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Review Article

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Molecular and cellular aspects of plasticity after neural injury

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This review focuses on our effort to address plasticity of the nervous system after neural injury. We have used different animal models to examine cellular mechanisms of plasticity underlying the pathological and repair processes. After severance of sensory input from one inner ear, topographic representations of space-centered coordinates in the brain undergo plastic changes. During vestibular compensation, tissue plasticity constitutes an important component for functional recovery of neuronal network. In Parkinsonian animals, modulation of signaling via glutamatergic synapses, neurotrophins and neurokinins contributes to the protection of basal ganglion neurons from degeneration, thereby delaying deterioration of motor functions. With the use of animal models of neural injury, we further overcome the molecular restriction at the glial scar to enhance neural regrowth and remyelination, pointing to the possibility of developing new therapeutic strategies to stimulate neural plasticity and repair in the adult nervous system.

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Modification of Space-centered Coordinates in the Brain after Unilateral Loss of Vestibular Function

Vestibular information is centrally processed for the recognition of spatial orientation and for sensory-motor coordination.[1,2] It is well documented that vestibular nuclear (VN) neurons receive otolith inputs arising from the two sides.[3-5] Immediately after unilateral vestibular neurectomy or labyrinthectomy, patients exhibit oculomotor and postural disorders as well as a corresponding change in their spatial perceptual judgments.[6,7] However, it is unknown whether central vestibular neurons receiving inputs solely from the ipsilateral or contralateral otoliths can encode spatiotemporal information during natural otolithic stimulation after unilateral loss of vestibular input from the inner ear. In normal rats, otolith-related VN neurons exhibited a spectrum of spatiotemporal properties, spanning from narrowly to broadly tuned patterns.[8-12] The response vectors of these neurons were found to point in all horizontal directions,[11] indicating that all horizontal head orientations are encoded across an ensemble of VN neurons.[13,14] In hemi-labyrinectomized (HL) preparations in which the labyrinthine input from one side was eliminated,[8] a number of deranged neural patterns were observed. Besides a significant increase in the proportion of broadly spatiotemporal-tuned neurons, there was an imbalance in the distribution of response vectors [9,15] resulting in deranged spatial coding after HL. Another finding was the emergence of unilaterally sensitive neurons that were not found in labyrinth-intact animals.[11,16] The latter neurons

showed large shifts in response vector with change in velocity,9 indicating that signals of head orientations would be erroneously transmitted by these neurons during head movements after HL. In addition, asymmetries in spontaneous discharge, response dynamics and spatial coding behaviour were evidenced between neuronal subpopulations on the two sides, [9,10,17] suggesting a segregation of otolith signals reaching the ipsilateral and contralateral VN. These physiological correlates may contribute to both biased spatial coding and maladjusted otolith reflexes accompanying vestibular compensation. We therefore suggest within the VN, gating of spatial and temporal cues arising from the bilateral labyrinths are crucial for the recognition of head orientations in the normal state.

Progress has also been made to bridge the gap between remodeling of the perineuronal matrix and re-tuning of synaptic transmission after unilateral vestibular lesion. Perineuronal nets, lattice-like extracellular structures in the matrix surrounding neurons, were found to be disorganized with severance of peripheral inputs from one labyrinth but the nets resumed following adaptation to the change.[18] It is noteworthy that degradation of perineuronal net by treatment with chondroitinase ABC reactivated cortical plasticity and promoted functional recovery of the lesioned visual system in adult animals.[19] Since the perineuronal nets appear to be restrictive to tissue plasticity,[20] our finding therefore offers a structural correlate for freeing the perineuronal environment to synaptic modulations that lead to functional recovery of VN neurons in the course of vestibular compensation. How the biophysical properties of the matrix influence the interactions with cellular receptors and consequent signaling cascades remain challenging questions for further investigations. Given that neurotrophin-mediated signaling is important for promoting survival of neuronal populations in the central nervous system [21] and for the survival of the vestibular ganglia,[22] we examined the expression of high affinity tyrosine kinase receptors TrkA-C in the VN. The vast majority of otolith-related neurons in various VN subnuclei of adult rats expressed TrkA, TrkB or TrkC receptors.[23,24] In hippocampal neurons, interaction of brain-derived neurotrophic factor (BDNF) / neurotrophin-4 with TrkB receptor altered the phosphorylation of NR125 and NR2B subunits,[26] thereby modulating the properties of N-methyl-D-asparate (NMDA) channels.[27,28] Within the VN which receives signals of head movements via glutamatergic vestibular primary afferents,[29,30] otolith-related neurons highly expressed NMDA receptors.[31,32] Co-expression of NMDA and α-amino-3-hydroxyl-5-methyl-4isoxazole-propionic acid (AMPA) receptor subunits was also observed in VN neurons,[33] implicating cross-modulation between these receptors. Pilot experiments using whole cell patch-clamp recording in VN neurons further demonstrated that changes in NMDA and AMPA receptor components are crucial for the differential demands of glutamatergic neurotransmission during the maturation of VN neurons.[34] That 90% of otolith¬ related VN neurons expressed either NR1 or NR231 and that a similar proportion expressed TrkB receptor [35] tempted us to infer that co-localization of TrkB and NR1/ NR2 receptors in most otolith-related VN neurons contribute to the survival of central vestibular neurons during vestibular compensation.

Role of Glutamatergic Synapses, Neurotrophins and Neurokinins in Neuroprotection

Glutamate is also a key neurotransmitter in the basal ganglia.[36] One of the possible causes of cell death in the substantia nigra of Parkinsonian patients is thought to be glutamate-mediated excitotoxicity and over-activity of glutamatergic pathways.[37,38] We have conducted a series of studies to investigate the contribution of glutamate neurotransmission, neurotrophins and neurokinins in protecting basal ganglia neurons of Parkinsonian animals from degeneration. Subpopulations of striatal neurons showed stage-specific combinations of NMDA subunits during postnatal development.[39,40] The change in expression patterns of NR subunits may be related to functional maturation of neurons in the neostriatum. Similar observations have been

reported for the localization and expression of AMPA receptors,[41-43] metabotropic glutamate receptors (Lam et al. 2005)[44] and γ-aminobutyric acid (GABA) receptors [45,46] in the neostriatum. We have also found that the expression of NMDA and AMPA receptor subunits in the neostriatum changed after the induction of Parkinsonism in a 6-hydroxydopamine (6-OHDA) ¬lesioned rat model of the disease.[47] Other than the use of antagonists to block glutamatergic transmission,48 we recently demonstrated that motor symptoms of Parkinson's disease in the rat model could be ameliorated after administration of an NR1 antisense oligonucleotide to the lesioned neostriatum.[13] These results thus shed new light on alternative treatments of motor problems associated with Parkinson's disease.

Several lines of evidence have shown that degeneration of dopaminergic neurons and onset of Parkinson's disease are closely related to the level of neurokinins (including substance P, neurokinin A and B) in the basal ganglia.[49-51] The biological functions of neurokinin as neurotransmitters or neuromodulators [52] are mediated by distinct G-protein coupled receptors. Neurons in the basal ganglia display distinct subclasses of neurokinin receptors, with a predominance of NK-3 receptor in the substantia nigra and NK-I receptor in the neostriatum.[53,54] Administration of NK-3 receptor agonist to mice treated with 1-methyl-4-phenyl¬ 1,2,3,6-tetrahydropyridine (MPTP) aggravated the motor symptoms of Parkinson's disease, indicating that NK-3 antagonism may improve the Parkinson's disease conditions after onset of the disease. In the ventral pallidum, cholinergic neurons expressed both receptors,[55,56] suggesting the differential roles of neurokinin receptors in the basal ganglia.

Substance P was also found to protect striatal cholinergic neurons from glutamate excitotoxicity, probably via modulating NMDA[57] and AMPA receptors.[43] In addition, the expression of substance P in striatal neurons was under the control of neurotrophic factors such as glial-derived neurotrophic factor (GDNF) and neurotrophin-4/5,[58] thus promoting the survival of dopaminergic neurons and prevention of neuronal death within the basal ganglia circuitry.[59]

Experiments have also been conducted to examine the contributory role of reactive astrocytes in the recovery of brain functions in Parkinsonism. In MPTP-treated mice, significant re-expression of nestin protein, an intermediate filament that is expressed in migrating and proliferating cells during embryogenesis but restricted to areas of regeneration in adults,[60] was found in the caudate putamen while no obvious change was detected in the globus pallidus and substantia nigra.[61,62] In the caudate putamen, the majority of nestin-immunoreactive cells displayed astrocytic morphology and expressed glial fibrillary acid protein (GFAP), a marker for astrocytic glial cells.[61] In addition, these nestin-expressing glial cells exhibited proliferative (Ki-67) and neurotrophic (BDNF) properties.[63] Taken together, these results suggest that reactive astrocytes, through their neurotrophic functions and active interaction with dopaminergic neurons or progenitors, play important roles in the protection of surviving dopamine cells, thereby delaying deterioration of dopaminergic neurons in Parkinson's disease.[64]

Neural Regeneration After Injury

Structural plasticity of neural tissue plays a key role in the remodeling and regeneration of the adult nervous system after injury. The association of extracellular matrix molecules with neural regeneration or remodeling has been increasingly acknowledged.[65-68] For example, heparan sulfate proteoglycan is considered to play a permissive role while chondroitin sulfate proteoglycan has been conferred a restrictive role. Using a nerve bridge model, we demonstrated that supplementation of soluble heparan sulfates to the regenerative environment of sciatic nerves enhanced axonal reconnection of the severed nerve with the target muscle.[69] A full recovery of the nerve conduction velocity was also evidenced in the course of 20 weeks. Upregulation of chondroitin 6-sulphotransferase-1 was demonstrated to result in

enhanced mobility of Schwann cells that guided axonal regrowth in the injured sciatic nerve.[70] Within the spinal cord of adult rats, co-localization of syndecan-3, a transmembrane heparan sulfate proteoglycan, with heparanase was revealed in neurons and oligodendrocytes,[35] providing cellular basis for further study on the role of these components in enhancing regeneration and plasticity after spinal cord injury. Another extracellular matrix component, the chondroitin sulfate proteoglycans, were found to be up-regulated in regions of reactive gliosis after spinal cord injury.[71] We hypothesized that chondroitin sulfate proteoglycans deposited at the gliotic front constitute a molecular barrier to axonal growth into the transected spinal cord. Despite success in guiding axonal growth into the cellular graft that bridges across the transected cord, regeneration across the distal graft-host interface into the host spinal cord was limited.[72,73] We exploited activity of chondroitinase ABC in vivo to resolve restriction due to chondroitin sulfate moieties at the glial scar to enhance neural regrowth and remyelination in the host cord.[74] Our findings indicate that the regrowing axons could advance through the diminished chondroitin sulfate barrier at the interface, thus facilitating axonal regeneration into the caudal host spinal cord. Also, the prospect of the therapeutic use of the Schwann cell-seeded channel as a bridge to facilitate axonal regrowth across traumatic injury in the spinal cord is advanced.

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