<Further Development 23_07>

Understanding the Different Effects of 20E

The effects of these two 20E pulses can be extremely different. One example of this is the ecdysone-mediated changes in the larval salivary gland. The early pulse of 20E activates the *Broad* gene, which encodes a family of transcription factors through differential RNA splicing. The targets of the Broad complex proteins include genes that encode the salivary gland “glue proteins”—proteins that allow the larva to adhere to a solid surface, where it will become a pupa (Guay and Guild 1991). At this time, 20E binds to the EcR-A isoform of the ecdysone receptor (Figure 1). When complexed with Usp, EcR-A activates the transcription of early response genes *E74*, *E75*, and *Broad*. But now a different set of targets is activated. The transcription factors encoded by the early genes activate the genes encoding the apoptosis-promoting proteins Hid and Reaper, as well as blocking the expression of the *diap2* gene (which would otherwise repress apoptosis). Thus, the first 20E pulse stimulates the function of the larval salivary gland, whereas the second pulse of 20E calls for the destruction of this larval organ (Buszczak and Segraves 2000; Jiang et al. 2000).

Like the ecdysone receptor gene, the *Broad* gene can generate several different transcription factor proteins through differentially initiated and spliced messages. Moreover, the variants of the ecdysone receptor (EcR-A, EcR-B1, and EcR-B2), when partnered with Usp, may induce the synthesis of particular variants of the Broad proteins. Organs such as the larval salivary gland that are destined for death during metamorphosis express the Broad Z1 isoform; imaginal discs destined for differentiation express the Z2 isoform; and the central nervous system (which undergoes marked remodeling during metamorphosis) expresses all isoforms, with Z3 predominating (Emery et al. 1994; Crossgrove et al. 1996).

When juvenile hormone is present, however, the *Broad* gene is repressed, and metamorphosis does not take place (Riddiford 1972**;** Zhou and Riddiford 2002; Hiruma and Kaneko 2013). JH maintains the status quo of larval-to-larval molts by binding to its nuclear receptor—the Met protein[i]—and converting this receptor into a transcription factor. The JH-bound Met protein activates the *Kr-h1* gene, whose product, a repressive transcription factor, blocks the activation of the *Broad* gene (see Figure 1B; Minakuchi et al. 2008**;** Charles et al. 2011; Li et al. 2011). Thus, in the presence of JH, the *Broad* gene is not activated and metamorphosis is blocked.

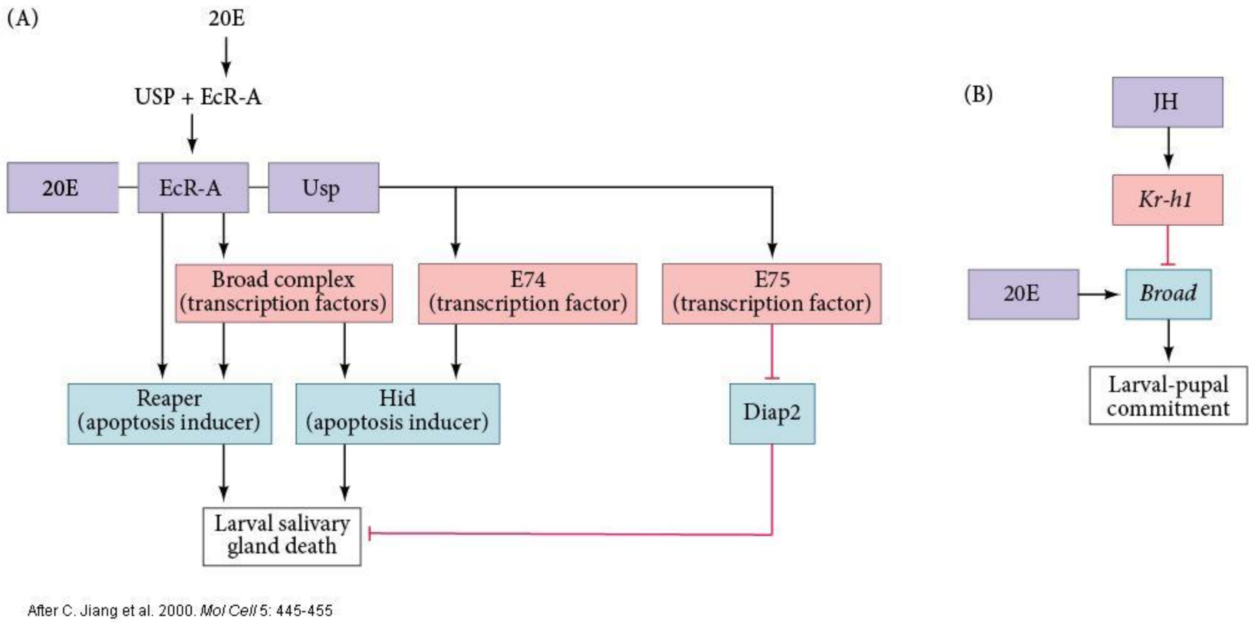

Figure 1 (A) Postulated cascade leading from ecdysone reception to death of the larval salivary gland. 20E binds to the EcR-A isoform of the ecdysone receptor. After complexing with Usp, the activated transcription factor complex stimulates transcription of the early response genes *E74A*, *E75B*, and the *Broad* complex. The products of these genes promote apoptosis in the salivary gland cells. (C) When juvenile hormone binds to its receptor, Met, it activates the *Kr-h1* gene. Kr-h1 protein is a repressive transcription factor that blocks activation of the *Broad* gene by 20E.

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[i]Not to be confused with the unrelated Met receptor in vertebrates (which is a cell membrane receptor for hepatocyte growth factor), the Met receptor for JH was identified by its ability to bind methoprene, an insecticide that works by mimicking JH, thus preventing metamorphosis (Konopova and Jindra 2007; Charles et al. 2011.