responses of neurons located in the output structures of basal ganglia, namely the entopeduncular nucleus (EPN) or the substantia nigra *pars reticulata*.

Both 5-HT_{2C} agonists and inverse agonists increased abnormal orofacial movements via 5-HT_{2C} receptors. c-Fos imaging studies indicated that different 5-HT_{2C} controls are expressed in the input structures of the basal ganglia, the striatum and the subthalamic nucleus. In addition, agonists and inverse agonists altered neuronal activity in the output structures which could be associated with the emergence of orofacial movements. 5-HT_{2C} controls are influenced by the level of DA transmission. Indeed, DA neurons lesion potentiated behavioural and electrophysiological responses induced by a 5-HT_{2C} agonist by acting in the EPN. The stimulation of D2 receptors enhanced oral dyskinesia and electrophysiological responses of the cortico-subthalamonigral pathway; these effects were suppressed by selective 5-HT_{2C} antagonists. This work illustrates the complexity of the controls exerted by 5-HT_{2C} receptors and their outcome with respect to central DA transmission. A better understanding of the controls in these regions would permit to apprehend possible treatments using $5-HT$ and/or 5-HT_{2C} agents.

KEY WORDS: Serotonin 2C receptor, basal ganglia, dopamine, dyskinesia, parkinson's disease, entopeduncular nucleus, subthalamic nucleus, substantia nigra pars reticulata, striatum.

P2.7
POTASSIUM CHANNELS AS A TARGET OF CNS DISORDERS

D'Adamo Maria Cristina[1], Servettini Ilenio[1], Guglielmi Luca[1] and Pessia Mauro[1]
[1]Section of Human Physiology, University of Perugia School of Medicine, Perugia, Italy
Correspondence Email: maria.dadamo@unipg.it

K^+ channels are critical for neuronal excitability and they are essential effectors of neurotransmitter-mediated signaling. They are distinguished by being the largest and most diverse class of ion channels, being encoded by more than 70 genes. In the past decades several types of human diseases have been associated to dysfunction of K^+ channels, resulting from mutations in their encoding genes. Indeed, K^+ channels defects underlie a number of distinct forms of epilepsies that have been named "K^+ *channelepsies*". Also different types of ataxias have been associated with altered K^+ channels function. In particular we have shown that episodic ataxia type 1 (EA1), a K^+ channelopathy, which manifests with short attacks of cerebellar ataxia, is caused by *loss-of-function* mutations in Kv1.1 (KCNA1) channels. The direct and indirect involvement of K^+ channels in a number of psychiatric disorders including autism spectrum disorders (ASDs), schizophrenia, and mental retardation has been reported. ASDs are characterized by impaired ability to properly implement environmental stimuli that are essential to achieve a state of cultural and social inter-relationships. The main features of this disease are marked impairments of verbal and non-verbal communication with restricted and repetitive behaviors. We have performed the genetic analysis of individuals affected by autism and epilepsy and identified new heterozygous point mutations in the KCNJ10 gene that encodes the inwardly-rectifying K^+ channel Kir4.1, expressed predominantly, but not exclusively, in astrocytes. Functionally, the mutated channels exhibited a phenotype consistent with *gain-of-function* defects. These new findings highlight the emerging role of inwardly-rectifying K^+ channels and astrocyte dysfunction in autism spectrum disorders associated with epilepsy.

KEY WORDS: Potassium channels, mutation, epilepsy, ataxia, K^+ channelopathy, ASD, astrocyte dysfunction, inward- rectifying K^+ channels.

P2.8
EFFECT OF ACUTE AND REPEATED NICOTINE ADMINISTRATION ON THE ELECTRICAL ACTIVITY OF THE LATERAL HABENULAR NEURONS IN RATS

Massimo Pierucci[1], Antonella Marino Gammazza[2], Giuseppe Di Giovanni[1]
[1]Department of Physiology and Biochemistry, University of Malta, Malta
[2]Sezione di Anatomia Umana, G. Pagano, Dipartimento di Biomedicina Sperimentale e Neuroscienze Cliniche, UniversitÃ degli Studi di Palermo, Italy
Correspondence Email: massimo.pierucci@um.edu.mt

Tobacco smoking represents a well-known risk factor for health that still accounts for a high number of deaths. So far, existing smoking cessation therapies have not been proven very successful at quitting this habit and a better undrstanding of the neurobiology of tobacco dependence is still needed. Nicotine is the neuroactive compound contained in tobacco that is responsible for its rewarding and reinforcing properties by acting on the midbrain dopaminergic system. The lateral habenula (LHb) is an epithalamic structure involved in pain, stress, depression and in encoding aversive stimuli. This structure is known to indirectly

inhibit the DA system through the activation of the RMTg, a GABA-ergic area located at the back of the VTA. The RMTg receives a strong glutamatergic imput from the LHb and is activated by the systemic injection of nicotine in rats. Thus the LHb might represent a possible target for the action of nicotine. Our data shows that systemic administration of nicotine dose-dependently increases the activity of single LHb neurons recorded extracellularly in vivo in rats, particularly at high doses. Following two weeks of nicotine chronic treatment, this response is drastically decreased while after 1 day of withdrawal only low doses of nicotine are again able to significantly increase the firing activity of the LHb neurons compared to the control group. These evidences strongly suggest that the LHb might play an important role in mediating the effects of nicotine on the midbrain DA system thus participating to the mechanism of addiction to this drug.

KEY WORDS: Drug of addiction, extracellular recording, serotonin, dopamine.

P2.9
OLIGODENDROCYTE PATHOPHYSIOLOGY AND TREATMENT STRATEGIES IN ISCHEMIA

Gabriella Mifsud[1]
[1]Department of Physiology & Biochemistry, University of Malta, Malta
Correspondence Email: gabriella.mifsud.08@um.edu.mt

Oligodendroglia, the myelin-forming cells of the CNS, form a functional unit with axons and play a crucial role in axonal integrity. An episode of hypoxia-ischemia causes rapid and severe damage to these particularly vulnerable cells via the overactivation of glutamate and ATP receptors (excitotoxicity), oxidative stress and mitochondrial disruption. Oligodendrocytes appear to be more vulnerable to HI than other CNS glia, and in certain brain regions and stages of development, more vulnerable than neurons, due to the possession of numerous features, which predispose them to injury. The cardinal effect of oligodendrocyte pathology is demyelination and dysmyelination, and has profound effects on axonal function, transport, structure, metabolism and survival. The oligodendrocyte is a primary ischemic target, in adult-onset stroke and especially in periventricular leukomalacia, and should therefore also be considered a primary therapeutic target. Further emphasis is required on therapeutic strategies targeting oligodendroglia, myelin and their receptors, as these have the potential to significantly attenuate white-matter injury in hypoxia-ischemia.

KEY WORDS: Excitotoxicity, hypoxia-ischemia, oligodendrocyte, oxidative stress, stroke.

P2.10
AMYLOID NEURODEGENERATION: FROM ELECTROPHYSIOLOGY TO FLIES

Michelle Briffa[1], **Stephanie Ghio**[2], **Ruben Cauchi**[1] **and Neville Vassallo**[1]
[1]Dept. of Physiology & Biochemistry, University of Malta, Malta
Correspondence Email: michelle.briffa@um.edu.mt

Alzheimer's, Parkinson's and Motor Neuron disease are characterized by the deposition of abnormally aggregated forms of Aβ1-42, α-synuclein and TDP-43, respectively. An intriguing possibility that is being investigated, is the possibility of pore formation in mitochondrial membranes by aggregates of these proteins. Such pores can have deleterious consequences on the electrical physiology of a neuron.
Electrophysiology studies are performed using a lipid bilayer workstation, which allows detailed electrophysiological characterisation upon incubation of amyloid aggregates with mitochondrial membranes. Electrical currents at the level of a single channel are recorded, and changes in membrane permeability can be correlated to toxic channel activity. The potential of natural polyphenols and bioactive extracts to block amyloid pores will be assessed, thereby preventing disruption of neuronal ion homeostasis.
Currently there are no drugs or clear-cut pathogenic mechanisms that do more than improve the symptoms associated with these diseases. Identification of compounds that lead to a marked and consistent recovery, will be a great asset to developing new therapeutic approaches.
Drosophila models of neurodegenerative disease have been successfully used in whole-genome screens aimed at identifying genetic modifiers, which can lead to the discovery of drug targets. The disease fly models are being generated by the overexpression of the respective human transgene in the wild-type fly brain.
A graded dose of a select group of test drugs are being tested and adult flies monitored for survival and climbing ability using well-established protocols. Data will be analysed to determine whether the drug-supplemented diet markedly, and consistently ameliorates the phenotypic defects intrinsic to the disease fly models.

KEY WORDS: Amyloid, neurodegeneration, Drosophila, mitochondria, aggregates, drugs.