Institutionen för Kvinnors och Barns Hälsa

Role of calcium in developing cellular network: Ca2+ in human neural stem cells and rat neontal cardiomyocytes

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ABSTRACT

This thesis aimed to study Ca^{2+} homeostasis and its regulation in developing heart and brain cells. Cardiomyocytes rapidly developed a fast calcium machinery, (1) to regulate cytoskeletal protein interactions to the extracellular matrix of neighboring cells through gap junctions, and (2) to induce Ca^{2+}-induced Ca^{2+} release (CICR) from sarcoplasmic reticulum (SR), (3) to generate rapid energy supply of ATP from mitochondria. In contrast, the developing human brain cells undergo a slow nurturing process to proliferate and differentiate into various specific cell types with multi-functions through specialized endoplasmic reticulum (ER) and mitochondria. Although, I used two different developmental stages (fetal, postnatal) in two different cell types (brain cells, cardiomyocytes) from two different origins of lineages (ectoderm, mesoderm) both have regulation of Ca^{2+} homeostasis as a vital component for their development and function.

The fetal brain undergoes proliferation, migration, differentiation, region patterning and specification of cell morphology and function and Ca^{2+}signaling is involved in all developmental stages. Morphological, immunocytochemical and functional phenotypes were characterized over time in expanded and differentiated fetal (11-13 week old) human neural stem cells (hNSC) from three sources. During proliferation, gap junctions were involved in spontaneous calcium oscillations and coordinated Ca^{2+} waves between cells. The role of gapjunctions decreased during differentiation of hNSC but was still prominent in several cells. Purinergic receptor activation by ATP induced Ca^{2+} signals in proliferating hNSC that were independent from gapjunction signaling. In contrast both glutamate- and GABA-induced Ca^{2+} signals, partly depend on gap junction signaling. Purinergic signaling plays a crucial role in spontaneous development and neurotransmitter-induced Ca^{2+} regulation in proliferating and differentiating hNSC. I demonstrate that calcium homeostasis in three primary fetal hNSC is regulated through ATP and purinergic receptors during all stages of proliferation and differentiation studied. Glutamate-induced Ca^{2+} signals were dependent on purinergic receptors in BDNF+GDNF-differentiated cells. The role of GABAergic induced changes in calcium homeostasis increased with differentiation time and seemed to be independent of gapjunction and purinergic signaling.

Neonatal lupus is induced by maternal anti-Ro52 autoantibodies. Cardiac manifestations include AV-block. We found that the electrical signal transmission was delayed in neonatal hearts of pups born to female rats injected with Ro52 monoclonal antibodies specific for the p200 epitope. We studied the effect of the Ro52-p200 antibodies on cultured neonatal cardiomyocytes, and found disturbed Ca^{2+} regulation following application of anti-Ro52 monoclonal antibodies. The effects on calcium homeostasis were time- as well as dose-dependent and could be the initial mechanism for development of congenital cardiac pathology in fetuses to mothers with autoimmune disease and SSA antibodies.

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