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SYMPOSIUM OVERVIEW

The synapse: center stage for many brain diseases

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Synapses are anatomical specializations at the interface of two neurons. They have fascinated researchers ever since Sherrington coined the term 'synapse' in 1879. Studies of synapses have provided amazing insight into their function and were boosted by the discovery, now more than 30 years ago, that synapses can undergo long-term activity-dependent plasticity. Over the last two decades much effort has been devoted to the study of long-term synaptic plasticity as a candidate mechanism underlying learning and memory. More recently dysfunctional synaptic plasticity has been implicated in several brain diseases, such as depression, addiction, dementia and anxiety disorders. Here we report on an international meeting that took place in Geneva in July 2008 that brought together scientists who study synapses and disease mechanisms.

Brain diseases constitute a major burden to society. In Europe, alone, it is estimated that direct and indirect costs of brain diseases represent more than 350 billion euros per year. When broken down into individual diseases the most costly are depression (105 billion euros, a sum equal to the cost of all cardiovascular diseases), addiction (56 billion even without including nicotine abuse), dementia (54 billion) and anxiety disorders (40 billion), followed by autism and schizophrenia.

The Synaptic Basis of Disease meeting, which was organized as a satellite meeting to the July 2008 FENS meeting in Geneva (Fig. 1), was convened to bring together leading researchers working on basic synaptic mechanisms with those working on neurological disorders. Indeed, many labs at the meeting have programs working on both aspects. The main focus of the meeting was to generate discussion amongst some of the leading experimentalists working on synaptic and disease mechanisms.

Synaptic mechanisms

Approximately half of the speakers addressed basic mechanisms of synaptic function, with presentations on the molecular, cellular or circuit aspects of synaptic function.

Figure 1. The poster for the symposium

Molecular mechanisms of synapses. A major theme in the molecular talks was postsynaptic mechanisms regulating synapse function. One theme in the molecular talks was novel roles of and mechanisms regulating NMDA receptor subtypes. Isabel Perez-Otaño (Pamplona, Spain) presented recent work investigating the role of NR3A subunits in the formation of novel NMDA receptor subtypes that are preferentially expressed early in postnatal development.

Another important theme was the role of PSD95 and other postsynaptic density proteins in regulating AMPA receptor function at synapses. Morgan Sheng (Cambridge, MA, USA) described recent work showing that phosphorylation and dephosphorylation of specific sites on PSD95 regulate AMPA receptor number at synapses and interact with mechanisms of long-term synaptic plasticity in hippocampal neurons. Bernardo Sabatini (Boston, MA, USA) described work on the role of phosphorylation of specific sites on PSD95 in regulating spine structure and PSD95 mobility into and out of spines in CA1 pyramidal neurons. Jon Hanley (Bristol, UK) discussed recent work investigating the role of the AMPA receptor GluR2/3 subunit interacting protein, PICK1, in orchestrating AMPA receptor trafficking at synapses through an interaction with actin.

Mechanisms regulating the mobility of AMPA receptors at synapses was another topic of discussion. Daniel Choquet (Bordeaux, France) described recent work which implicates a rapid lateral movement of AMPA receptors in the neuronal plasma membrane in synaptic response variability and synaptic AMPA receptor desensitization. Mike Ehlers (Durham, NC, USA) presented his work showing a requirement for myosin Vb in activity-dependent AMPA receptor trafficking during long-term potentiation at hippocampal CA1 synapses. Peter Seeburg (Heidelberg, Germany) described intriguing work on knock-out mice lacking forebrain AMPA receptors questioning the accepted role of AMPA receptor-mediated synaptic transmission in brain function. Katherine Roche (Bethesda, MD, USA) presented recent work from her lab concerning the role of

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mGluR7 trafficking and phosphorylation in regulating mGluR7 surface expression and an mGluR7-dependent form of plasticity at mossy fibre–stratum lucidum interneuron synapses.

Cellular electrophysiological studies of synapse function. A number of speakers addressed basic mechanisms of synaptic function at the cellular electrophysiological level. One prominent topic was GABAergic synaptic function. Kaspar Vogt (Basel, Switzerland) described work in which different $GABA_A$ receptor subtypes specifically mediating phasic or tonic forms of inhibition in CA1 pyramidal neurons have been characterized. Tamas Freund (Budapest, Hungary) described how endocannabiniod signalling can selectively regulate different subtypes of GABAergic inputs onto hippocampal CA1 pyramidal neurons. Massimo Scanziani (San Diego, CA, USA) compared the impact of somatic *versus* dendritic $GABA_A$ receptor mediated inhibition on hippocampal pyramidal cells. He showed that both inhibitory interneurons targeting soma and those targeting dendrites are hyperpolarizing, but that the two types of inhibition differentially regulate the input output relationship of pyramidal cells.

Another theme was basic synaptic mechanisms at glutamatergic synapses. Roger Nicoll (San Francisco, CA, USA) discussed his recent findings showing that the differential trafficking of subtype-specific NMDA receptors by PSD95 and SAP102 underlies synapse development. Christophe Mulle (Bordeaux, France) spoke about spike transmission and short-term synaptic plasticity at mossy fibre–CA3 pyramidal cells, and showed how pre- and postsynaptic kainate receptors concur to control the efficacy of information transfer at this synapse. Matthew Frerking (Portland, OR, USA) showed that hippocampal interneurons at the border of stratum radiatum and stratum lacunosum-moleculare express a slow component to the EPSC that lasts for hundreds of milliseconds and is mediated in part by GluR5-containing kainate receptors, and in part by AMPA receptors. The reasons for the slow kinetics of this component remain unclear, but it is largely absent from interneurons in stratum oriens.

Synaptic plasticity at glutamatergic synapses was another important topic at the meeting. Pablo Castillo (New York, NY, USA) described recent work showing a postsynaptic form of LTP at hippocampal mossy fibre–CA3 synapses that is expressed solely as an increase in NMDA receptor-mediated synaptic transmission. This potentiation requires postsynaptic calcium, and is due to a PKC-dependent recruitment of NMDARs to the synapse and is likely to provide a dynamic and potentially powerful mechanism for regulating mossy fibre–CA3 synaptic efficacy. Graham Collingridge (Bristol, UK) discussed work in which he and colleagues have shown that GSK3β plays a central role in the expression of hippocampal LTD and in the regulation of the ability of synapses to express LTP. Chris McBain (Bethesda, MD, USA) discussed recent work on the molecular mechanisms of mGluR7-dependent synaptic plasticity that underlies a metaplastic switch at the hippocampal mossy fibre–CA3 stratum lucidum interneuron input.

Synaptic basis of circuit function. An important theme at the meeting was the synaptic basis of circuit function. Carl Petersen (Lausanne, Switzerland) described recent work in which multiple simultaneous patch-clamp recordings were used to define connectivity throughout the barrel cortical column. This work provides a detailed description not only of the connections within and across cortical layers, but also the functional properties of these connections. Keeping with the barrel cortex theme, John Isaac (Bethesda, MD, USA) discussed the synaptic mechanisms contributing to the development of layer 4 and layer 6 circuits in barrel cortex during the first postnatal week. He showed that mechanisms exist for the selective strengthening of specific thalamocortical and cortico-cortical connections contributing to the emergence of functional layer 4 and layer 6 circuits by the end of the second postnatal week. Anthony Holtmaat (Geneva, Switzerland) presented work using *in vivo* imaging showing that sensory experience drives the stabilization of new spines on layer 5 neurons in barrel cortex. Rosa Cossart (Marseille, France) described work on early circuit activity in neonatal neocortex. Using calcium imaging combined with electrophysiology in slices she showed that two different types of network oscillations (giant depolarizing potentials; early network oscillations) exhibit different developmental profiles, dynamics and mechanisms. Karl Deisseroth (Stanford, CA, USA) described tools recently developed for the optical control of neuronal excitability, namely light-activated ion channels (channelrhodopsins including VChR1 and ChR2), and light-driven chloride pumps (halorhodopsins including NpHR and eNpHR). He showed how such approaches can be used to rapidly alter neuronal excitability *in vivo*.

Disease mechanisms

Many of the speakers presented work related to specific diseases.

Autism. Autism spectrum conditions (ASCs) are heritable conditions characterized by impaired reciprocal social interactions, deficits in language acquisition, and repetitive and restricted behaviours and interests. Several such monogenic heritable ASC forms are caused by loss-of-function mutations in genes encoding regulators of synapse function in neurons, including the cell adhesion protein neurologin 4. Nils Brose (Göttingen, Germany) showed that there is a reorganization of postsynaptic density protein networks in neuroligin KO mice, which alters the synaptic clustering of NMDARs and AMPARs, and the corresponding synaptic responses. Neuroligin-4 deficient mice, which genetically model certain forms of monogenic heritable autism, exhibit highly selective deficits in reciprocal social interactions and communication that are reminiscent of autism spectrum disorders in humans.

Fragile X is a frequent from of syndromic mental retardation that is associated with an expansion of triplet repeats in the gene of FMRP. Studies over recent years have made the case that a loss of FMRP may enhance protein synthesis-dependent forms of long-term depression in the hippocampus. Kimberly Huber (Dallas, TX, USA) reported that synaptic connections in neocortex are also affected in FMR1 mutant mice. Her lab observed a substantial deficit in local excitatory drive (50%) targeting fast-spiking (FS) inhibitory neurons in layer 4 of the barrel cortex. As a result neocortical circuits become hyperexcitable.

Mental retardation and dementia. The leading cause of dementia is Alzheimer's disease (AD), which is associated with the production of β-amyloid protein

that eventually forms aggregates. However, much research has now established that such aggregates only loosely correlate with the clinical disease. Therefore recent research has focused on soluble β-amyloid, which alters the function of many synapses. Roberto Malinow (San Diego, CA, USA) addressed the synaptic mechanism by which soluble β-amyloid alters the function of excitatory synapses in CA1 pyramidal neurons of the hippocampus showing that long-term depression and the loss of synaptic function observed in this model of AD share a number of mechanistic similarities.

Another player in the pathophysiology of AD is ADAM10. This disintegrin/metalloprotease interacts directly with SAP97, a protein involved in trafficking of glutamate receptors, and it is this interaction that is required for its enzymatic activity. Monica Di Luca (Milan, Italy) addressed the effect of activity-dependent synaptic plasticity on ADAM10 trafficking. She found that the induction of LTP caused an increase of ADAM10 in the postsynaptic compartment, but without increase of ADAM10 insertion in the cell membrane. In contrast, induction of LTD led to the delivery of ADAM10 to the postsynapse that was associated with an increase of the surface pool of ADAM10. These results show an interdependence between synaptic plasticity and ADAM10 trafficking.

Addiction. While addictive substances invariably cause adaptive changes in the brain, only a fraction of individuals will eventually become addicted. Research is therefore aimed at dissecting the molecular and cellular mechanism that underlie these adaptive changes and asking how such changes may differ in addicted subjects. The lab of Christian Lüscher (Geneva, Switzerland) is focusing on the observation that addictive drugs evoke specific forms of synaptic plasticity, starting hours after a first exposure with an enhancement of the excitatory afferents on dopamine neurons in the Ventral Tegmental Area (VTA). This plasticity can be detected *ex vivo* in brain slices by measuring the AMPA/NMDA ratio and the rectification of evoked AMPAR-mediated synaptic currents. Recent data now suggest that the reversal of this plasticity *in vivo* depends on the activation of metabotropic glutamate receptors (mGluR1). Consistent with this idea, a stereotaxic injection of a Transactivating Regulatory Protein (TAT) conjugated peptide that disruptions the interaction of mGluR1 and homer, significantly increases the persistence of the plasticity.

Olivier Manzoni (Bordeaux, France), using a sophisticated cocaine self-administration protocol in rodents that models the stochastic nature of the disease, provided the first electrophysiological analysis of rats that fulfilled the behavioural criteria for addiction (i.e. strong motivation to obtain the drugs, administration even when punished and perseveration of self-administration behaviours in the absence of reward). His observations point to synaptic changes in the nucleus accumbens that may underlie addictive behaviours.

Anxiety disorders. Clinical observations and fMRI studies along with animal studies implicate the amygdala in anxiety disorders. A rodent model for core components of these disorders is fear conditioning where the freezing of a mouse in response to a conditioned stimulus (CS) is observed. Subsequent presentations of the CS without the electric shock will lead to extinction, effectively switching off the fear behaviour. New data from Andreas Lüthi (Basel, Switzerland) now suggest that states of high and low fear are triggered by a rapid switch in the balance of activity between two distinct populations of basal amygdala neurons. A set of elegant experiments combining *in vivo* electrophysiology with local pharmacological interventions and behavioural observations suggest that the selective activation of 'extinction neurons' in the basal amygdala can turn off the fear behaviour. Chris Lowry (Bristol, UK) discussed evidence for the involvement of other brain areas in anxiety, showing roles for specific populations of neurons in the dorsal raphe projecting to distinct targets in forebrain.

Ischaemia and epilepsy. Ischaemic insults to the brain result in neuronal death and hyperexcitability that can lead to epilepsy. This is a particular problem in neonates and the elderly. Suzanne Zukin (New York, NY, USA) described elegant studies investigating the mechanisms and roles of epigenetics in hippocampal pyramidal neurons in response to cerebral ischaemia. Hippocampal pyramidal neurons are particularly sensitive to ischaemia-induced neuronal death and it was shown that an important mechanism underlying this sensitivity is a loss of the GluR2 AMPA receptor subunit producing calcium permeable AMPA receptors that mediate excitotoxicity. This pathological change in AMPA receptor composition is due to chromatin remodelling mediated by histone modification. Dietmar Schmitz (Berlin, Germany) discussed his recent work on the mechanisms underlying febrile seizures. Such seizures are prevalent in early childhood, are associated with increased risk for temporal lobe epilepsy in later life and involve a change in extracellular pH. He discussed the mechanisms by which a rise in pH in hippocampus leads to hyperexcitability in pyramidal neurons that can underlie such seizures.

Outlook

The Synaptic Basis of Disease meeting reflects a growing interest of the scientific community in the role of synaptic dysfunction underlying brain diseases. The examples above are by no means a comprehensive list, but illustrate that many neurological disorders are complex and remain poorly understood. Whether the concept of a synaptic disease or 'synaptopathy' really lives up to its promise will be determined in the next few years. One of the many challenges is to use the vast molecular and cellular knowledge of the synapse to design approaches in which synaptic mechanisms can be studied during behavioural paradigms in disease models. It will also be important to establish the role of synaptic dysfunction in the aetiology of disease: are changes in synaptic function a simple by-product of the disease process or is synaptic dysfunction causally involved? In addition, it will take time to make use of our knowledge about synaptic mechanisms to improve diagnostic accuracy of disorders, for example by defining vulnerability traits for conditions such as addiction. It is likely that a more mechanistic understanding of the synaptic basis of disease processes will also lead to refined clinical definitions, for example when considering schizophrenia as a single entity or an ensemble of many diseases. Ultimately, the hope is that restoring synaptic function, or exploiting synaptic plasticity, may lead to symptomatic improvements and thus reduce the burden of disease for many patients and their families.