Postsynaptic Proteins Play a Major Role in Neurological and Psychiatric Disease

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At the turn of the 20th century[1] Sir Charles Sherrington coined the term synapse to describe the specialised junction between nerve cells. While it has been known for decades that synapses show abnormal structure and function in diseases, the awareness that many important neurological and psychiatric diseases can be caused by synapse dysfunction has only recently been appreciated. The term 'synaptopathy'[2] is now used to describes pathology of the synapse. Recent advances in our understanding of the protein composition of human synapses together with genetics has provided the first systematic view of the genetic basis of human synaptopathies.[3] Mutations of postsynaptic proteins cause a striking number and range of diseases, and through the use of systems biology approaches it is now possible to understand the relationships between these diseases. In addition, molecular network diagrams of the proteins and diseases can be used to explore new therapeutic strategies. In this review, we will highlight some of the insights from this recent study on the proteome of neocortical synapse disease.[3]

Synapses are formed by the contact between the axonal presynaptic terminal on one neuron and the postsynaptic terminal on dendrites of another neuron and information is transmitted between neurons by the release of neurotransmitters. Thus, the postsynaptic terminal is the point on the surface of a neuron where information is received. In the late 1950s[4] electron microscopy showed that the postsynaptic terminals of excitatory synapses had an electron-dense zone beneath the postsynaptic membrane (Figure 1a,b) which was named the Post-Synaptic Density (PSD). This electron density is caused by the high concentration of proteins, which allows for it to be isolated using biochemical fractionation.[5] While it has been possible to isolate PSDs for several decades we have had to wait until recent improvements in proteomic methods to have a detailed identification of the individual proteins and the genes that encode them. PSD proteins can be systematically identified using sensitive mass spectrometry and DNA sequence information which form the basis of much modern proteomic technology.

The uses of proteomics for identification of large numbers of synapse proteins began a decade ago with studies in the mouse and we now know that the PSD of rodents comprises over 1000 proteins.[6,7] A recent paper by the present authors used synapse proteomic methods on the PSD isolated from human neocortex (hPSD) and discovered 1461 different proteins. It is worth noting that this is a high number compared to the proteomes of other subcellular structures (e.g. 917 proteins have been identified in human mitochondria[8]). The mammalian PSD is a highly complex structure, comprised of subsets of proteins assembled into multiprotein complexes, which together form a supramolecular structure with an overall mass estimated to be a thousand times larger than a ribosome.[9]

This remarkable complexity poses novel analytical problems and opportunities, which require bioinformatic methods such as those employed in the field of systems biology. Systems Biology is a rather new and still evolving area of biological research that essentially addresses the study of cells and organisms from a holistic point of view.[10,11] For example, it is possible to use knowledge on the interactions between pairs of proteins to construct network maps of hPSD proteins. These networks were used to show how 'hub' proteins (highly connected proteins) organise subsets of PSD proteins; and allow to explore the relationships of proteins involved in particular diseases or disease phenotypes.

To understand the hPSD 'system', the 1461 different proteins were analysed individually and collectively. The first approach aimed at having an overview of the number and classes of diseases caused by mutations in hPSD genes, while the second aimed at identifying those diseases most relevant to the PSD compared to other neuronal or brain proteins. To perform the first analysis, the genes encoding human PSD proteins were searched against the database of inherited monogenic diseases (Online Mendelian Inheritance in Man, OMIM[12]). Genes in the hPSD caused a total of 269 monogenic diseases, but more importantly, approximately half (133) were primary nervous system disorders. 114 hPSD proteins caused these nervous system diseases, a figure that will certainly grow as new mutations are discovered in large-scale genomic sequencing projects currently underway on patients.

Of all nervous system diseases identified, ~80% were central nervous system (CNS) pathologies. Using the International Classification of Disease (ICD-10) CNS diseases caused by hPSD genes could be classified into 4 of the 22 ICD-10 chapters (Figure 2a): Endocrine, Nutritional and Metabolic Diseases; Mental and Behavioural Disorders;

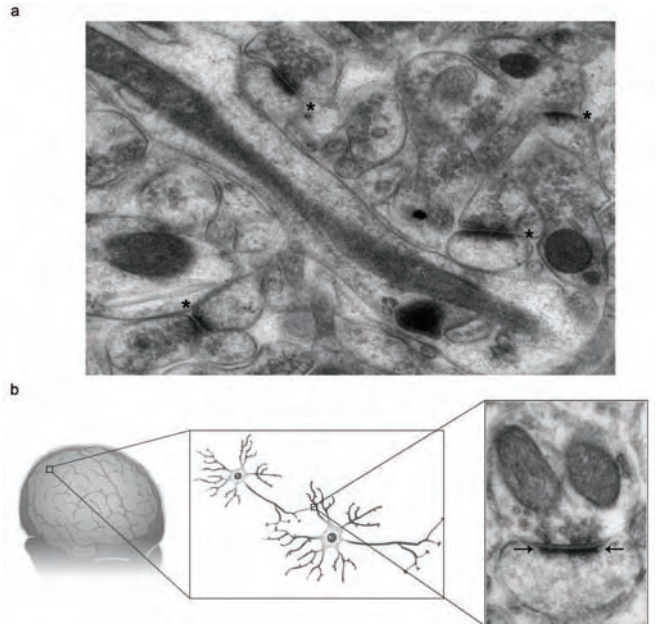

Figure 1: Electron microscopy images of synaptic and postsynaptic structures.
a. Field electron micrograph of hippocampal CA1 region from mouse brain. Several excitatory synapses can be identified (marked with asterisks).
b. Excitatory synapses mediate neuronal signal transmission in the brain. Nerve cells, represented in the middle panel, have very long branches and contact one another at synapses. Excitatory synapses (right image) are characterised by an electron-dense structure beneath the postsynaptic membrane known as the postsynaptic density (PSD), here shown between arrows.

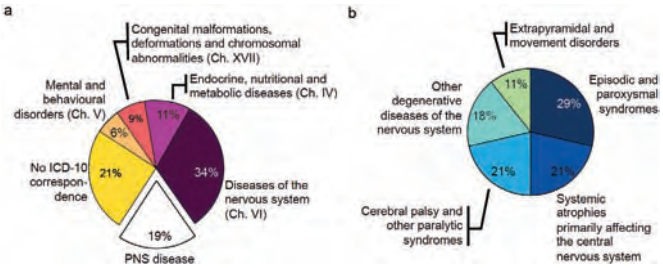

Figure 2: Classification of Nervous System diseases caused by hPSD proteins.
a. Distribution and relative abundance of monogenic Nervous System diseases caused by hPSD proteins. Central nervous system diseases were classified using the International Classification of Disease (ICD-10) from the World Health Organisation (WHO) and are shown in coloured sections. The proportion of Peripheral Nervous System (PNS) diseases is also shown.
b. Distribution and relative abundance of CNS diseases caused by hPSD proteins within Diseases of the Nervous System (Chapter VI, ICD-10).
Figure adapted from Bayés et al.[3]

Congenital, malformations, deformations and chromosomal abnormalities; and Diseases of the Nervous System. Interestingly, within the 'Diseases of the Nervous System' chapter, the range of disease types caused by hPSD genes was quite wide and included neurodegenerative diseases, movement disorders, epilepsies or atrophies and paralytic syndromes (Figure 2b).

Diseases are characterised by their constellation of symptoms and signs, and often, different diseases share some symptoms, but not others. For example, cognitive impairments or motor dysfunction, such as ataxia, can result from mutations in many different genes and are found in different diseases. The symptoms and signs of diseases caused by mutations are called phenotypes, and those found in genetic diseases have been catalogued in databases of gene-to-phenotype relationships.[13] These databases make it possible to ask: which symptoms and signs are more common in diseases caused by hPSD mutations? It is also possible to link these phenotypes to specific proteins and identify the subsets of hPSD proteins that are involved with cognition, ataxia and other phenotypes. These analyses provided a 'functional' understanding of the human synapse and led to a new model of disease where subsets of hPSD proteins work together to control human phenotypes. These molecular maps should be useful for identifying biochemical pathways underlying the particular disease symptoms as well as suggesting new drug targets or genetic susceptibility genes.

These phenotypic analyses produce large amounts of data, therefore, statistical methods can be applied to address another question: to which diseases and phenotypes is the hPSD most important, particularly when compared to other neuronal or glial proteins? Two main conclusions arose from approaching this problem: firstly general nervous system disease phenotypes (i.e. Neurological Abnormality or Abnormality of the Central Nervous System) were overrepresented by hPSD genes revealing that the hPSD has a higher burden of these diseases than other brain structures. The second conclusion was that the hPSD is most relevant to cognitive disorders (particularly mental retardation) and motor diseases.

A systems biology study of the hPSD in psychiatric diseases with complex genetics, such as schizophrenia or autism, has not yet been done. Nevertheless, amongst the rapidly growing lists of genes associated with these devastating diseases there are many well known postsynaptic molecules[14] and a preeminent role of synaptic dysfunction in schizophrenia,[15,16] autism[17] or mood disorders (bipolar disorder and major depression[18]) is becoming conceivable.

Nowadays it is widely accepted that proteins do not function on their own but as parts of supramolecular complexes operating in a structurally organised fashion. The postsynaptic density might be one of the most sophisticated of these structures found in nature and as bewildering as its complexity might seem today, its study could have a transformative impact on neurology and psychiatry. The methods of synapse proteomics with neuroinformatics are now primed for studies of brain disease in living and post-mortem material and together with genetic approaches provide new strategies for disease diagnosis, categorisation and drug development. ◆

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