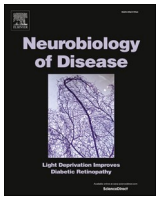
Neurobiology of Disease 176 (2023) 105968

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi



Editorial

Editorial to the special issue: "The neurobiology of synaptic dysfunction in brain disorders"

To ensure basal body functioning and to perform behaviours that are required to respond and adapt to environmental stimuli, synapses undergo physiological modifications, known as synaptic plasticity, changing in terms of number, morphology, molecular components, efficacy, *etc.*, a phenomenon which allows adapting to different situations, create memory engrams, and encode new behavioural patterns. On the other side, the complex molecular, cellular and/or physiological changes leading to synaptic dysfunction can be encompassed among the causes or the consequences of a given disease. For example, synaptic dysfunction is a common feature of several brain disorders spanning from neurodevelopmental, such as autism spectrum disorder (ASD) and intellectual disability, to neurodegenerative diseases such as Parkinson's (PD) and Huntington's disease (HD), as well as psychiatric disorders and addiction. Accordingly, the term "synaptopathy" has been introduced relatively recently to define conditions in which the alteration of synaptic structure and/or function is the main feature and, possibly, the primary determinant. In this context, the goal of this Special Issue was to gather international experts to provide a broad and updated overview of the current knowledge and the latest discoveries and standpoints on synaptic dysfunction in brain disorders.

***Synaptic genes and neurodevelopmental disorders: From molecular mechanisms to developmental strategies of behavioural testing* (by Michetti C, Falace A, Benfenati F, Fassio A).** Synapse dysregulation or synaptopathy in different brain circuits translates into altered animal behaviours encompassing cognitive, sensory, motor and socio-emotional domains. The time windows represent a crucial point for studying behaviour to understand the synaptic processes primarily affected by a given neural circuit. This issue is critical concerning the study of synaptopathies associated with neurodevelopmental disorders. Ideally, to understand the mechanisms underlying these disorders, it would be essential to start the study early in life to identify the onset of the manifestations and track their evolution during development. In this context, the review by Michetti et al. provides an overview of the main achievements obtained in murine models of synaptopathies by behavioural testing. It proposes new behavioural tasks with a correct predictive validity that might expand our knowledge of the symptoms and favour their early identification, to improve the efficacy of potential treatments.

***Postsynaptic autism spectrum disorder genes and synaptic dysfunction* (by Bonsi P, De Jaco A, Fasano L, Gubellini P).** Among neurodevelopmental disorders, there is a large consensus in considering ASD as a synaptopathy. Accordingly, ASD risk genes either code for synaptic components or belong to gene regulatory networks that regulate synaptic activity and homeostasis during development and adulthood. These ASD-linked genes can be classified, based on the location of the coded protein at the synapse, as pre- and postsynaptic. The impaired functions relate to the regulation of neurotransmitter release, synaptic adhesion, maintenance of the correct structural architecture of the synapse through the action of scaffold proteins, receptor activity, *etc.* Several ASD-linked mutations involving synapses have been identified in humans and modelled in mice, and recently the attention has been focused on identifying shared molecular mechanisms. A connection emerges within transcriptional networks during brain development leading to alterations in gene expression and splicing, mainly due to mutations in transcriptional factors and RNA-binding factors, that can originate in ASD-like phenotypes associated with synaptic dysfunction. The review by Bonsi and co-authors provides an updated overview of the ASD-linked genes involved in postsynaptic functions from a molecular to a functional point of view.

***Pleiotropic effects of BDNF on the cerebellum and hippocampus: Implications for neurodevelopmental disorders* (by Camuso S, La Rosa P, Fiorenza MT, Canterini S).** Neurodevelopmental disorders can arise from communication defects between neurons due to the alterations in the soluble signals that sustain survival, neuritis growth, synaptic strength and plasticity. One of the essential soluble factors is a brain-derived neurotrophic factor (BDNF), which has different roles ranging from cell survival to apoptosis. Although abnormalities in BDNF homeostasis have been reported to contribute to neurodevelopmental disorders, including ASD, experimental results on the levels of BDNF in the blood and the brain of children with ASD are conflicting. The review by Camuso and collaborators is centred on the role of BDNF in regulating synaptic dynamics in the cerebellum and the hippocampus, with a particular focus on the changes associated with neurodevelopmental disorders.

***Synaptic alterations as a neurodevelopmental trait of Duchenne muscular dystrophy* (by De Stefano ME, Ferretti V, Mozzetta C).** Several neuromuscular diseases characterized by muscular dystrophy due to mutations in the *Dmd* gene encoding for dystrophin (Dp427) are associated with neurodevelopmental disorders such as epilepsy and neuropsychiatric conditions. The severity of the behavioural alterations depends on the location and type of genetic defect in the *Dmd* gene. At the molecular level, it has been shown that dystrophin has a role at the post-synaptic terminal in stabilizing and clustering the $GABA_A$ receptors. Therefore, its alterations can lead to dysfunctional synaptic inhibition in different brain areas. This suggests that the pathology affects the neuro-muscular junction and the other brain regions from the early onset of the pathology. The review by De Stefano et al. focuses on the neurological aspect of Duchenne muscular dystrophy, presenting and discussing the most relevant morphological and functional synaptic alterations in both central and autonomic nervous systems, spanning

https://doi.org/10.1016/j.nbd.2022.105968

Available online 17 December 2022

from animal models to human pathology.

***Striatal glutamatergic hyperactivity in Parkinson's disease* (by Campanelli F, Natale G, Marino G, Ghiglieri V, Calabresi P).** Glutamate is the primary neurotransmitter of excitatory synapses in the central nervous system (CNS), playing a pivotal role in fundamental functions of the developing and mature brain. The dopaminergic modulatory control of glutamatergic neurotransmission is crucial to regulate information processing through the basal ganglia, thus controlling action selection and execution. In PD, the nigrostriatal denervation results in an enhanced glutamatergic transmission in the striatum, the main input nucleus of the basal ganglia. Such glutamatergic hyperactivity is involved in PD progression and the onset of levodopa-induced dyskinesia (LID). The review by Campanelli and co-authors provides an overview of the experimental and clinical evidence supporting glutamatergic hyperactivity as a critical mechanism underlying striatal alterations in both early and advanced PD stages and in the manifestation of LID. Additionally, the review provides an update on the current pharmacological strategies to modulate the glutamatergic systems at the pre- and post-synaptic levels. The correlation of glutamatergic hyperactivity with the extent of striatal denervation in models and PD patients provides unique insights into the mechanisms underlying PD pathophysiology, suggesting that innovative therapies may target specific time-dependent alterations of glutamatergic signalling.

***Striatal synaptic adaptations in Parkinson's disease* (by Shen W, Zhai S, Surmeier DJ).** The striatum is densely innervated by mesencephalic dopaminergic neurons that modulate the acquisition and vigour of goal-directed actions and habits. This innervation is progressively lost in PD, contributing to movement deficits. Although boosting dopaminergic signalling with levodopa early in the course of the disease alleviates these deficits, later, this strategy leads to the emergence of debilitating LID. The review by Shen and co-authors discusses recent advances in understanding how striatal cells and circuits adapt to progressive dopaminergic denervation and levodopa therapy in PD, with a particular focus on corticostriatal long-term potentiation (LTP) and depression (LTD). Striatal spiny projection neurons (SPNs) of the direct (dSPN) or indirect (iSPN) pathways are well-suited to fulfil a role as convergence detectors of dopaminergic signalling. Activation of D1-like dopamine receptors increases dSPN somatodendritic excitability, enhances glutamatergic transmission and facilitates LTP.

In contrast, activation of D2-like receptors has the opposite effect, promoting LTD. Dopamine depletion triggers cell type-specific, homeostatic changes in SPNs that tend to normalize striatal activity and disrupt the synaptic architecture sculpted by experience. In addition to discussing significant advances, the review also stresses some still unanswered questions related to the role of cholinergic and nitric oxide-releasing interneurons and the recently published evidence from a progressive PD model, suggesting that striatal pathways imbalance is necessary but not sufficient to produce overt parkinsonism.

***Oxidative stress and synaptic dysfunction in rodent models of Parkinson's disease* (by Imbriani P, Martella G, Bonsi P, Pisani A).** Growing evidence supports the central role of mitochondria in synaptic transmission and plasticity, which are processes entailing high energy consumption levels. Dysregulation of mitochondrial functions, signalling or transport, especially under stress conditions, is expected to cause detrimental effects on synaptic activity. Imbriani and co-authors propose that any early mitochondrial perturbation (*e.g.* derived from environmental neurotoxins, genetic predisposition, or ageing) occurring during the preclinical stage of PD may have harmful consequences on synaptic transmission. The review illustrates the results obtained from rodent models indicating that mitochondrial dysfunction and the ensuing oxidative stress represent key pathogenic events occurring at the prodromal stage of PD and affecting synaptic activity, thus generating a vicious circle. In this scenario, the authors conclude that strategies targeting mitochondria and oxidative stress may represent a promising approach to counteract synaptic dysfunction and PD progression.

***Striatal synaptic dysfunction in dystonia and levodopa-induced dyskinesia* (by Scarduzio M, Hess EJ, Standaert DG, Eskow Jaunarajs KL).** Dystonia and LID are hyperkinetic movement disorders characterized, respectively, by involuntary muscle contractions resulting in abnormal postures and movements and by abnormal involuntary movements, often including chorea, athetosis, and dystonia, induced by chronic treatment with levodopa in PD patients. Both dystonia and LID share similar alterations in striatal synaptic plasticity and dysregulated neuromodulation. Acetylcholine plays a significant role in dystonia and LID, which benefit from similar pharmacotherapeutics. In addition, the corticostriatal inputs to SPNs display abnormalities in LTP, LTD and depotentiation in both disorders. Hence, a better understanding of the mechanisms and consequences of disruptions in synaptic function and plasticity in dystonia and LID will lend insight into their development. The review by Scarduzio and co-authors examines classical theories in light of recent research, focusing on synaptic dysfunction as a shared pathway channelling different pathophysiological mechanisms of dystonia and LID into common motor outputs, with the idea that this approach may be helpful also for other hyperkinetic movement disorders, such as tardive dyskinesia and HD.

***Dopaminergic modulation of primary motor cortex: From cellular and synaptic mechanisms underlying motor learning to cognitive symptoms in Parkinson's disease* (by Cousineau J, Plateau V, Baufreton J and Le Bon-Jégo M).** Dopamine, acting *via* its D1- and D2-like receptors, exerts a crucial modulatory role within the mammals' primary motor cortex (M1), with direct and indirect (circuit-mediated) effects on the excitability of both cortical projection neurons and GABAergic interneurons. The review by Cousineau et al. thoroughly explains how dopamine-mediated modulation has a profound impact on M1 circuitry and, consequentially, on the output of this structure to the pyramidal tract, the striatum, the contralateral cortex and the thalamus, reporting a broad literature arising from *ex vivo* and *in vivo* approaches in both rodents and primates. The drastic reduction of dopaminergic signalling in PD, due to the loss of dopaminergic neurons, disrupts M1 functioning, which results in dramatic changes that span from altered neuronal excitability to impaired synaptic transmission and plasticity, as well as an abnormal level of synchrony at beta frequencies. These changes play a crucial role in PD pathophysiology; accordingly, current PD treatments interfere with them. The authors conclude that targeting M1 might thus represent a promising perspective for alleviating both motor and non-motor PD symptoms. However, a more precise characterization of dopamine function in this structure is needed.

***Synaptic pathology in Huntington's disease: Beyond the corticostriatal pathway* (by Barry J, Bui MTN, Levine MS and Cepeda C).** HD is an autosomal dominant neurodegenerative disease caused by an increased CAG repeat mutation in the *huntingtin* (*HTT*) gene. HTT protein is widely expressed in many cell types and tissues and participates in several cellular processes such as transcriptional regulation, protein trafficking, vesicle transport and synaptic transmission. Since the earliest and most severe neurodegeneration due to the expression of mutant HTT (mHTT) occurs at the striatum (caudate-putamen) level, the majority of studies on HD have focused on this structure and the corticostriatal pathway using mouse models. This has provided a large amount of data that, although sometimes contradictory and/or model-specific, elucidated several molecular, cellular and synaptic mechanisms of HD's pathophysiology. Interestingly, the review by Barry et al. brings our attention to other pathways than the corticostriatal one, namely the external globus pallidus, the subthalamic nucleus and the substantia nigra pars compacta, as well as at the thalamus and its output to the cortex and striatum. Studies in these structures unveiled morphological and electrophysiological alterations showing that, besides the "classical" impairment of corticostriatal function, profound changes occur in the whole cortico-basal ganglia-thalamocortical loop circuit of the HD brain.

***GluA3-containing AMPA receptors: From physiology to synaptic dysfunction in brain disorders* (by Italia M, Ferrari E, Di Luca M,**

Gardoni F). Decades of research have indicated that activity-dependent changes in synaptic efficacy, particularly synaptic plasticity, represent cellular correlates for learning and memory. In the CNS, excitatory neurotransmission is mediated primarily by glutamate ionotropic receptors, including AMPA receptors mediating fast neurotransmission and NMDA receptors that regulate intracellular signalling and gene transcription to sustain the induction of long-term synaptic plasticity. The subunit composition of the AMPA receptor tetramer (GluA1–4) defines its functional properties. Over the last two decades, research has mainly focused on GluA1/GluA2 containing AMPA receptors, although the GluA3 subunit is the most enriched within the excitatory post-synaptic density. The review by Italia and co-authors summarizes the current knowledge on the physiopathological role of GluA3-containing AMPA receptors and their contributions to synaptic dysfunction in neurodegenerative disorders, such as Alzheimer's disease amyotrophic lateral sclerosis, neurodevelopmental disorders, and frontotemporal dementia. This overview highlights the need to identify tools targeting the GluA3 subunit as a novel approach to brain disorders characterized by AMPA receptor-mediated alterations at the glutamatergic synapse.

***Synaptic changes induced by cannabinoid drugs and cannabis use disorder* (by Augustin SM and Lovinger DM).** The endocannabinoid receptors CB1 and CB2, whose physiological activation negatively modulates synaptic neurotransmitter release in several brain areas, play a crucial role in synaptic functioning and neurodevelopment. Experimentally, the psychoactive constituents of cannabis-derived drugs (Δ9-tetrahydrocannabinol, cannabidiol and cannabinol) have been shown to exert complex actions by stimulating presynaptic CB1 and CB2 receptors, such as changes in synaptic transmission, impairment of long-term depression and potentiation, and CB1 receptor desensitization. Abuse or long-term use of cannabis-derived drugs and, in particular, fully synthetic CB1/CB2 agonists can lead to cannabis use disorder (CUD), which represents a significant health and social problem and is associated with several dysfunctions at the neurotransmitter and synaptic levels. The review by Augustin and Lovinger examines these issues, presenting studies at molecular, synaptic and functional levels spanning from *in vitro* models to humans, providing an exhaustive overview of the mechanisms underlying cannabinoid action and CUD, with a particular focus on the regulation of synaptic transmission and plasticity.

***Alcohol dependence and withdrawal increase the sensitivity of central amygdalar GABAergic synapses to the glucocorticoid receptor antagonist mifepristone in male rats* (by Khom S, Rodriguez L, Gandhi P, Kirson D, Bajo M, Oleata CS, Vendruscolo LF, Mason BJ, Roberto M).** Nervous system disorders, characterized by behavioural alterations, depend not only on the genetic background but can also be generated from lifestyle. This is the case of alcohol use disorder (AUD) that causes the activation of the hypothalamic-pituitary-adrenal axis (HPA), controlling the responses to both stress and alcohol. Primary cerebral circuits involved in AUD are in the central nucleus of the amygdala (CeA), mainly constituted of GABAergic neurons. AUD is also characterized at the cellular level by a higher release of glucocorticoids binding to the glucocorticoid receptor (GR). The article by Khom and collaborators show that GR inhibition by mifepristone, in preclinical trials on rats, reduces AUD symptoms by decreasing the release of GABA in the CeA.

***Environmental enrichment counteracts the effects of glioma in the primary visual cortex* (by Di Castro MA, Garofalo S, De Felice E, Meneghetti N, Di Pietro E, Mormino A, Mazzoni A, Caleo M, Maggi L, Limatola C).** The article by Di Castro et al. examines the effects of the enriched environment (EE), compared to the standard environment (SE), in the primary visual cortex (V1) of mice transplanted with syngeneic glioma (GL261) and controls. Their data show that EE drastically reduces tumour growth assessed by Ki-67 immunostaining. From a synaptic point of view, the analysis of the spontaneous synaptic activity in the peritumoral area shows that EE enhances glutamate release in SE control mice, confirming the powerful effect of this context on cortical function; on the other hand, glioma-injected mice show a slight decrease of glutamatergic activity, on which EE produces a moderate recovery. Similarly, GABA release is reduced in glioma-injected mice, and EE only exerts a mild improvement and little or no effect compared to SE. Data from stimulation-evoked synaptic responses confirm that glioma reduces both glutamatergic and GABAergic synaptic transmission, which EE normalizes. Moreover, EE increases the excitation/inhibition ratio compared to SE, but the effect of glioma and its interaction with EE and SE is not significant. Overall, these data show that glioma reduces both the excitatory and inhibitory transmission in the peritumoral area of V1 and that EE, which *per se* enhances synaptic transmission, accordingly partially rescues glioma's effects.

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