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Germ cells are specialized cells that can transmit genetic materials from one generation to the next in sexual reproduction. All of the other cells of the body are somatic cells. This separation of germ and somatic cells is one of the oldest problems in developmental biology. In many animal groups, a specialized portion of egg cytoplasm, or germ plasm, is inherited by the cell lineage which gives rise to germ cells. This cell lineage is called germline. The germline progenitors eventually migrate into the gonads, where they differentiate to form eggs and sperm when the organisms are physically matured. How this developmental transition from the juvenile stage to the adult reproductive stage is precisely regulated in response to developmental and environmental cues is a longstanding question in biology.

I. The mechanism regulating developmental transition from larvae to reproductive adults

In holometabolous insects, the steroid hormone ecdysone plays a pivotal role in metamorphosis. In *Drosophila*, ecdysone is produced in the prothoracic gland (PG) and then converted into its active form, 20-hydroxyecdysone (20E), in the peripheral organs. The activities of 20E terminate larval development and growth and initiate metamorphosis. Ecdysone biosynthesis is regulated in the PG by neuropeptides, enabling modulation of the timing of 20E pulses during development. The stimulator of ecdysone biosynthesis is prothoracicotropic hormone (PTTH) and Insulin-like peptides (Ilps), which activate the production of ecdysone biosynthetic proteins. In addition to these neuropeptides, the larval–prepupal transition is modulated by environmental cues such as nutritional conditions that influence larval body size. For example, early third-instar larvae attain the body-size checkpoint required for the transit from larva to prepupa. Although the checkpoint is believed to ultimately modulate ecdysone production in the PG, its downstream effectors and signaling pathway remain elusive.

We found that monoaminergic autocrine regulation of ecdysone biosynthesis in the PG is essential for metamorphosis. PG-specific knockdown of *Octβ3R*, resulted in arrested metamorphosis due to lack of ecdysone. Knockdown of tyramine biosynthesis genes expressed in the PG caused similar defects in ecdysone production and metamorphosis. Moreover, PTTH and Ilps signaling were impaired by *Octβ3R* knockdown in the PG, and activation of these signaling pathways rescued the defect in metamorphosis. Thus, monoaminergic autocrine signaling in the PG regulates ecdysone biogenesis in a coordinated fashion upon activation by PTTH and Ilps. We propose that monoaminergic autocrine signaling acts downstream of a body-size checkpoint that allows metamorphosis to occur when nutrients are sufficiently abundant.

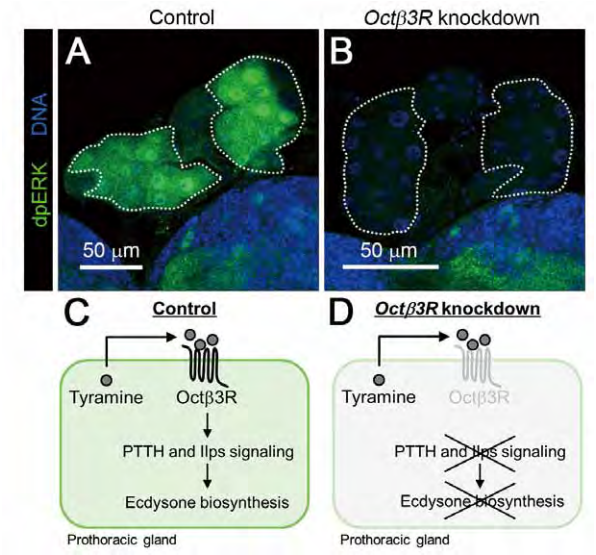

Figure 1. Tyramine-Octβ3R signaling is required for ecdysone biosynthesis.
(A and B) The PGs of control (A) and *Octβ3R* knockdown larvae (B) were labelled for the dephosphorylated form of ERK (dpERK, green) and DNA (blue). Expression of dpERK, a downstream signaling component of the PTTH pathway, was reduced in the PG of *Octβ3R* knockdown.
(C and D) Our model for the regulation of ecdysone biosynthesis. Tyramine is secreted from the PG after the attainment of body-size checkpoint. Tyramine-Octβ3R signaling activates PTTH and Ilps signaling, which leads to coordinated activation of ecdysone biosynthesis (C). In the PG of *Octβ3R* knockdown larvae, ecdysone biosynthesis is not activated due to loss of PTTH and Ilps signaling activity (D).

Publication List:

〔Original papers〕

- Mukai, M., Hira, S., Nakamura, K., Nakamura, S., Kimura, H., Sato, M., and Kobayashi, S. (2015). H3K36 trimethylation-mediated epigenetic regulation is activated by Bam and promotes germ cell differentiation during early oogenesis in Drosophila. Biology Open 4, 119-124.
- Ohhara, Y., Shimada-Niwa, Y., Niwa, R., Kayashima, Y., Hayashi, Y., Akagi, K., Ueda, H., Yamakawa-Kobayashi, K., and Kobayashi, S. (2015). Autocrine regulation of ecdysone synthesis by β3-octopamine receptor in the prothoracic gland is essential for Drosophila metamorphosis. Proc. Natl. Acad. Sci. USA 112, 1452-1457.

†: This laboratory was closed on 31 March, 2015.