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Ion Channels in Regulation of Neuronal Regenerative Activities

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Abstract

The regeneration of the nervous system is achieved by the regrowth of damaged neuronal axons, the restoration of damaged nerve cells, and the generation of new neurons to replace those that have been lost. In the central nervous system the regenerative ability is limited by various factors including damaged oligodendrocytes that are essential for neuronal axon myelination, an emerging glial scar, and secondary injury in the surrounding areas. Stem cell transplantation therapy has been shown to be a promising approach to treating neurodegenerative diseases because of the regenerative capability of stem cells that secrete neurotrophic factors and give rise to differentiated progeny. However, some issues of stem cell transplantation, such as survival, homing, and efficiency of neural differentiation after transplantation, still need to be improved.

Ion channels allow for the exchange of ions between the intra- and extracellular spaces or between the cytoplasm and organelles. These ion channels maintain the ion homeostasis in the brain and play a key role in regulating the physiological function of the nervous system and allowing the processing of neuronal signals. In seeking a potential strategy to enhance the efficacy of stem cell therapy in neurological and neurodegenerative diseases, this review briefly summarizes the roles of ion channels in cell proliferation, differentiation, migration, chemotropic axon guidance of growth cones and axon outgrowth after injury.

1. Introduction

Regeneration of the nervous system is achieved by the generation of new neurons, glia, axons, myelin, or synapses. However, in the central nervous system the regenerative ability is very limited compared to the peripheral nervous [1]. In the central nervous system, neuronal axons are myelinated by oligodendrocytes, which do not proliferate in response to injury and cannot be replaced after injury. Another barrier to neural regeneration is the extent of cell death that occurs in the central nervous system in response to injury not only in the directly damaged neurons, but also in the neurons in the surrounding vicinity that undergo apoptosis [2–4]. Additionally, in response to injury the pre-existing glial cells in a quiescent state can begin to activate and form a glial scar that serves as a physical barrier to axonal regeneration [5–7]. Increasing neuronal regeneration in the central nervous system is one of the current approaches to combat the neurodegenerative diseases.

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Compliance with Ethics Requirements

This is a review article that does not contain any studies with human or animal subjects. The authors assume that all original studies cited in this review followed institutional and national guidelines for the care and use of laboratory animals and guidelines for clinical trials on patients. However, the authors are not responsible for any violation of the guidelines in the original investigations.

Conflict of Interest:

The authors declare no competing financial interests.

Regenerative strategies are active research topics; those may include cell replacement, neurotrophic factor delivery, axon guidance, removal of growth inhibition, manipulation of intracellular signaling, bridging and artificial substrates, and modulation of the immune response [2]. Due to their capability to self-renew, giving rise to differentiated lineage cells, and secreting neurotrophic factors, stem cell transplantation has become a new method of introducing new neural cells to replace damaged ones and influence the remaining damaged tissue after injury [2, 8–15]. Traditionally, neural stem cells isolated from the hippocampus and subventricular zone were the main source of stem cells for replacement purposes [16, 17]. Recently, with the advancement of pluripotent stem cells, including mouse and human embryonic stem cells (mESC and hESCs) and induced pluripotent stem cells (iPSCs), new approaches for neural cell replacement are being developed [9, 10, 14, 15]. It has been increasingly recognized that satisfactory survival and differentiation of the transplanted cells in the brain is critical for maximal benefits from stem cell transplantation therapy. Some studies show that transplanted stem cells can survive and partly attenuated the behavioral deficits. However, majority of transplanted cells die within a few days after transplantation and only 1–30% transplanted cells survival and even fewer can differentiate into neurons. It is still at the early stage to understand whether and how transplanted cell become functional neurons and establish connections with the host neural network [10, 18–24]. Thus, optimizing transplantation condition and improving the cell survival and the efficacy of neural differentiation after transplantation are some of major challenges in the development of stem cell transplantation therapy.

Ion channels allow for the exchange of ions between the intra- and extracellular spaces or between the cytoplasm and organelles. Ion channels can be classified by the molecular structures, the nature of their activation and gating, the species of ions passing through those gates, and the regulation/localization of these proteins. Based on the type of ions, they can be classified to six main categories, which are chloride channels, potassium channels, sodium channels, calcium channels, proton channels and non-selective cation channels. These ion channels maintain the homeostases of the most abundant ions in the cell and play key roles in regulating the physiological function of the nervous system and the processing of neuronal signals [25–27]. Their dysfunction, called “channelopathies”, is involved in many neurological disorders and neurodegenerative diseases [28]. Ion channels have also been shown to influence regeneration [29, 30], mediated by their effects on cell proliferation, differentiation, migration, chemotropic axon guidance of growth cones and axon outgrowth after injury.

2. Ion channels in cell proliferation and differentiation

Extensive studies have demonstrated the role of ion channels in regulating cell proliferation, differentiation during development [30–37]. The changes in membrane potentials lead to different aspects of cell behavior and large-scale morphogenetic processes during regeneration [30]. For example, cell cycle progression has been reported to be associated with membrane potential fluctuation and the change of membrane potential appear to be required for both G1/S and G2/S phase transitions. Membrane hyperpolarization may induce cell differentiation, while membrane depolarization activates cell proliferation and de-differentiation. The regulatory action is achieved through bioelectric signaling mechanisms; the detailed molecular mechanism, however, remains largely unclear.

K⁺ channels are the most diverse class of ion channels, regulating K⁺ efflux from the K⁺-rich intracellular space to the extracellular compartment. The opening of these channels generally causes membrane hyperpolarization due to the negative K⁺ equilibrium potential under physiological conditions. Consequently, these channels are responsible for maintaining a negative membrane potential [25]. Inhibition of the K⁺ channels with high

resting conductance (e.g., specific K_{ir} and K_{2p} isoforms) could stimulate proliferation. Inhibition of K_v channel isoforms reduced the proliferation of neural stem cells/progenitor cells (NSC/NPC) cultured as neurospheres in vitro [38–40]. Consistently, inhibition of BK_{Ca} , the potassium-selective, calcium-activated ion channels, arrested the cells at the G0/G1 phase and reduced cyclin D1, cyclin E, p-ERK1/2, and p-Akt expression in human bone marrow-derived and human iPSC derived mesenchymal stem cells, indicating the essential role of BK_{Ca} stem cells proliferation and maintaining their physiological function [41, 42]. Calcium activated potassium channels have also been shown to regulate neuronal differentiation in pluripotent stem cells [25, 43]. Our previous studies demonstrated that KCNQ/M-channels regulate neuronal cell viability and differentiation in mouse embryonic stem cell (mESC)-derived neuronal cultures [25]. Blocking KCNQ channels with XE991 and linopirdine in mESC derived neurons reduced the frequency in electrophysiological recording while KCNQ channel opener N-ethylmaleimide increases the frequency in the recording [25]. These findings indicate that distinct K^+ channels are involved in development events.

Besides the large family of K^+ channels, other ion channels have also been found to be involved in cell proliferation and differentiation. Aquaporin-4 (AQP4) is a key molecule for maintaining water and ion homeostasis associated with neuronal activity in the central nervous system. Recently, AQP4 was found to play important roles in the proliferation, survival, migration and neuronal differentiation of adult SVZ neural progenitor cells (NPCs) via modulation of intracellular Ca^{2+} dynamics [44, 45]. Transient receptor potential channel 1 (TRPC1) may be up-regulated under proliferative conditions in NPCs. On the other hand, knockdown of TRPC1 and the use of an antibody against TRPC1 markedly reduced proliferation of NPCs [46].

3. Ion channels in chemotropic axon guidance and neurite outgrowth

Calcium-mediated signaling contributes to many aspects of development of a functional nervous system [47]. Besides its roles in regulation of various stages of neuronal development including proliferation, migration, differentiation, and survival, Ca^{2+} signaling plays a critical role in regulating pathfinding of growing axons and neurite outgrowth [47–53]. Transient receptor potential canonical (TRPC) channels are a superfamily of cation channels permeable to calcium ions. TRPC channels contribute to guidance factor-induced elevation of Ca^{2+} at the growth cone and they are required for chemo-attractive turning [48–50, 54–56]. In cultured *Xenopus* neurons the diffusible guidance factor netrin-1 induced turning response depends on Ca^{2+} influx through TRPC channels. Reduction of Ca^{2+} signals converted the netrin-1-induced response from attraction to repulsion. In the absence of netrin-1, activation of Ca^{2+} -induced Ca^{2+} release from internal stores with a gradient of ryanodine triggered either attractive or repulsive responses [49]. The pharmacological inhibition of TRPC channels also abolished the growth-cone turning response induced by BDNF [54]. These data suggest that functional TRPC channels are present in growth cones and can be modulated by chemotropic guidance cues.

Evidence has shown the essential role of Ca^{2+} influx mediated by TRPC channels in chemotropic molecule induced axon guidance. However, how these chemotropic molecules activated TRPC channels is still an open question. TrkB-PLC- γ -IP3 has been proposed as a signaling pathway that activates TRPC channels, thus mediating the Ca^{2+} influx required for the turning response induced by BDNF in the growth cone [54, 57]. Recently, peptidyl-prolyl isomerase FKBP52 was shown to regulate TRPC1 channel opening through isomerization, and that it was required for the chemotropic guidance of neuronal growth cones in developing spinal cord [58]. Semaphorin 3A is a secreted guidance peptide that binds to the neuropilin-1/plexin A1 receptor complex. Clapham group proposed that TRPC5

acts downstream of semaphorin signaling to cause either attraction, repulsion, or collapse of neuronal growth cones during the nervous system development [59].

TRPC channels are also implicated in modulating neurite outgrowth by mediating intracellular Ca^{2+} concentration. In cultured hippocampal neurons, pharmacological or small interfering RNA inhibition of TRPC5 channels suppressed Ca^{2+} /calmodulin kinase kinase (CaMKK) and its downstream target Ca^{2+} /calmodulin kinase I (CaMKI)-mediated activation of CaMKI γ as well as axon formation, indicating that TRPC5 channels might activate CaMKK and of CaMKI γ to promote axon formation [60]. However, a discrepancy was found in the role of TRPC5 channel in axon outgrowth. Some studies show that TRPC5 plays a negative role, rather than promoting axon outgrowth. The TRPC5 channel was down-regulated during NGF induced neurite outgrowth in PC12 cells. Overexpression of TRPC5 increased the receptor-activated Ca^{2+} influx, however it suppressed neurite outgrowth in PC12 cells [61, 62]. The opposite roles of TRPC5 in different studies may be due to the use of different differentiation/maturation stages of neuronal cells since it may be predicted that the role of TRPC5 in regulating neurite outgrowth might be developmental dependent.

Other than the Ca^{2+} permeable channel TRPC, sodium channels and sodium pump have been shown to regulate axonal growth. The change of neuronal excitability induces intracellular Ca^{2+} concentration change with increased neuronal excitability increases intracellular Ca^{2+} . Mutations that decrease excitability, including mutations of the sodium pump *nkb-1* and the sodium channel *unc-8*, induce poor axon regeneration after injury. In contrast, mutations that affect K^+ channel or the K^+ channel regulator *mps-1* increase the cell excitability and in turn enhance axon growth [63]. Voltage-gated Na^+ channel protein $\text{Na}_V1.9$ is localized in axons and growth cones. Suppression of $\text{Na}_V1.9$ expression reduced axon elongation. The function of $\text{Na}_V1.9$ is essential for activity-dependent axon growth, acting upstream of spontaneous Ca^{2+} elevation through voltage-gated Ca^{2+} channels [64].

The axon regeneration is regulated by neuronal environment and the intrinsic factors, which either promote or inhibit the regeneration. Due to the essential role of ion channels in axon growth during the development, studies on the impact of ion channels on axon regeneration after injury would help to better understand the failure of axonal regeneration under many pathological conditions. After injury, intracellular Ca^{2+} increases as a result of extracellular Ca^{2+} entry from breached axonal member and the release from intracellular stores. It has been demonstrated that L-type Ca^{2+} and TRPC4 channels are required for regeneration of neurites after injury [65, 66]. These observations are consistent to the notion that Ca^{2+} signaling is involved in regulating pathfinding of growing axons and neurite outgrowth, which is critical for the regeneration of surviving neurons after injury [63].

Recently, TRPC channels found to be involved in neurite outgrowth in human embryonic stem cell derived neurons. Pharmacological inhibition or down-regulation of TRPC1 and TRPC4 proteins significantly reduced the neurite extension of stem cell derived neurons [67]. Stem cells as a cell replacement resource in neuronal regeneration after injury have been widely studied recently. Their ability of differentiation to neuronal cells and engraftment to endogenous tissue is critical to achieve the good therapeutic effects in the brain. A better understanding of the role of ion channel in axonal growth may provide insights to improve the stem cell therapy.

4. Ion channels in cell migration

During the CNS development and the regeneration after injury, the migration of neural stem cells and the migration of newly generated neural cells to their proper positions in the cerebral cortices are very important. The mechanisms of cell migration involve multiple

aspects, including the polarization, cell-matrix interactions adhesion, and chemotaxis for directed migration. Multiple ion channels have been reported to be involved in the migration process during development and after injury [68–71]. The mechanism of ion channels regulating cell migration is through their roles in regulating cell membrane potential and cell volume [69]. The families of ion channels that are involved in cell migration and underlying mechanisms have been well summarized by Albrecht Schwab in 2012. Due to the importance of improving the cell migration to the injury region in stem cell therapy, the role of ion channels in stem cell migration is reviewed here [24, 72].

Ca^{2+} signaling during migration also plays an essential role. Cell migration is a Ca^{2+} -dependent process and many Ca^{2+} sensitive molecules are involved in this process; for example, myosin II, calpain, and Ca^{2+} /calmodulin-dependent protein kinase [73–76]. During migration, there is a $[\text{Ca}^{2+}]_i$ activity gradient along the rear-to-front axis of migrating cells with a higher $[\text{Ca}^{2+}]_i$ located closer to the rear. [77–79]. Those ion channels releasing Ca^{2+} from intracellular stores or removing Ca^{2+} from the cytosol into intracellular stores or across the plasma membrane into the extracellular space are usually involved in the migration process [80, 81]. In the very early stages of neural stem cell differentiation, both high-voltage-activated Ca^{2+} channels and low-threshold voltage-dependent Ca^{2+} channels are expressed in neural stem/progenitor cells. Blocking the low-voltage-activated Ca^{2+} channels decreases the number of active migrating neuron-like cells and neurite extensions [82]. Similar results were also found in human neural stem cells and oligodendrocyte precursor cells (OPC) [83–86]. Several kinases such as PKC and tyrosine kinases receptors (TKRs) were found to modulate voltage-operated Ca^{2+} uptake in OPC and therefore participate in the regulation of essential early OPC developmental functions such as processes extension and migration [83]. In endothelial progenitor cells, knockdown of TRPC1 significantly reduced of the amplitude of store-operated Ca^{2+} entry and reduced the cell migration, indicating the potential role of TRPC1 in inducing vascular repair [87].

Since most migrating cells dramatically change their shape while moving, local swelling and shrinkage are necessary for migrating cells when they are obliged to squeeze through narrow spaces of the dense fiber meshwork of the extracellular matrix [88, 89]. In addition to regulation of the cell membrane potential and consequent Ca^{2+} influx [71, 90, 91], K^+ channels are key players in regulating cell volume by creating an optimal intracellular environment required for the cytoskeletal migration machinery [92, 93]. The essential role of ion channels in migration has been shown in many cell lines including stem cells [24, 94–98]. Our recent study found that Kv2.1 K^+ channel is involved in bone marrow mesenchymal stem cell migration by activating focal adhesion kinase (FAK). FAK is a key adhesion protein in many cell types for integrin-mediated cell adhesion and migration. We demonstrated that Kv2.1 channel could act as an “adhesion protein”, form a complex with FAK, and promote the activation of FAK. We further showed that by increasing FAK phosphorylation and activation, increased Kv2.1 channel expression/activation promotes the migration and homing of bone marrow mesenchymal stem cell after transplantation into the ischemic heart [24].

Other than the large family of K^+ and Ca^{2+} channels, water channels were shown to influence the cell migration in stem cells as well [45]. Aquaporin 1 (Aqp1) enhances the ability of bone marrow mesenchymal stem cells to migrate through the FAK pathway and partially through the β -catenin pathway [99]. Knockdown of AQP4 inhibits the migration and neuronal differentiation of neural stem cells by mediating intracellular Ca^{2+} dynamics [44]. Taken together, these data suggest the important role of ion channels in the migrating neural stem/progenitor cells.

5. Future directions--Targeting ion channels for improving stem cell transplantation therapy

Stem cell transplantation therapy has been shown to be a promising approach to treat neurodegenerative diseases because of the regenerative capability of stem cells that secrete neurotrophic factors and give rise to differentiated progeny. However, the efficiency and efficacy of stem cell therapy is limited by the fact that very few transplanted cells survive and home to the injured tissues, and the functional recovery often is inadequate [10, 24]. To improve the efficacy of stem cell transplantation, different strategies have been applied before transplantation, for example, hypoxia or aplin3 preconditioning, up regulating survival genes in stem cells before transplantation [12, 14, 24, 72, 100, 101]. As reviewed above, ion channels play an important role in cell proliferation, differentiation and migration, chemotropic axon guidance of growth cones, and axon outgrowth during development and regeneration after injury. Selective modulation of ion channels might provide a more effective way to grow and differentiate stem cells that are to be used for the treatment of neurodegenerative disorders or regeneration of the damaged tissues. Our observation on the increased activation of FAK by the formation with Kv2.1 K⁺ channel provides an example how the study on ion channel may reveal new mechanisms to improve cellular activities and therapeutic properties of stem cells [102–105].

TRPCs have been shown to regulate cell proliferation, differentiation and axon guidance and outgrowth during the development and after injury. Ca²⁺ transient inhibition by TRPC channel antagonists resulted in a significant reduction of proliferation of progenitor cells, however do not affect the neurite outgrowth of post-mitotic neurons that derived from human embryonic stem cells. Inhibition of TRPCs with pharmacological antagonists, for example SKF96365 may limit unwanted proliferation of transplanted progenitor cells and guide neurites towards their targets, which may help to achieve desired therapeutic effects of stem cell transplantation [67]. Modulating the activity of specific members of the TRPC family such as TRPC1, TRPC4 or TRPC5 in stem cell-derived progenitor cells may reduce the tumor formation, provide better engraftment after transplantation and provide a safe and effective cell-replacement therapy for neurodegenerative disorders.

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