Department of Basic Medical Sciences

Division of Neuronal Network
神経ネットワーク分野

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Our major research interest is the molecular mechanisms of higher brain functions in mammals such as emotion, and learning and memory. We are especially focusing on the roles of functional molecules localized in synapses, for instance, neurotransmitter receptors, signal transduction molecules and adhesion molecules, in neuronal information processing. We are examining receptor functions, synaptic transmission and plasticity, and their roles in the whole animal with electrophysiological, biochemical, molecular genetic and behavioral approaches. We are also trying to elucidate fundamental aspects of psychiatrical and neurological disorders using model animals.

1. The adhesion molecule cadherin 11 is essential for acquisition of normal hearing ability through middle ear development in the mouse

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Cadherin 11 (Cdh11), a member of the cadherin adhesion molecule family, is expressed in various regions of the brain as well as the head and ear. To gain further insights into the roles of Cdh11 in the development of the ear, we performed behavioral tests using Cdh11 knockout (KO) mice. KO mice showed reduced acoustic startle responses and increased thresholds for auditory brainstem responses, indicating moderate hearing loss. The auditory bulla volume and ratio of air-filled to non-air-filled space in the middle ear cavity were reduced in KO mice, potentially causing conductive hearing loss. Furthermore, residual mesenchymal and inflammatory cells were observed in the middle ear cavity of KO mice. Cdh11 was expressed in developing mesenchymal cells just before the start of cavitation, indicating that Cdh11 may be directly involved in middle ear cavitation. Since the auditory bulla is derived from the neural crest, the regulation of neural crest-derived cells by Cdh11 may be responsible for structural development. This mutant mouse may be a promising animal model for elucidating the causes of conductive hearing loss and otitis media.

2. AMPA receptor activation-independent antidepressant actions of ketamine metabolite

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Ketamine, an N-methyl-D-aspartate receptor antagonist, exerts robust antidepressant effects in patients with treatment-resistant depression. The precise mechanisms underlying ketamine's antidepressant actions remain unclear, although previ-

ous research suggests that α-amino-3-hydroxy-5-methyl - 4 - isoxazole propionic acid receptor (AMPAR) activation plays a role. We investigated whether (S)-norketamine and (R)-norketamine, the two main metabolites of (R,S)-ketamine, also played a significant role in ketamine's antidepressant effects and whether the effects were mediated by AMPARs. Cellular mechanisms of antidepressant action of norketamine enantiomers were examined in mice. (S)-Norketamine had more potent antidepressant effects than (R)-norketamine in inflammation and chronic social defeat stress models. Furthermore, (S)-norketamine induced more beneficial effects on decreased dendritic spine density and synaptogenesis in the prefrontal cortex and hippocampus compared with (R)-norketamine. Unexpectedly, AMPAR antagonists did not block the antidepressant effects of (S)-norketamine. The electrophysiological data showed that, although (S)-norketamine inhibited N-methyl-D-aspartate receptor-mediated synaptic currents, (S)-norketamine did not enhance AMPAR-mediated neurotransmission in hippocampal neurons. Furthermore, (S)-norketamine improved reductions in brain-derived neurotrophic factor-tropomyosin receptor kinase B signaling in the prefrontal cortex of mice susceptible to chronic social defeat stress, whereas the tropomyosin receptor kinase B antagonist and a mechanistic target of rapamycin inhibitor blocked the antidepressant effects of (S)-norketamine. In contrast to (S)-ketamine, (S)-norketamine did not cause behavioral abnormalities, such as prepulse inhibition deficits, reward effects, loss of parvalbumin immunoreactivity in the medial prefrontal cortex, or baseline γ-band oscillation increase. Our data identified a novel AMPAR activation-independent mechanism underlying the antidepressant effects of (S)-norketamine. (S)-Norketamine and its prodrugs could be novel antidepressants without the detrimental side effects of (S)-ketamine.

3. Combating herpesvirus encephalitis by potentiating a TLR3-mTOR axis

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TLR3 is a sensor of double-stranded RNA that is indispensable for defense against infection with herpes simplex virus type 1 (HSV-1) in the brain. We found here that TLR3 was required for innate immune responses to HSV-1 in neurons and astrocytes. During infection with HSV-1, TLR3 recruited the metabolic checkpoint kinase complex mTORC2, which led to the induction of chemokines and trafficking of TLR3 to the cell periphery. Such trafficking enabled the activation of molecules (including mTORC1) required for the induction of type I interferons. Intracranial infection of mice with HSV-1 was exacerbated by impairment of TLR3 responses with an inhibitor of mTOR and was significantly 'rescued' by potentiation of TLR3 responses with an agonistic antibody to TLR3. These results suggest that the TLR3-mTORC2 axis might be a therapeutic target through which to combat herpes simplex encephalitis.

Publications

Kiyama, Y., Kikkawa, Y.S., Kinoshita, M., Matsumoto, Y., Kondo, K., Fujimoto, C., Iwasaki, S., Yamasoba, T. and Manabe, T. (2018). The adhesion molecule cadherin 11 is essential for acquiring normal hearing ability through middle ear development in the mouse. *Lab. Invest.* 98: 1364-1374.

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