Synaptopathies: Dysfunction of Synaptic Function

Abstract

Synaptopathy is an increasingly popular term used to define key features of neurodegenerative and psychiatric disease. It implies that disruptions in synaptic structure and function are potentially the major determinant of such brain diseases. The Synaptopathies: Dysfunction of Synaptic Function Biochemical Society Focused Meeting brought together several invited speakers, supplemented with short communications from young scientists, who addressed this possibility. The talks spanned the full gamut of approaches that brought molecular, cellular, systems and whole-animal experimentation together to address how fundamental synaptic biology was increasingly informing on dysfunction in disease. The disease and models thereof discussed included Alzheimer’s disease, prions, Huntington’s disease, Parkinson’s disease, schizophrenia and autism. The audience were asked to reflect on whether synaptopathy, although attractive and conceptually useful, provided a significant explanation as the cause of these major diseases. The breadth of the meeting reinforced the complexity of these brain diseases, supported the significance of synaptic dysfunction in disease, but left open the issue as to whether the prime cause of these disorders could be resolved as simple synaptic dysfunction. Thus, despite revealing a value of synaptopathy, further investigation will be required to reveal its balance in the cause and effect in each of the major brain diseases.

The Synaptopathies: Dysfunction of Synaptic Function Biochemical Society Focused Meeting drew together a gathering of some 100 participants to discuss the principle of ‘synaptopathy’. As the assembled masses learnt from a little known and forgotten correspondence between Dr Fintan O’Toole and Dr Nero Bliss, ‘synaptopathy’ pertains to the concept that disease (Greek πάθος, pathos) can derive from the dysfunction of synapses between nerve cells in the brain. Indeed, the central role that is played by synapses as the specializations at which chemical signalling occurs in the normal brain would support the consideration of such a possibility.

Since Sherrington’s observation that these interneuronal juxtapositions appear to clasp at each other, it was clear that the term synapse (from Greek σύν, syn, together, and ἁπτεῖν, to clasp) would figure perfectly in the terms that describe their biology [1,2]. ‘Pathos’ (Greek πάθος) then, meaning disease or suffering, broadly clarifies the sense of the term ‘synaptopathy’. However, all good terms attract potentially distracting semantic arguments, and it appears that the age of ‘synaptopathy’ may be afflicted by such a difficulty.

Indeed, the North American school seems to favour the term ‘synapsopathy’ (http://www.youtube.com/watch?v=hY-CY7mvAPM). This conceptually identical descriptor is a bit rich in sibilants and therefore clearly less lyrical than ‘synaptopathy’. In addition, the gut feeling of all Greek contemporaries we consulted favored ‘synaptopathy’, and the number of Google hits for ‘synaptopathy’ exceeds those for ‘synapsopathy’ by a factor of 63.4. Thus, by law of mass action and considering that our Greek colleagues found that ‘synapsopathy’ sounded weird, ‘synaptopathy’ must be right. Unfortunately, the problem is much more complex if one takes formal linguistic arguments into account. A professor of ancient Greek linguistics argued that ‘synaptopathy’ refers to the verb
συνάψης, synhabit, whereas a disease of the synapse and not necessarily of its clamping (or synaptic) activity is meant. Therefore the term 'synaptopathy' may have its merits. Final arbitration on the most suitable term was obtained from an eminent retiring synaptic, not synaptic, grandee who pointed out that a plethora of synaptic phenomena, including a host of synaptic proteins, contain 'synapo' as the preferred prefix. Having thus settled upon the preferred term 'synaptopathy', the meeting proceeded to reflect on the significance or potential for such a concept to inform on major brain diseases.

The idea of the meeting was to define core aspects of the synapse and consider whether changes in these subcompartments of neurons are a cause for or a consequence of brain disease. Put in simple terms, we know that the presynapse releases transmitter in a discrete way on to postsynaptic cells. This is achieved through the trillions of synaptic structures in the brain that contain the molecular machinery to release transmitter and detect it using cognate postsynaptic receptors that produce downstream ionic or metabotropic signalling. The highly organized synaptic structure arises as a consequence of protracted developmental programs in the course of which synapses are assembled and stabilized in the mature brain while retaining sufficient flexibility to exhibit plasticity of structure and function.

The accumulation of synapses on neuronal processes, although well served by transport links, means that they must operate remotely from the biosynthetic processes provided by the cell body. Owing to this ‘isolation’, a number of underpinning processes evolved in synapses. These include local membrane and protein turnover [3–5], compartmentalized metabolic capability [6] and a host of local modulatory signal cascades supported by synaptic protein scaffolds [7], which together compose a picture of staggering molecular complexity. This complexity is increased further when the generics of synaptic structure, as depicted above, are considered in the context of the vast number of synapses in the human brain, which exhibit an array of distinct functional characteristics. Indeed, one impression that emerged from the meeting was that synapses are highly diverse. The segmentation of synapses according to transmitter type, for example, cannot adequately reflect the extensive diversity of synapses using one type of transmitter with regard to location and function. In addition to this molecular, cellular and functional complexity, it is essential to recognize that synapses operate as ensembles within defined neural networks to direct the level of neuronal activity. This, in turn, controls the output of anatomically defined networks, which is ultimately represented as ‘normal’ behaviour.

With this complexity at the heart of the normal physiological processes, the potential for perturbation of synaptic function is large. Moreover, and in spite of their partial autarky, synapses are still dependent on the biosynthetic and metabolic support of the cell body, such that more general cellular dysfunctions can become manifest as perturbed synaptic function and thus be called synaptopathies, although synapse function itself is not primarily affected. Despite this difficulty, the picture that emerges from many pathological conditions supports a serious consideration of the notion that synaptopathies play a fundamental role in brain diseases.

Many major neurodegenerative diseases are characterized by a decrease in synapse numbers and synapse function, which often precedes neuronal loss and cell death [8,9]. Similarly important support for a potential synaptopathic origin of many neurological and psychiatric diseases is provided by genetic studies in which genes encoding synaptic proteins were shown to be altered in the corresponding neurological and psychiatric disorders [10,11]. This includes proteins that are intimately involved in synapse formation, synaptic signalling or synaptic metabolism.

Overall, the accumulating evidence from studies on many different neurodegenerative and psychiatric diseases supports the notion that ‘synaptopathy’ is a worthwhile concept. Accordingly, the audience and speakers at the meeting were asked to reflect on the information presented in order to see whether synaptopathies are a reality and whether the synaptopathy concept is likely to advance the investigation and understanding of major brain diseases. The flavour of this is reflected in the meeting submissions that are included in this issue of Biochemical Society Transactions. The collection of articles reflects the broad coverage of techniques, basic biology and disease models that were discussed at the meeting by keynote speakers and the young scientists selected to give oral presentations. When considering that the meeting included a further 30 poster presentations, the true breadth may only be hinted at by the included articles. This should not distract from the fact that, for the most part, what is discussed converges on the concept of synaptopathy: dysfunction of synaptic function?

References