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EDITORIAL

Synaptic metabolism and brain circuitries in inborn errors of metabolism

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Abbreviations
IEM inborn errors of metabolism

More than 300 new inborn errors or metabolism (IEM) have been described during the last 5 years and most of them have major neurological symptoms (Ferreira et al. 2018; Saudubray and Garcia-Cazorla 2018). These disorders have changed paradigms transforming the concept and classification of IEM and are contributing enormously to our understanding of mechanisms in neurological diseases. A pioneer initiative in this direction was the description of the vast new group of complex lipid synthesis and remodelling defects that stands at the frontier between classical IEM and cellular neurobiology (Lamari et al. 2015). More recently, many defects affecting systems involved in intracellular vesiculation, trafficking, processing and quality control of complex molecules, such as protein folding and autophagy (Ebrahimi-Fakhari et al. 2016), have described a number of diseases with important repercussion in the brain.

The -omics era is currently transforming neurology, and in particular child neurology, with the description of an increasing amount of new monogenic diseases. However, the pathophysiological approach to these disorders is mostly based on neuroanatomy, neurophysiology and the description of individual proteins. The role of metabolism, which strongly orchestrates neuronal function, has been mostly neglected in the study of brain disorders. On the other hand, the description of biological mechanisms of disease in the field of IEM has not fully considered the particularities of the nervous system. The human brain is a unique system that exhibits a complex architecture and a great diversity of functions and cellular types. Neurons are large and highly polarised cells consisting of axons and dendritic arborisations that communicate with each other through synaptic contacts, which are essential to their function. To integrate information within and between compartments, neurons need sophisticated transfer mechanisms, ensuring that necessary molecules are available in the right place at the right time. Metabolism is regulating these functions and appears to have specific properties at every single neuronal compartment. Metabolism has also specific rules depending on the specific subtype of nervous cell (different populations of neurons, glia, oligodendrocytes, microglia…). An important model of compartmentalised signalling and metabolism occurs at the synapse, which is the main topic of this special issue.

The synapse is a highly specialised cell junction that connects a presynaptic transmitting neuron with a postsynaptic receiving neuron. Synapses connect more than one hundred billion neurons present in the human brain, and wire-select neurons into functional circuits, enabling the brain to process and transfer information (Südhof 2013). The concept of "synaptic metabolism" is introduced in this special issue and is the conducting wire of most of its articles; it could be defined as the specific chemical composition and metabolic functions occurring at the synapse. The presynaptic and postsynaptic terminals have specific patterns of proteins and lipids; and even within each of these compartments, there are specialised areas. As an example, the active zone, a specialised region for neurotransmitter release at the presynaptic plasma membrane has a unique protein and lipid composition compared to other areas of the neuronal membrane (Cortès-Saladelafont et al.

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2018; Mochel 2018). The same is true for the postsynaptic density, characteristic of the postsynaptic element of excitatory synapses (Bayés and Grant 2009). Mitochondria, for instance, are concentrated at the presynaptic terminal, where they have specific bioenergetic properties, yet they are absent from the postsynaptic compartment. Additionally, the synaptic vesicle (SV) cycle, crucial to neurotransmission, is a complex mechanism involving many different elements: the structure and composition of the SV itself, exocytic and endocytic processes and interactions between proteins and lipids among other biological functions. Since the SV is an independent organelle, such as mitochondria and lysosomes, diseases of the synaptic vesicle may encompass a category of disorders itself (Cortès-Saladelafont et al. 2018). These diseases present with the constant features, including neurodevelopmental delay or intellectual disability, and a spectrum of signs comprising epilepsy, behavioural problems and movement disorders.

Interestingly, and as an innovative aspect in the field of IEM, our knowledge about synaptic metabolic diseases remains almost exclusive to the presynaptic and astrocytic level. In fact, little is known about the metabolic pathways operating at the postsynaptic terminal, although its complex signalling machinery has been strongly related with intellectual disability. This postsynaptic approach is described in this issue by Dr. Àlex Bayès (Bayés 2018; Bayés et al. 2011) as a global overview and by Drs. Abela and Kurian (Abela and Kurian 2018) in the case of movement disorders.

In practical terms, deeping into the concept of synaptic metabolism will contribute to a better understanding of the biological basis of neurometabolic diseases as well as providing potential new categories of IEM (such as the diseases of the SV). Additionally, it represents a perfect example of the necessity of combining classical metabolism and cell biology in neurometabolic and neurogenetic diseases in general (García-Cazorla and Saudubray 2018). This integrative approach will probably redefine the current perspective about the pathophysiological categories of IEM and, most importantly, will provide new therapeutic options. The study of the cerebrospinal fluid by means of new -omic techniques (metabolomics, lipidomics and proteomics) seems a promising strategy to search for biomarkers leading to a better characterisation of these diseases. Finally, in order to face this extremely changing and complex field, clinical neurologist and metabolic physicians will need renewed and advance educational programmes able to efficiently combine the traditional clinical approach with a pathophysiological-based perspective.

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Compliance with ethical standards

Conflict of interest Àngels García-Cazorla, Rafael Artuch and Àlex Bayès declare that they have no conflict of interest.

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Animal rights Not applicable.

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