ACADEMIC LECTURE

NEW VISTAS ON COMMUNICATION MODES AND INTEGRATIVE MECHANISMS OF CHEMICAL SIGNALS AND THEIR POTENTIAL CLINICAL IMPACT

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"Integration" is a key term in describing how nervous system can perform high level functions. A first condition to have "integration" is the presence of efficient "communication processes" among the parts that have to be combined into the harmonious whole. In this respect, two main types of communication processes, the wiring transmission (WT) and the volume transmission (VT) allow the exchange of signals not only between neurons, but rather among all cell types present in the central nervous system (CNS). The major criterion for this classification is the different characteristics of the communication channel with physical boundaries well delimited in the case of WT (axons and their synapses; gap junctions) but not in the case of VT (the extracellular fluid filled tortuous channels of the extracellular space and the cerebrospinal fluid (CSF) filled ventricular space and sub-arachnoidal space). Recently, evidence of subtypes of WT and VT has been obtained, namely the "tunnelling nanotube type of WT" and the "Roamer type of VT." In this novel type of VT microvesicles (MVs) are vesicular carriers for intercellular communication of proteins, mtDNA and RNA flowing in the extracellular fluid of the brain along energy gradients to reach target cells. In the tunnelling nanotubes proteins, mtDNA and RNA can migrate as well as mitochondria. Although the existence and the role of these new types of intercellular communication are still a matter of investigation their potential importance for brain function in health and disease is highly likely.

The second fundamental condition to have "integration" is the recognition/decoding process of signals at target cell level. As far as this point is concerned, increasing evidence emphasizes the importance of supra-molecular allosteric complexes of receptors generated by direct receptor–receptor interactions or via adapter proteins. These complexes allow a first integration of the incoming chemical signals already at plasma membrane level.

The two basic features of "integration" can be simultaneously affected since intercellular transfer of receptors via the Roamer Type of VT is possible (Guescini *Exp Brain Res* 318: 603-613; 2012). The physiological and pathological implications of these findings are still unexplored. Actually, the Roamer type of VT could also be relevant for a new approach to the Brain-Body Medicine. As a matter of fact, not only has it been shown that MVs can pass the blood-brain barrier (Colombo *Frontiers in Physiology* 29 March 2012) but it has also been pointed out that an anatomical connection from subarachnoid spaces along nerves into peripheral tissues represents an important route through which pathogenic CSF contents, including possibly MVs, leave the subarachnoid spaces along nerves to reach the interstitial fluids of the respective peripheral tissues (Bechter K. *NPBR* 2011:51-66).