NEURONAL RESPONSE TO EXPERIMENTAL INTERRUPTION OF THE NEURAL CIRCUITS: A MOLECULAR AND STRUCTURAL STUDY IN AUTONOMIC GANGLIA

IN VIVO

SUMMARY

The organization of synaptic contacts in neural circuits bears a basic relevance to the accomplishment of brain functions, behavioural control and cognitive activities. The formation, maintenance and remodelling of synaptic contacts are complex processes that occur during development as well as in mature neurones and are regulated by a cohort of intra and extracellular events. They reflect the response of neurones to their own bioelectrical activity, to the presence of extracellular soluble factors and components of the extracellular matrix, to interactions with neighbouring neurones, glial cells and target organs, and to pathological processes and injuries. Autonomic ganglia, in the peripheral nervous system, constitute a model system particularly suited to experimentally address these complex interactions. Ganglia display rather complex connectivity and share many features with the CNS. They lack the wide variety of neurotransmitters, neuronal cell types and circuitry variations of the CNS, but on the other hand they have synapses relatively accessible and the anatomy and pharmacological basis of ganglionic transmission are essentially well known. Ganglionic neurones can be easily subjected to various patterns of activation, easily deprived of their neuronal input (denervated), or otherwise injured (axonotomy) by simply cutting or crushing the pre- or post-ganglionic nerve trunks, respectively; reinnervation, regeneration of the axonal output and recovery of synaptic function can be monitored both in vivo and in vitro. In order to identify factors and mechanisms controlled by input and output connections in autonomic ganglia, structural, immunocytochemical and molecular approaches will be combined. Two different, but complementary, experimental animal models will be used on account of their peculiar structural and functional organisation: the rodent sympathetic superior cervical ganglion (SCG), and the quail parasympathetic ciliary ganglion (CG). The project is articulated in two main lines: 1) We will investigate the molecular mechanisms involved in intraganglionic synapse remodelling, induced by injury of the SCG and CG nerves, paying particular attention to the role of extracellular proteases and extracellular matrix proteins; 2) The relevant pathological changes produced by lack of dystrophin, a protein of the cortical cytoskeleton, will be investigated in mdx mice, an animal model for Duchenne muscular dystrophy. The following aspects will be analysed: a) large-scale analysis of gene expression in mdx mouse SCG to search for genes affected by the spontaneous mutation in the dystrophin gene and possibly responsible for the altered reaction to axotomy of SCG neurones previously observed; b) analysis of the nicotinic currents in slices of mdx mouse SCG, in which the nicotinic acetylcholine receptors containing the α3 subunit (α3nAChRs) are drastically reduced compared with the wild-type; c) damage to SCG muscular target organs and its relation to the loss of ganglionic neurones observed in adult mdx mice, by measuring the levels of trophic factors and their receptors; d) the neurone-target interplay, by co-culturing explants of wild-type and mdx mouse SCG with the respective target organs (iris, heart, submandibular gland) or with those derived from the other strain (wild-type SCG versus mdx target organs and viceversa).

**Scientific credentials of the participants to the research project**

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Full professor of General Physiology and in charge of the Neurobiology course in the Department of Cellular and Developmental Biology, University of Rome "La Sapienza". National Coordinator of MURST Cofin Research Projects. Principal investigator of research programs of Ateneo (University "La Sapienza"). Visiting Professor Dept. of Genetics and Anatomy, and Bioarchitectonics Center, School of Medicine, Case Western Reserve University, Cleveland, Ohio (1982-1992).

List of the last five years publications related to the project