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A NOVEL TRAIL TO NEUROINFLAMMATION: COMMON CLUES TO NEURODEGENERATIVE DISORDERS

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Convincing evidence supports the pathophysiologic relevance of inflammatory mediators expressed by injured cells during neurodegenerative processes. Among these, proapoptotic/proinflammatory cytokines belonging to the TNF family and their receptors are regarded as sustainers of the accelerated cell death rate occurring in neurodegenerative processes related to various CNS disorders. In this line, tumor necrosis factor-related apoptosis inducing ligand, or TRAIL, a proapoptotic cytokine which acts through its two DR4 and DR5 death receptors, has been shown to potently mediate prominent neuronal loss in conditions of neuronal injury, such as amyloid accumulation, brain ischemia, and traumatic spinal cord injury. In fact, these conditions share increased TRAIL, DR4 and DR5 expression, associated with activation of caspases, augmented neuronal death rate, gliosis, and overexpression of an array of proinflammatory mediators. Furthermore, high TRAIL expression is proportional to functional decline, which eventually brings about, for example, severe impairment of related functions. In animal models of neurodegeneration, immunoneutralization of TRAIL by means of a monoclonal antibody results in significant rescue of injured neurons from death. In fact, molecular, tissue, and functional parameters show dramatic improvement in individuals receiving anti-TRAIL treatment. In synthesis, TRAIL is a detrimental factor activated by damaged neurons. TRAIL efficiently sets into motion redundant neurodegeneration–related cell death processes, and its neutralization implies either significant attenuation or abrogation of phenomena typical of neurodegeneration. For these reasons, the TRAIL system, which represents a common clue to many neurodegenerative processes, should be regarded as a potential target for efficacious, innovative therapeutic strategy of neurodegenerative disorders, aimed to restrain overshooting neuroinflammation and its detrimental consequences.

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MICROGLIAL MICROVESICLES ALTER EXCITATION-INHIBITION BALANCE IN THE BRAIN

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This brief congress report summarizes the oral communication held by Martina Gabrielli at the National Meeting of PhD Students in Neuroscience "New Perspectives in Neurosciences", which took place in Naples on February 26th, 2015. The presentation highlighted the role of extracellular vesicles (EVs) released from reactive microglia in the modulation of synaptic transmission. Special regard was given to novel evidence that microglial EVs carry on their surface active endocannabinoids (eCBs), thus serving as vehicles for their transport across the extracellular space.

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INNOVATIVE ROBOTIC AND AUTOMATED TOOLS FOR ASSESSMENT OF MOTOR RECOVERY IN STROKE MOUSE MODELS

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Post-stroke motor rehabilitation has been extensively studied for many years, but the neurophysiological mechanisms of recovery remain incompletely understood. Moreover, key questions on whether restoration of function occurs via compensation and "true recovery" remain to be answered. Here, we summarize data in the literature and two recent studies from our group describing innovative tools for evaluating post-stroke forelimb motor deficits in mouse models. The first part describes a robotic platform for measuring and training forelimb function after stroke. Kinetic and kinematic parameters during the robot-mediated retraction task efficiently detect the post-stroke motor deficit. In addition, training on the platform has beneficial effects on motor function. The second part shows the implementation of a semi-automated tool to study pre- and post-stroke forelimb kinematics during the single pellet reaching task. This tool effectively reveals the use of compensatory strategies even after partial recovery in end-point measures (i.e. the number of correct grasps). We finally discuss the benefit of using these innovative tools to design and test novel rehabilitative strategies, aimed at improving post-stroke motor function, by combining motor training with modulation of spontaneous neuroplasticity.

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

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NEUTRALIZATION OF THE SECOND ARGININE ALONG THE S_4 SEGMENT OF Kv7.2 POTASSIUM CHANNEL SUBUNITS PRODUCES GAIN-OF-FUNCTION EFFECTS AND CAUSES EPILEPTIC ENCEPHALOPATHY

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Mutations in the *KCNQ2* gene, encoding for Kv7.2 voltage-gated K^+ channel subunits underlying the neuronal M-current, have been associated with a wide spectrum of early-onset epileptic disorders ranging from benign familial neonatal seizures to severe epileptic encephalopathy. In the present conference report, we describe our latest results in which, by using mutagenesis, electrophysiology, biochemical, and multistate modeling techniques, the molecular mechanism(s) underlying channel dysfunction caused by mutations affecting the R201 residue of Kv7.2 recently found in patients affected with epileptic encephalopathy (R201C or R201H) have been investigated. Electrophysiological studies revealed that the mutations, affecting the second arginine (R2) in the voltage sensing domain (VSD), destabilized the resting state of the channel, thereby producing gain-of-function effects, opposite to the loss-of-function effects produced by previously found disease-causing mutations. Multistate structural modeling revealed that the R2 residue stabilized the resting state of the VSD by forming an intricate network of electrostatic interactions with neighboring negatively-charged residues (E130 and E140 in S_2, D172 in S_3), a result also confirmed by disulfide trapping experiments. Thus, the Kv7.2 mutations affecting the R2 residue selectively impair the stability of the resting VSD state, favoring channel opening. In conclusion, the results obtained suggest that mutation-induced increase in Kv7.2 function can be responsible for epileptic encephalopathy in humans.

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