Patch-Clamp Array Chips for Advanced Neurodegenerative Disease Models and Faster Pharmacological Development

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In-vitro models are used extensively to study the molecular mechanisms that regulate the transmission and processing of information in the brain through synaptic communication in neuronal networks. Ion channels are proteins embedded in cell membranes that regulate ion currents and are important therapeutic targets for pharmacological intervention. Their activity is traditionally monitored by the glass-pipette patch-clamping method, the importance of which was recognized in Neher and Sakmann's 1991 Nobel Prize in medicine, and that remains the gold standard of electrophysiology. In this method, a small-tipped glass pipette filled with electrochemically conductive (physiological saline) solution is sealed to a patch of cell membrane by suction and its voltage potential clamped with respect to a reference electrode immersed in the electrochemically conductive culture medium. Small currents resulting from ion channel activity across the membrane are then recorded. This technique has remarkable resolution but is an extremely laborious process and is very invasive to cells. This represents a bottleneck for high-throughput pharmacological screening and drug development, and considerable effort has been invested in automating patch-clamping. Recently, this has resulted in the development of planar patch-clamp chips, where the apex of the pipette is replaced by a microscopic hole micromachined in a self-supported film on which the cell is placed. The chip is then mounted in a two-chamber setup: the top one serving as the culture dish; the bottom one as the equivalent of the inside of the glass pipette and containing the physiological saline. Current planar patch-clamp chip technology, however, still does not address a second limitation of the patch-clamping technique, namely the difficulty in simultaneously recording the activity of several cells engaged in synaptic connectivity. This significantly restricts the power of in-vitro models for diseases whose symptoms are synaptic dysfunctions, such as Alzheimer's and other cognitive diseases.

NRC is developing a multiple-patch chip consisting of micro-holes patterned in self-supported membranes and integrated subterranean microfluidic channels aligned to them to miniaturize the glass-pipettes, as well as growth cues to guide cells in organized networks in alignment with the interrogation sites. I will show the different stages of development of the chip and actual electrophysiological activity recorded from cultured neurons. This chip will provide more powerful model to neurobiologists and electrophysiologists studying other diseases in which network activity plays an important role, such as cardiac arrhythmia. The control of networks into simple organized patterns also offers more direct models to advance computational neuroscience. Finally, in vitro studies of neuronal networks offer fascinating models to study the integrative information processing principle of the brain that may one day complement Boolean information processing. Thus, our neurochip may also help further the exploration of new computing paradigms.