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Editorial

Neurobiology and neuropharmacology of monoaminergic systems

1. Neuropharmacological journey in monoaminergic fields

The extensive research conducted on monoaminergic systems including dopaminergic, serotonergic, noradrenergic, histaminergic and, to a lower extent melatonergic systems, continues to expand our current knowledge. The topic has enormous health, economic, scientific and conceptual stakes, with engagement across disciplines covering medicinal chemistry to neuropsychiatric and neurological diseases. This special issue presents scientific updates with in depth analyses on selected aspects of this complicated topic.

Antipsychotic and antidepressant drugs opened the way to intensive research on monoaminergic systems. The serendipitous discoveries of these treatments in the 1950s led to the identification of monoaminergic systems as the main origin of their efficacy. Under the scope of neurosciences and biological psychiatry, much fundamental research has identified the proteins involved in the function of monoaminergic systems. As illustrated on Fig. 1, each monoamine can act on a variety of receptors distinctly expressed in the brain, and displaying some selectivity for each monoamine. While the picture roughly illustrates the main families of these receptors, molecular biology has revealed the existence of several subtypes for most of these receptors coming from alternative splicing, posttranscriptional and/or posttranslational processes. The identification of specific monoaminergic targets involved in the beneficial and side effects of these drugs has enabled medicinal chemistry to produce drugs favouring one or several good targets over the deleterious ones. The article by Butini et al. is an illustration of the pharmacological profile and chemical requirements of new antipsychotic or anti-Parkinsonian drugs to achieve good efficacy with low or no side-effects (Butini et al., 2016). Several receptors or enzymes are usually targeted leading to the new popularity of multitarget drug design (Millan, 2009; Ramsay et al., 2016; Weinreb et al., 2016).

The pharmacological profile of a multi-target drug is even more complicated because the molecular environment of one target is specific to the cell expressing this target, leading to biased agonists. This means that a drug behaves differently on its target depending on the tissue. Interesting achievements have been obtained with drugs preferentially activating somatodendritic 5-HT_{1A} autoreceptors versus heteroreceptors and *vice versa* that could be pertinent for the treatment of mood disorders or dyskinesia induced by L-DOPA. While the specifications are growing for producing newer drugs, the molecular pharmacology becomes more insightful in conceptualizing the partnerships of neurotransmitter receptors in space and time. Wirth et al. report an interesting perspective of molecular signalling events in the morphogenic effects of serotonin (5-HT) (Wirth et al., 2017). These effects include a variety of 5-HT receptors that modulate synaptogenesis, neurite outgrowth, dendritic spine shape and density. These regulations occur at different stages of the development, are region-dependent and could maintain aberrant modelling of networks and pathophysiology.

The refinement of pharmacological drugs has helped elucidate a better understanding of the pathophysiology of numerous CNS diseases. A better knowledge of pathophysiology is surely a step for the identification of new pharmacological targets, perhaps beyond the symptomatic treatment (Millan et al., 2015). At a time where the *pathology-to-drug* discovery approach is in expansion, our certitudes regarding the treatment of Parkinson's disease and the mechanism of action of the lead antiparkinsonian treatment L-DOPA are disappearing. The metabolic precursor of dopamine (DA), L-DOPA is administered to patients soon after the identification of the loss of dopamine in the putamen and caudate nucleus of Parkinson patients. De Deurwaerdère et al. have reported numerous data dampening the idea that the benefit and side effects of L-DOPA were related to an increase in DA in the caudate nucleus and the putamen (De Deurwaerdere et al., 2017). The mechanisms of L-DOPA appear to be much more subtle, widespread in the brain and distinct from dopaminergic agonists. Referring again to Fig. 1, it is noteworthy that monoaminergic systems share enzymes for their biosynthesis, the vesicular monoamine transporter for their translocation into the vesicles of exocytosis, enzymes for their catabolism as well transporters for the reuptake. Some transporters and enzymes are also present in neighbouring glial and neuronal cells. Consequently, the administration of amino acid precursors such as L-DOPA or drugs that act on degrading enzymes such as monoamine oxidase inhibitors can only result in ectopic effects.

Serendipity has played an important role in the development of drugs aimed at treating the symptoms of schizophrenia, mood disorders or Parkinson's disease. This point of view is further stressed in considering that diseases like Alzheimer's disease or epilepsy still do not have monoaminergic-based treatments (Di Giovanni et al., 2016; Svob Strac et al., 2016). The paper by Simic et al. recalls that Alzheimer's disease is also marked by several perturbations of monoaminergic systems (Simic et al., 2017). Hopefully, the numerous clinical trials they report with monoaminergic drugs targeting neuroreceptors will end up soon in a more appropriate medical care of the disease. The other side of

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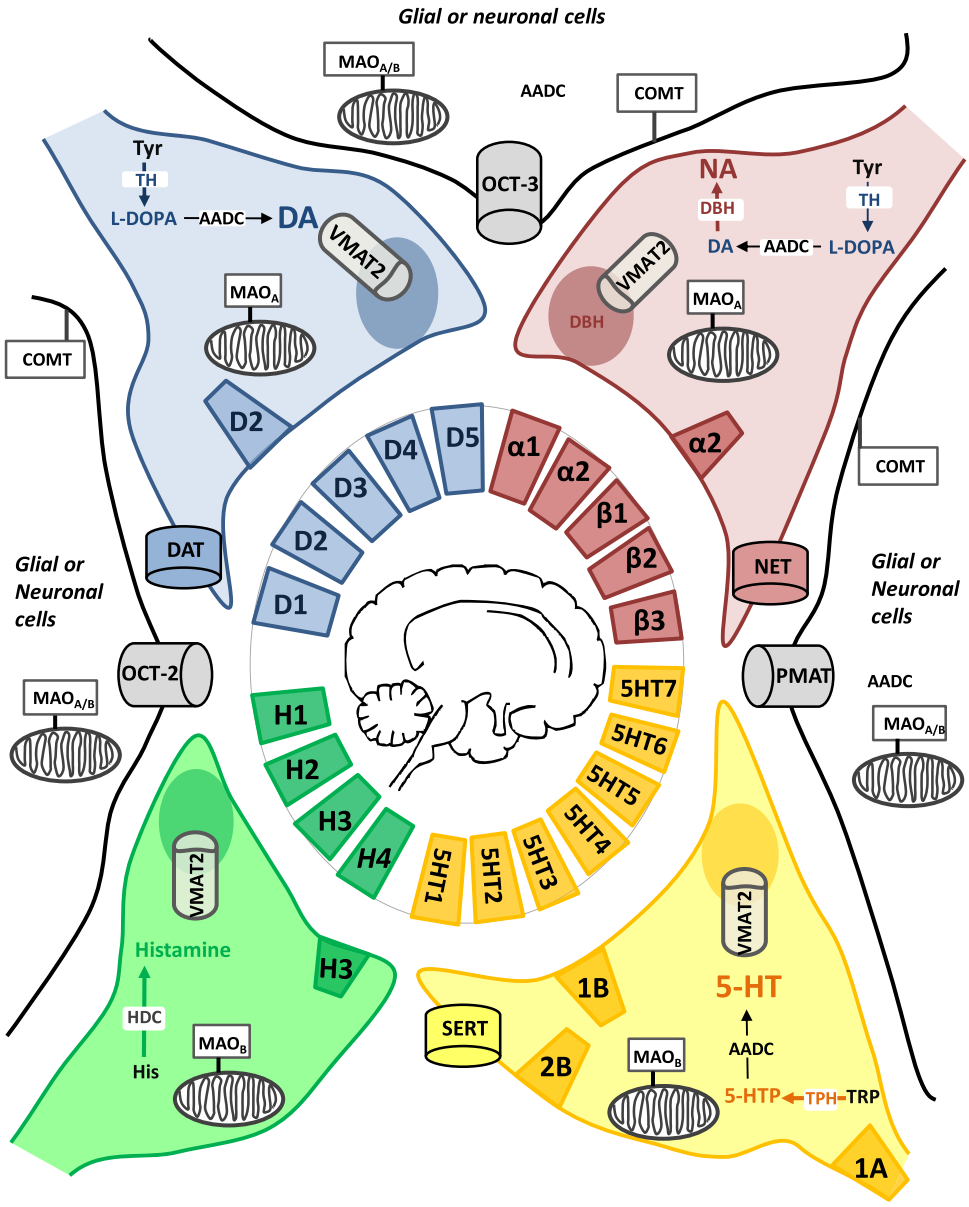

Fig. 1. Molecular organization of central monoaminergic systems.
The figure shows each monoamine system (dopamine, DA; noradrenaline, NA; serotonin, 5-HT; histamine); the biosynthesis, metabolism, the receptors and transporters. Colors are used to identify the proteins that are selective for each system while the black color is used for non-specific proteins. The terminals of each monoaminergic neurons contact post-synaptic elements in the brain that express a variety of receptors which are more or less specific for each monoamine. The main families are represented. Autoreceptors can be located at terminals and cell bodies for most monoaminergic systems. In the case of serotonergic cells, 5-HT_{1A} autoreceptors are addressed at cell bodies and 5-HT_{1B} autoreceptors are addressed at terminals; 5-HT_{2B} autoreceptors would be addressed at both sites. The post-synaptic elements (neurons, glial cells) also express enzymes involved in the metabolism of monoamines (MAO-A/B or COMT) as well as non-specific transporters. DBH is mainly expressed in vesicles of exocytosis in noradrenergic terminals. AADC, aromatic L-amino acid decarboxylase; DBH, dopamine β-hydroxylase; TPH, tryptophan hydroxylase; VMAT2, vesicular monoamine transporter; SERT, 5-HT transporter, DAT, DA transporter; NET, NA transporter; OCT, organic cation transporters; PMAT, plasma membrane monoamine transporter; HDC, L-histidine decarboxylase; MAO, monoamine oxidase (A or B); COMT, catechol-*O*-methyl transferase.

this thought is that it is often difficult to understand the role of monoaminergic systems in the benefit and side effects of efficacious therapies. Here, two articles by Faggiani and Benazzouz and by Galati et al., focus on the impact of deep brain stimulation of the subthalamic nucleus in the treatment of Parkinson's disease with specific regards on monoamines and on non-motor and motor effects of the treatment, (Faggiani and Benazzouz, 2017; Stefani et al., 2017), respectively. Numerous neurochemical effects are triggered by the deep brain stimulation of the subthalamic nucleus on monoaminergic systems but the extent to which these modifications lead to therapeutic effects is still a matter of debate.

At one point one may wonder why it is so difficult to progress and to understand the function of these systems. Maybe the organization and the morphology of these systems is a real issue. In fact, the cell bodies of these neurons are confined in hypothalamus (histamine), mesencephalon (DA, 5-HT), pons (5-HT) or medulla (noradrenaline) and innervate widely the entire encephalon with thousand sites of release for only one neuron. The neurohumoral way of contacting neurobiological networks and long distance neurons imply local and distal interactions. In addition, the monoaminergic systems establish complex interactions in the brain. De Deurwaerdère and Di Giovanni emphasise the interaction

between 5-HT and DA systems (De Deurwaerdere and Di Giovanni, 2017). Beyond the molecular and cellular complexity of the mechanisms involved in the influence of 5-HT on DA neuronal function, the authors highlight also the multiplicity of regions and dimensions implicated in this interaction, which is important for the mechanism of action of antipsychotic, antidepressant, anti-Parkinsonian and anti-addictive drugs.

While there has been a lot of progress in molecular pharmacology, it is also mandatory to progress on the physiological roles of these monoaminergic systems in the brain. The neuropharmacological approaches brought many indications and still will bring more. Lorincz and Adamantidis in this issue highlight the use of new technologies such as optogenetic targeting specifically subsets of neurons, systems or receptors to study the function of monoaminergic systems (Lorincz and Adamantidis, 2017). These new approaches will shed another light on monoaminergic systems to better understand the efficacy of various medicines used to treat CNS diseases.

The tale continues.

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