Neuropeptide Y mediates injury-induced adult neuroregeneration

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Abstract

Olfactory sensory neurons are easily damaged due to direct contact with environmental toxicants and continuously regenerate throughout adulthood. This means that the olfactory epithelium (OE) is a good model to study the mechanisms of injury-induced neuroprotection, neuronal apoptosis, and neurogenesis. We found that neuropeptide Y (NPY), which induces cell proliferation in the OE in vitro, is predominately expressed in non-neuronal, inositol triphosphate receptor 3 (IP3R3)+ microvillous cells. Microvillous cells send long cell process to the olfactory stem cells and become a component of the stem cell niche. We hypothesize that NPY plays a role in injury-induced adult neuroregeneration in the mouse OE. As damage to the OE releases ATP, we used ATP to mimic injury. Intranasal ATP administration significantly increased NPY protein levels and the number of NPY+ cells. ATP significantly increased NPY release as measured by ELISA. Furthermore, ATP-induced NPY release was significantly (1) blocked by IP3 receptor inhibitor 2-APB, (2) increased following uncaging of “caged IP3” and (3) impaired in IP3R3-deficient mice. These data indicate that injury stimulates the release of NPY in an IP3R3-dependent process. Next, we examined whether NPY release is involved in injury-induced neuroregeneration. ATP significantly increased progenitor cell proliferation and neuroregeneration, measured by BrdU incorporation and proliferating cell nuclear antigen expression, via activation of MAP kinase p44/42 ERK. Intranasal instillation of NPY Y1 receptor antagonist BIBP3226 following ATP treatment significantly inhibited p44/42 ERK activation and BrdU incorporation. This suggests that ATP indirectly activates p44/42 ERK in the OE via ATP-induced NPY release and subsequent activation of Y1 receptors in progenitor cells to promote proliferation and neuroregeneration. Collectively, these data indicate that injury initiates neuroregeneration via NPY up-regulation, NPY release, and Y1 receptor mediated-p44/42 ERK activation. Thus, the NPY system is a pharmacological target to promote regeneration of damaged neurons.

This is an Oral Presentation
Overall Research

Our research is focused on neurogenesis and neurotoxicology. We seek ways to prevent or ameliorate the adverse effects of toxicants on the nervous system. Overall, the adult central nervous system has a limited capacity to undergo post-injury repair, which is why nerve injury and neurodegenerative diseases can have devastating effects. However, some regions in the central nervous system, such as dentate gyrus and subventricular zone, make new neurons (undergo neurogenesis) from stem cells in adulthood. The signals or growth factors that activate a stem cell to turn into a neuron are not fully understood.

We use the olfactory epithelium in the nose as a model because olfactory sensory neurons are the only neurons in direct contact with airborne environmental pollutants, toxicants and microbes, and are easily damaged. Therefore the olfactory sensory neurons continuously regenerate throughout adulthood at a rate higher than other adult neuroregeneration regions. Therefore, the olfactory epithelium is a good model to study the mechanisms of injury-induced neuroprotection, neuronal apoptosis, and neurogenesis. Stem cells in the olfactory epithelium are similar to stem cells in the central nervous system. But olfactory stem cells are more numerous and are easy to obtain via a simple biopsy. In addition, substances such as growth factors instilled into the nose can travel directly into the brain bypassing blood brain barrier. Thus, the information we gather on growth factors and mechanisms of neuroprotection and neurogenesis in the olfactory system will also contribute to the development of therapeutics to treat damage and degenerative diseases.

In the present study, we investigated the mechanisms underlying injury-induced neuroregeneration in mouse olfactory epithelium. First, by using transgenic mouse models (knock in and knock out), we observed that neuropeptide Y, which induces cell proliferation in the OE in vitro, is predominately expressed in non-neuronal, inositol triphosphate receptor 3 (IP3R3)+ microvillous cells. These cells send long cell process to the olfactory stem cells and become a component of the stem cell niche. Second, combining in vivo study, ex vivo olfactory epithelium slice culture, and in vitro olfactory epithelium primary cell culture, we found that injury induces NPY up-regulation and IP3R3-dependent NPY release in the microvillous cells. NPY released from microvillous cells activates Y1 receptor-mediated MAP kinase p44/42 ERK in the olfactory stem cells to initiate neuroregeneration. These results will contribute to the development of therapeutics to enhance recovery and restore function in the olfactory system and to repair and regenerate the central nervous system following injury or disease.

I have not had a chance to attend the conference mainly targeted on neuropeptide Y. Attending this meeting will provide a formal introduction to other functions of the NPY system and extend my knowledge of NPY from olfaction to the other systems. By doing this, it will also inspire new ideas for my future research.

Travel Plan

1. Meeting name: The 10th International NPY-PYY-PP Meeting
2. Meeting date: June, 30 – July, 4, 2012
3. Meeting location: Montreal, Canada