We induced mild, transient brain ischaemia in rats and mice by injection of endothelin-1, and 3-7 days later found: microglial activation, induction of MFG-E8 and MerTK, and neuronal nuclei inside microglia. MFG-E8 knockout mice and MerTK mutant rats had: reduced microglial phagocytosis of neurons at 3 days and reduced brain atrophy and motor deficits at 28 days.

Injection of LPS into the brain induced neuronal loss in vivo that was prevented by co-injection of VNR or P2Y6 inhibitors, or in MFG-E8 knockout mice. Chronic peripheral LPS resulted in neuronal loss specifically in the substantia nigra that was prevented in P2Y6 knockout mice. Injection of amyloid beta into brain ventricles resulted in neuronal loss and memory deficits, prevented in P2Y6 knockout mice. Thus blocking microglial phagocytosis of neurons via VNR, MerTK or P2Y6 protects against inflammatory brain pathology.

doi:10.1016/j.jns.2017.08.106

82

WCN17-3632

T12: THE ROLE OF MICROGLIA IN NEUROLOGICAL DISEASE

Neuron-glia metabolic coupling: Role in plasticity and neuroprotection

P. Magistretti. *Magistretti Pierre, EPFL-Switzerland and KAUST-KSA, EPFL-Switzerland-KAUST, Saudi Arabia*

A tight metabolic coupling between astrocytes and neurons is a key feature of brain energy metabolism (Magistretti and Allaman, Neuron, 2015). Over the years we have described two basic mechanisms of neurometabolic coupling. First the glycogenolytic effect of VIP and of noradrenaline indicating a regulation of brain homeostasis by neurotransmitters acting on astrocytes, as glycogen is exclusively localized in these cells. Second, the glutamate-stimulated aerobic glycolysis in astrocytes. Both the VIP-and noradrenaline-induced glycogenolysis and the glutamate-stimulated aerobic glycolysis result in the release of lactate from astrocytes as an energy substrate for neurons (Magistretti and Allaman, Neuron, 2015).

We have recently shown that lactate is necessary not only as an energy substrate but is also a signaling molecule for long-term memory consolidation and for maintenance of LTP (Suzuki et al, Cell, 2011).

At the molecular level we have found that L-lactate stimulates the expression of synaptic plasticity-related genes such as *Arc*, *Zif268* and BDNF through a mechanism involving NMDA receptor activity and its downstream signaling cascade Erk1/2 (Yang et al, PNAS, 2014). L-lactate potentiates NMDA receptor-mediated currents and the ensuing increases in intracellular calcium. These results reveal a novel action of L-lactate as a signaling molecule for neuronal plasticity.

We have also recently shown that peripheral administration of lactate exerts antidepressant-like effects in three animal models of depression (Carrard et al, Mol.Psy., 2016).

doi:10.1016/j.jns.2017.08.107

83

WCN17-3624

T09B: NEUROGENETICS

Extensive genetic analysis on taiwanese patients with inherited neuropathy

Y.C. Lee. *Taipei Veterans General Hospital, Department of Neurology, Taipei, Taiwan R.O.C.*

From 2001 to 2016, we have recruited more than 570 unrelated patients with inherited neuropathy, including 411 with Charcot-Marie-Tooth diseases (CMT), 76 with hereditary neuropathy with liability to pressure palsy (HNPP), 60 with transthyretin-mediated familial amyloidotic polyneuropathy and 16 with distal hereditary motor neuropathy (dHMN) in Taiwan. They are all of Han Chinese origin. To elucidate the genetic causes, we initially screened the CMT patients for *PMP22* duplication and *GJB1* mutations. Then, we screened both CMT and dHMN patients for mutations in 61 neuropathy-implicated genes by a targeted NGS panel. Furthermore, we utilized whole exome sequencing to analyze selected large pedigrees with molecularly unassigned inherited neuropathy. With these strategies, we identified the pathogenic mutations in 294 (71.5%) CMT patients, including 249 (86.5%) patients with demyelinating CMT and 45 (36.6%) patients with axonal CMT, as well as 3 (19%) dHMN patients. At the same time, we also identified that *GNB4* and *WARS* are causal genes for CMT and dHMN, respectively, and the *TFG* p.Gly269Val mutation can cause a typical autosomal dominant axonal CMT with distal predominant symptoms, whereas *TFG* mutations were initially identified in Japanese patients with hereditary motor and sensory neuropathy with proximal dominance. *In vitro* functional studies also support the pathogenic role of mutations in *GNB4, WARS*, and *TFG* in neuropathy. Our studies demonstrate the mutational spectrum of inherited neuropathy in Taiwan, expand the list of causal genes of inherited neuropathy and disclose the importance of *GNB4, WARS*, and *TFG* in peripheral nerve functioning.

doi:10.1016/j.jns.2017.08.108

84

WCN17-3687

PLENARY LECTURE 06: NEUROLOGICAL MANIFESTATIONS OF CONGENITAL ZIKA SYNDROME

Neurological manifestations of congenital zika syndrome

A. Pessoa[a], A. Delfino[b], T. Furtado[c], E. Ribeiro[d]. *[a]Hospital Infantil Albert Sabin/Universidade Estadual do Ceará- UECE, Pediatric Neurology/Neurogenetics, Fortaleza, Brazil; [b]Universidade Estadual do Ceará-UECE, Medicina, Fortaleza, Brazil; [c]Universidade Christus, Medicine, Fortaleza, Brazil; [d]Hospital Infantil Albert Sabin/Universidade Christus, Medicine, Fortaleza, Brazil*

In the summer of 2015, several months after the Zika virus (ZIKV) epidemic was recognized in northeastern Brazil, pediatric neurologists and obstetricians noticed an increased number of fetuses with malformations and the Brazilian Ministry of Health soon reported that the birth prevalence of microcephaly had increased from 0.6 to 2.8 per 10,000 live births in regions reporting ZIKV transmission. At the Hospital Infantil Albert Sabin, Fortaleza-Brazil, we have accompanied 107 patients with Congenital Zika Syndrome, 91 with congenital microcephaly and 16 who were born with normal head circumference and evolved with postnatal microcephaly. Our data demonstrate features of both fetal brain disruption and primary cortical malformation, and define the nature and spectrum of the disorder and five important points that together comprise a recognizable pattern of disruption and malformation when seen together strongly support a diagnosis of congenital Zika syndrome.

(1) prenatal exposure to ZIKV carries a high risk of causing fetal anomalies including fetal brain disruption sequence, especially during the first and second trimesters, and that the risk may be higher among mothers with symptomatic ZIKV infections;
(2) severe microcephaly with partially collapsed skull; thin cerebral cortices with subcortical calcifications; enlarged ventricles at birth but in 15 cases there was evolution to increase dilation and hypertensive hydrocephalus.
(3) macular scarring and focal pigmentary retinal mottling;
(4) congenital contractures and the occurrence of arthrogryposis