Zebrafish as a model system for study of fear
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Recent progress has revealed that the arrangements of the major components of the brain regions involved in regulation of emotion are largely conserved throughout evolution of vertebrates. By taking advantage of this knowledge, we are using zebrafish to study the neural circuit mechanisms for regulation of emotion and behaviors.

(a) Optical imaging of neural activity of the telencephalon in emotionally motivated goal directed behavior

Recent evidence supports the view that the telencephalon has conserved basic structures and functions during evolution of the vertebrate. One exception for this conservation is that the fish telencephalon develops in a characteristically different manner from that of the other vertebrate telencephalons, i.e. eversion in fish v.s. evagination in the other vertebrates, which has put the medio-lateral arrangements of the corresponding parts of the pallium largely inverted between the teleost and the other vertebrate telencephalons. Taking advantage of this characteristic arrangements in fish brain, i.e. all parts corresponding to the hippocampus, amygdala and cortex are exposed on the dorsal surface of the telencephalon, we have been trying to carry out the simultaneous observation of the activities of these parts of the brain. Using the transgenic zebrafish expressing Inverse-Pericam in all neurons in collaboration with Dr. Miyawaki and Dr. Arata at Dr. Ito’s lab., we have recently demonstrated that a restricted part of the pallial telencephalon indeed shows distinctive activation in response to the presentation of the conditioned light stimulus after establishment of the active avoidance learning. This result has supported our expectation that, by using zebrafish as a research material, we can visualize the process by which neural ensembles encoding proper behavioral programs embedded in the cortico(pallio)-basal ganglia-thalmic loops are selected in response to the given surrounding situations. We are now examining how the brain activation pattern changes in response to the change of the rule in the conditioned learning.

(b) Functional analysis of the habenulo-interpeduncular projection in control of fear response

The habenula is a part of an evolutionarily highly conserved conduction pathway within the limbic system that connects telencephalic nuclei to the interpeduncular nucleus (IPN) of the midbrain. In mammals, the medial habenula receives inputs from the medial septum, thus collecting information on the surrounding physical environments and their salience from the hippocampus and the amygdala by way of the medial septum, and relaying such information to the IPN. In contrast, the lateral habenula receives inputs from the ventral pallidum, and collect information regarding the selected behavioral programs in response to the given individual situations. Therefore, the physical adjunction of these two habenular nuclei gives an anatomically favorable situation if the selected behavioral programs would be examined whether they are suitable for the given individual situation. We have recently elucidated that zebrafish has the equivalent structure as the mammalian habenula, i.e. the dorsal habenula of zebrafish corresponds to the medial habenula of mammals, while the ventral habenula of zebrafish corresponds to the lateral habenula of the mammals (J. Neuroscience. in revision). In addition, we already showed in zebrafish a prominent asymmetric habenulo-interpeduncular projection caused by a prominent left-right (LR) difference in the size ratio of the medial and lateral subnuclei of the dorsal habenulae, each of which specifically projects either to the ventral or dorsal IPN targets (Aizawa et al., Current Biol. 2005, Dev. Cell. 2007).

To further investigate the physiological meaning of this prominent asymmetric axonal projection pattern, we have established the transgenic zebrafish line expressing Gal4-VP16 specifically in the dorsal habenular
subnuclei. By crossing such lines with other transgenic lines carrying the tetanus toxin gene or the nitroreductase gene under control of the target site of Gal4-VP16, we have succeeded in establishing the lines in which the neural signal transmission by way of the lateral subnucleus of the dorsal habenula is selectively impaired either constitutively or conditionally. In the fear conditioning, the manipulated fish showed extremely enhanced levels of freezing response to presentation of the conditioned stimulus, very similarly as human patients suffering from PTSD (post-traumatic stress disorder). This result suggests the tract connecting the left-dominant lateral subnuclei of the dorsal habenula with the dorsal IPN may normally function to suppress excessive fear response after establishment of fear conditioning, and is especially intriguing if we take the previous report into consideration on the preferential right eye use by zebrafish when they are approaching novel objects.

Furthermore, we have recently discovered that the neurons in the dorsal IPN specifically send the descending axons along the central gray in the hindbrain, and the neurons in the ventral IPN project to the raphe (J. Neuroscience, in revision). Considering that the central gray is involved in instinctive defense behaviors such as freezing and that the raphe and its serotonin neurons are involved in more adaptive behaviors, we are now suspecting that the dorsal and ventral IPN may be involved in the alternative behavioral choice in the face of danger, such as whether to react in a panic or to cope with it in more sedate manners.
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Five Selected Publications


All Publication in English


Development (Mech. Devel.) 26, 107-118.


mediates the formation of an initial axon scaffold essential for establishment of precise glomerular map in the zebrafish olfactory system. Development, 132:1283-93.


