EJN European Journal of Neuroscience

FENS Federation of European Neuroscience Societies

European Journal of Neuroscience, Vol. 39, pp. 1057–1058, 2014 doi:10.1111/ejn.12560

EDITORIAL
The synaptic basis of disease

Scott Thompson[1] and Christian Luscher[2]
[1]Department of Physiology, University of Maryland School of Medicine, Baltimore, MD, USA
[2]Department of Basic Neuroscience, Medical Faculty, University of Geneva, Geneva, Switzerland

Neurological and neuropsychiatric disorders place a very high social and economic burden on the world's population. Altogether, as many as 60 million Americans, and one of four Europeans, suffer from disorders that affect the nervous system, including migraine, anxiety disorders, depression, dementia, epilepsy, Parkinson's disease, autism, and schizophrenia (Olesen *et al.*, 2006; di Luca *et al.*, 2011). For addiction alone, the number of individuals battling with this condition is far higher than the number of people with cancer and heart disease combined. In economic terms, these conditions leave Europe with a total direct and indirect cost exceeding €800 billion, and in the USA the bill is trillions of dollars in medical expenses and lost productivity annually, with an incalculable personal toll.

Evidence is accumulating that many neurological and neuropsychiatric disorders stem from dysfunction of receptors and ion channels underlying synaptic communication between nerve cells. The articles gathered in this special issue of EJN are devoted to this topic.

The idea of 'synaptic diseases' has its roots in the finding that acquired and congenital defects in ion channel function, known as channelopathies (Kass, 2005), contribute to many neurological diseases, as well as a variety of pathologies in other secretory and excitable cells. Studies linking mutations in ion channel genes to disease states such as epilepsy, various forms of ataxia, paralysis, and migraine, together with electrophysiological characterization of pathological changes in neuronal excitability and ion homeostasis, have offered mechanistic insights into the causes of these disease states, and have provided clues regarding promising therapeutic targets. Indeed, it has been estimated that up to 15% of all prescription drugs act on ion channels as a main mechanism of therapeutic action.

The synapse is capable of a remarkable number of forms of short-term and long-term plastic changes, and this plasticity underlies a variety of important processes in the healthy brain, including the maturation of neuronal circuits during development, experience-dependent refinement of circuits mediating sensory perception, and learning and memory. We are now beginning to appreciate the role of developmental abnormalities in the cellular mechanisms underlying these processes and how they contribute to autism spectrum disorders, Fragile X syndrome, and other forms of cognitive disability. It is also becoming apparent that specific circuits can become hijacked to subserve maladaptive functions in the normal reward circuitry to mediate addiction; and we have begun to understand how these dysfunctions produce the behavioral symptoms that characterize this condition. We are also learning more about how synapses can become perturbed by the accumulation of aberrant misfolded proteins in chronic neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's disease. The implication of synaptic dysregulation in neurodegenerative diseases is particularly remarkable, and carries the promise of solving the conundrum that cell death and clinical manifestations are often only poorly correlated (Hardy & Selkoe, 2002).

Therefore, a better understanding of the cellular and molecular events underlying synaptic dysfunction is vital if we are to halt or even reverse the inexorable deterioration currently observed in neurodegenerative disorders. This Special Issue of EJN is composed of a collection of articles and reviews highlighting the latest insights into the fundamental involvement of synapses in a range of neurological and neuropsychiatric disorders, sparked by discussions during the second 'Synaptic Basis of Disease' meeting held in summer 2012 in Geneva in conjunction with the FENS forum. The Special Issue opens with a series of contributions summarizing the evidence for the involvement of synaptic factors in schizophrenia (Booth *et al.*, 2014; Gardner *et al.*, 2014; Pocklington *et al.*, 2014; Randall *et al.*, 2014). They are followed by articles highlighting the role of synaptic type I metabotropic glutamate receptor and AMPA receptor pathways (Kato *et al.*, 2010) in disorders characterized by cognitive disability and social dysfunction, such as autism spectrum disorders and Fragile X syndrome (Baudouin, 2014; Boda *et al.*, 2014; Lussier *et al.*, 2014; O'Connor *et al.*, 2014; Zhang *et al.*, 2014). Neuromodulatory factors that alter synaptic function, such as brain-derived neurotrophic factor, monoamines, stress hormones, and endocannabinoids, are discussed next, in the context of addiction, reward, and depression (Lecca *et al.*, 2014; Melis *et al.*, 2014; Polter & Kauer, 2014; Reimers *et al.*, 2014). Three contributions explore the role of two key proteins implicated in the pathophysiology of Alzheimer's disease, β-amyloid and the phosphoprotein tau, at glutamatergic synapses, where they might act together or independently to impair the trafficking of AMPA-type glutamate receptors in excitatory synapses to cause the devastating cognitive impairments characteristic of this condition (Alfonso *et al.*, 2014; Liao *et al.*, 2014; Miller *et al.*, 2014). Finally, the Special Issue closes with a Technical Spotlight introducing a novel procedure to purify neuronal nuclei from specific neuronal populations for biochemical analysis (Marion-Poll *et al.*, 2014).

It is the hope and belief of all of the contributors gathered at the 'Synaptic Basis of Disease' meeting that, from the insights that we are striving to obtain, will come not only a greater knowledge of the fundamentals of synaptic function, but also an appreciation of potential targets for biomarkers, objective strategies for differential diagnosis, and improved therapeutic options. Ultimately, it is our hope that meaningful progress will soon be made in the fight against the scourges of cognitive disability, mental illness, and addiction.

Correspondence: S. Thompson, as above.
E-mail: sthom003@umaryland.edu

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