Xjenza Online - Journal of The Malta Chamber of Scientists
www.xjenza.org
DOI: 10.7423/XJENZA.2014.2.07

Meeting Report

Neuropathology and Neuropharmacology of Monoaminergic Systems

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Abstract. The third EU COST Action CM1103 "Structure-based drug design for diagnosis and treatment of neurological diseases: dissecting and modulating complex function in the monoaminergic systems of the brain" Annual Conference entitled "Neuropathology and Neuropharmacology of Monoaminergic Systems" was hosted by the University of Bordeaux, France on 8-10 October 2014. The conference, organized by Prof. De Deurwaerdére, was supported by COST (European Cooperation in Science and Technology) and LABEX (LABEX Brain, University of Bordeaux). The program took the form of a three-day meeting, comprising a series of French and international invited talks and breakout sessions designed to identify key gaps in current knowledge and potential future research questions. The aims of this Conference were two-fold: 1. To identify the current state-of-the-art in the understanding of the pathological mechanisms that contribute to different neuropsychiatric disorders, and to what extent, monoamines a multi-target drugs and/or other interventions might prevent these changes. 2. To identify specific areas of research where information is sparse but which are likely to yield data that will impact on future strategies to treat neurodegenerative disorders.

Meeting report

COST Action CM1103 (http://www.cost.eu/domains_actions/cmst/Actions/CM1103) *Structure-Based Drug Design For Diagnosis And Treatment of Neurological Diseases: Dissecting and Modulating Complex Function in the Monoaminergic Systems of the Brain* was established to stimulate an interdisciplinary approach to the task of understanding the molecular basis of neurological and psychiatric disorders. Medicinal chemistry now has many computational tools to aid in the design of novel drugs targeting either one or several proteins. Biological insights are essential to evaluate the efficacy of these novel drugs and to propose also new targets and approaches. Commonalities amongst the brain monoamine neurotransmitters, dopamine (DA), noradrenaline (NA), adrenaline (A) serotonin (5-HT) or histamine, are evident as these systems of neurotransmission are all involved in the pathophysiology of all major neuropsychiatric disorders and brain affections, such as mood disorders, schizophrenia, autism-spectrum disorders, Parkinson's disease (PD), Alzheimer disease, epilepsy, ischemia and dementias. Indeed, the efficacy of numerous medicines against the above-mentioned pathologies has been related at least in part to an action of these chemical drugs on the monoaminergic systems. The collaborative work in the action is a permanent interaction between bottom-up and top-down analyses towards understanding the neuropathology and neuropharmacology of monoaminergic systems. The extended abstracts in these Proceedings are a selection from the contributions to the third annual meeting, held in Bordeaux, of groups actively working towards these goals.

Chemical developments come from existing molecules and their modification either via classical or new ways of synthesis, and computational modeling. Reported at this conference are compounds for single targets such as acetylcholinesterase or aldo-ketoreductase by Magdalena Majekova (Slovak Academy of Sciences, Bratislava), or families of compounds such as benzothiazoles by Kamil Musilek (Kadir Has University, Istanbul) or quinolines by José Marco-Contelles (Consejo Superior de Investigaciones Científicas, Madrid) synthesized and studied with the goal of treating Alzheimer disease, Parkinson's disease or stroke by Mercedes Unzeta (Uni-

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versitat Autonoma de Barcelona). A series of multi-target compounds has been also designed with action on specific pairs (or multiples) of targets. Ligands carefully designed to bind to multiple targets are another accepted strategy in tackling the complex neurodegenerative diseases (Cavalli et al., 2008; Geldenhuys and der Schyf, 2013) but producing the best combinations to explore phenotypic results is not a trivial task (Prati et al., 2014). With large numbers of compounds tested and published in databases, one starting point comes from data-mining existing knowledge. Theoretical prediction of pharmaceutical targets for new compounds is possible using a probabilistic method to build a model of any compound from the ChEMBL dataset. Then, using the circular fingerprint descriptors, a cheminformatic method, developed to explore known off-target interactions of known compounds, was applied to identify which of the new compounds that should bind to the desired targets. This and confirmation of the predicted efficacies are included in this topic.

Reuptake transporters are targets to modulate amine levels in the synaptic cleft, but, unfortunately, crystal structures are not available yet. Nonetheless, homology models of the transporters in conjunction with mutational studies are beginning to define the molecular determinants of binding to these proteins. Structure-based drug design together with good pharmacological data provides the basis for designs combining the features needed for each target into one molecule. These molecular determinants predict quite nicely the behaviour of some compounds (amphetamine, tyramine, cocaine, DA, 5-HT; Yelekci and Connaly, this conference) toward the dopamine transporter in models *in vitro* or *in* vivo (Navailles and De Deurwaerdère, 2011).

Drug design and computational studies are rendered easier by the crystal structures that identify the interaction of the protein with a ligand. Structures for the enzymes that degrade the monoamine neurotransmitters (MAO and COMT) are available for computational exploration of molecular determinants of binding. Inhibition of monoamine oxidases (MAO A and MAO B) by several irreversible inhibitors and a few new, well-tolerated, reversible inhibitors used over the last 30 years, results in increased levels of brain amines (Youdim and Bakhle, 2006). Docking and molecular dynamic studies of the inhibitor in the active site are now standard tools for medicinal chemists aiming to improve inhibitor binding or decide which part of a molecule may be changed without loss of affinity (Samadi et al., 2012). Using structure-based techniques, complete theoretical searches for new lead compounds are also possible (Vilar et al., 2012). Finally, using these models, it is possible to address the selectivity of series of new compounds toward MAO. More recently, the crystal structure of glutamatergic AMPA receptors has been obtained, leading to conceive new series of compounds targeting the GluR1 subunit of the AMPA receptor hopefully as efficiently as antinociceptive compounds as described by Stefania Butini (University of Siena).

Pharmacological evaluation is still a necessary step to determine the accurate efficacy of compounds and to evaluate the selectivity towards other targets. Several MAOI are not selective for MAO and display good affinities for other targets such as lysine-specific demethylases or cytochrome P450 (Binda et al., 2010); Massimo Valoti (University of Siena); Thomas Malcomson (University of St Andrews). Lysine-specific demethylases are involved in epigenetic, cytochrome oxidase are involved in the metabolism of xenobiotics. These other targets together may participate in the behavioural effects of these compounds in animal models and in humans. Indeed, as detailed by Marco Bortolato (University of Kansas) gene deletion of MAOA gives surprising results compared to pharmacological compounds (Finberg, 2014). Apart from the longitudinal and developmental dimensions inherent to gene deletion, Keith Tipton (Trinity College, Dublin) showed that the differences suggest that the biological effects of MAOI do not only result from their interaction with MAO (Finberg, 2014).

Neuropharmacological explorations of the mechanism of action of current drugs are a big challenge in neurobiology in order to identify the targets, ameliorate the phenotype, and limit the side effects. Even if these drugs are currently used in clinic, their mechanism of action is often misunderstood, not only for MAOI. L-DOPA is the gold standard medication in Parkinson's disease but the numerous motor and non-motor side effects occurring after years of treatment lead to conceive other therapeutic strategies and to focus on its mechanism of action (Meissner et al., 2011). Numerous strategies are developed to find new chemical compounds able to stimulate the DA D2 and D3 receptors, the primary mechanism thought to underline the efficacy of L-DOPA. The chemical development of new compounds unmasks new pharmacological concepts and the development of compounds will integrate these new concepts such as biased signaling or heterodimerization of receptors, as detailed by Holger Stark (Heinrich Heine University). Abdelhamid Benazzouz (Université de Bordeaux) emphasized the importance of the deep brain stimulation that also permits to highlight unpredicted targets such as D5 receptors, 5-HT_{2C} receptors in the control of DA neurons (De Deurwaerdère et al., 2013) or to highlight the involvement of 5-HT and NA neurons in the control of dopamine-mediated function (Di Matteo et al., 2008; Navailles, Di Giovanni and De Deurwaerdère, 2014; Navailles, Milan et al., 2014). Finally, Philippe De Deurwaerdère (Université de Bordeaux) presented evi-

Figure 1: Some members of EU COST Action CM1103 "Structure-based drug design for diagnosis and treatment of neurological diseases: dissecting and modulating complex function in the monoaminergic systems of the brain" at the Annual Conference "Neuropathology and Neuropharmacology of Monoaminergic Systems" hosted by the University of Bordeaux, France on 8-10 October 2014.

dence that the chronic use of L-DOPA could affect the activity of MAO enzymes in vivo showing that the different topics developed in the action are interconnected.

Understanding the interactions of neurotransmission systems is an important step for the optimization of therapeutic strategies. The plurality of targets that potentially bind antipsychotics or antiparkinsonian, antidepressant drugs favours the need to develop multitarget compounds. Because neurobiological systems of neurotransmitters establish close relationships (Chesselet, 1984), it is likely that a pharmacological action toward one system will more or less directly affect the other one. This is highlighted perhaps by famous associations and links between some neurotransmitter systems such as the 5-HT/DA interaction (Di Giovanni et al., 2008; Di Matteo et al., 2008), the glutamate/DA interaction (M. Carlsson and A. Carlsson, 1990), the 5-HT/GABA interaction (Soubrié, 2010) and so one. The role of monoamines still remains unresolved even in pathologies such as depression or anxiety where the connection between monoamines and the diseases has been known for years. In epilepsy, although monoamines were thought to control the excitability of hippocampal cells via a lowering influence on depolarizing current, Giuseppe Di Giovanni (University of Malta and Cardiff University), found that 5-HT_{2C} receptors do not modify the electrophysiological responses in the model of maximal dentate activation (MDA) of temporal lobe epilepsy (TLE) while they undergo to a cellular redistribution in the hippocampus of epileptic rats (Orban et al., 2014). Di Giovanni also showed that in the pilocarpine-model of TLE, the activation of the 5-HT_{2C} receptors surprisingly induce a powerful antiepileptic effect, probably mediated by interacting with GABA and glutamate. These findings highlight a strong model-dependence of the 5-HT_{2C} receptor effects which is especially true for TLE epilepsy.

Moreover, the physiopathology of numerous pathologies is still misunderstood. Nela Pivac (Rudjer Boskovic Institute, Zagreb) presented some data concerning the post-traumatic stress disorder, a pathology that probably involves monoamines, but devoid of efficient treatment.

A better understanding of the relationships of chemical systems in the brain relies on the availability of good chemical compounds for research and diagnosis and good models to address the efficacy of compounds and the physiopathology of brain diseases. These models are sometimes classical as those that have been developed in rodents to study numerous neuropsychiatric diseases or less classical as the use of crayfish to study the neurobiological bases of anxiety as underlined by Pascal Fossat (Université de Bordeaux) (Fossat et al., 2014).

Acknowledgments

We thank the numerous contributors, the guest speakers and especially Prof. Giuseppe Di Giovanni for publishing the proceedings of the conference as collection of short communications in Xjenza. We also acknowledge the support by LABEX (LABEX Brain, University of Bordeaux).

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