

In Down syndrome, neurons present several abnormalities. For instance, both in mouse models for DS and in brains of individuals of DS there is a reduction in the arborization of neurons, which is important for receiving information coming from other neurons. Brain is a plastic structure and changes in response to new experiences such as learning. In DS, these changes (also called neuronal plasticity) are altered[6]. In fact, both neuronal alterations and neuronal plasticity deficits are signatures of cognitive dysfunction. However, besides the alterations in the neuronal component, a growing number of evidences support that astrocytes are also contributing to the cognitive dysfunction in DS.

Given that astrocytes can not only influence but also synchronize neuronal communication, we propose that astrocyte dysfunction in DS may have negative effects in the neuronal populations that are involved in learning and memory, such as the

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hippocampus. In particular, we suggest that in DS, astrocytes impair how neurons change in response to learning according to previous studies that report that higher astrocyte activation reduces neuronal activity[1].

Our research

During the last few years, evidence has demonstrated that astrocytes are involved in brain function beyond the classical view of supporting cells. In fact, a single astrocyte can sense and respond to the activity of several neurons influencing how neurons communicate.
Additionally, it has been demonstrated that astrocytes can influence in how neurons change in response to learning[5]. Astrocyte activity can strengthen the communication between two neurons, which is the main mechanism proposed to contribute to the generation of new memories. These strengthening in the communication between neurons is altered in different mouse models for DS. These models also present deficits in learning and memory. Very recently, it was reported in mice, that only the astrocyte activation the hippocampus, a brain structure important for learning and memory could improve memory formation[2]. Finally, it was also demonstrated inhibiting the communication between astrocytes and neurons also impaired learning and memory in mice[5].

Traditionally, neuroscientists have focused their attention onto the neuronal component of the brain to understand the basis of cognitive deficits in DS. However, the contribution of astrocyte alterations to the cognitive deficits in DS has not been investigated. Studies performed in brains of individuals with DS[4] revealed an increased number and size of astrocytes together with alterations in the mechanisms that astrocytes use to communicate with neurons5. Besides, the astrocytes in DS present increased activity which reduce neuronal activity[1]. Therefore, our research project aims to discover to what extent astrocyte dysfunction in DS can contribute to the learning and memory deficits observed in mouse models for DS. To this aim, we are studying how astrocytes are able to influence neuronal activity in DS by using the Ts65Dn mouse model, which present most of the brain alterations and memory deficits of individuals with DS. We showed that the number and size of astrocytes are increased in particular regions of the hippocampus that are related to memory formation and in the recall of memories while neuronal population is not altered (**Figure 1**). We have also found some alterations mainly in the astrocytes suggesting that astrocytes are bigger compared to control mice. Our next steps include the study of the astroglial mechanisms involved in how astrocytes communicate with neurons together with how astrocytes respond and integrate neuronal activity.

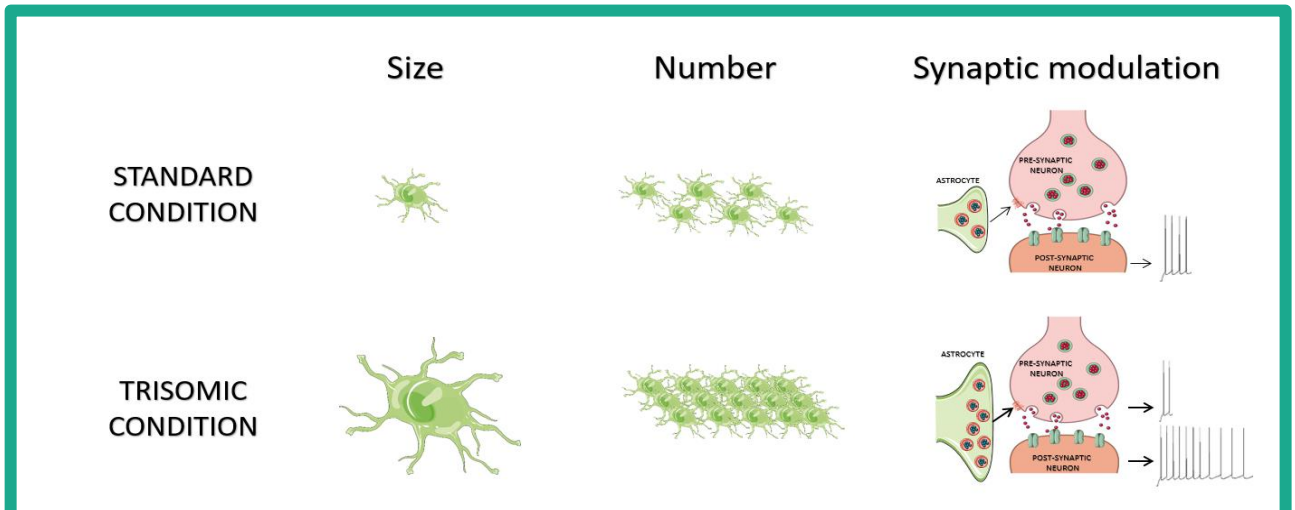

Figure 1 Schematic representation astroglial changes in the hippocampus comparing control mice with trisomic mouse models for DS. We found that astrocytes are increased both in number and size in several regions of the hippocampus of Ts65Dn mice. We hypothesize that these changes together with alterations in how astrocytes influence neuronal activity in Down syndrome can contribute to impair how neurons communicate with each other either by increasing or decreasing the signals that neurons generate (called action potentials) which are essential in the hippocampus for learning and memory processes.

Implications for people with Down syndrome, their family members and caregivers.

Despite this research project is still in its initial steps, it will provide us a new vision of the basis of cognitive deficits in DS, uncovering possible new mechanisms involved in the learning and memory deficits of this human condition. Moreover, it will provide us new targets to develop novel therapeutic strategies.

Conclusion

An increase in the number and size of astrocytes is found in the hippocampus of a trisomic mouse model for DS (Ts65Dn) which may affect astrocyte-neuron communication in this structure important for learning and memory.

Physiological neuronal properties of hippocampal CA1 neurons in Ts65Dn are preserved.

Given that intact function of local astrocyte networks is critical for complex cerebral functions, we suggest that altered balance of astrocyte-neuronal signaling can contribute to Down syndrome cognitive impairment.

References

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Take home message

- Astrocytes play an important role as modulators of neuronal activity
- Astrocytes pathophysiology is a hallmark of Down syndrome, presenting increased number and size.
- Study how astrocyte are capable to modulate the communication among neurons is disrupted in DS can provide better understanding of neuropathological basis of DS and new targets to develop novel therapies.