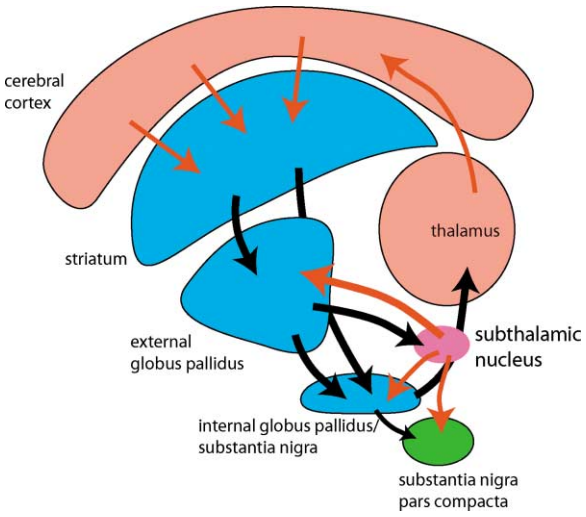

Figure 1. The Subthalamic Nucleus and Associated Brain Structures

A simplified, schematic diagram cortico-basal ganglia-thalamic loop that shows the strategic position of the subthalamic nucleus. Excitatory, glutamatergic connections are shown in red; inhibitory, GABAergic connections are shown in black.

produce symptomatic relief in PD patients? A growing number of animal and human studies argue that the problem in PD is not simply that the GP and SN discharge at an abnormally high rate. Rather, the problem is the pattern of GP and SN discharge. In PD, GP and SN neurons discharge synchronously in rhythmic bursts. DBS may work by suppressing this pattern of activity. But this must come at a cost to normal functioning of the STN and basal ganglia. An alternative therapeutic strategy could come from an identification of the factors controlling the pathological pattern. One factor is the synaptic reciprocity in the loop between the STN and GP (see Figure 1) (reviewed by Bevan et al., 2002). But are there other factors? The report by Do and Bean suggests that the distinctive Na^+ channels of STN neurons are also of potential significance, particularly to pathological rhythmic bursts of activity. If so, developing pharmacological or molecular tools that alter these properties or that enhance slow inactivation of them could lead to new treatments for PD that do not involve surgery.

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NPY and the Regulation of Behavioral Development

Neuropeptide Y is implicated in the regulation of feeding in vertebrates, but recent studies in transgenic mice are contradictory. In this issue of *Neuron*, Wu et al. show a dual role for the *Drosophila* NPY (dNPF) in the developmental regulation of larval foraging and social behaviors, demonstrating a conserved role for this peptide in complex behaviors.

It is common for an individual to change behavior as it matures—birds acquire song, honey bees switch from working in the hive to foraging, adolescent animals grow up and initiate courtship rituals, and human infants learn languages. Understanding the molecular and neural mechanisms underlying behavioral modifications during development is an important challenge for the next decade. One approach is to use simple model genetic organisms such as the nematode worm *C. elegans* and the fruit fly *D. melanogaster*, because they exhibit surprisingly complex behaviors and present us with a superb array of genetic, molecular, neurobiological, and genomic tools (Sokolowski, 2001). Moreover, genes and molecular pathways discovered using these simpler systems share remarkably similar functions with those found in vertebrates. By and large, the molecular and neural components of behaviors studied in simple organisms can reveal the building blocks used to assemble more elaborate behavior patterns. Although it is the early days, evidence is accumulating that molecules and pathways from simpler behavioral systems are retained in the assembly of more complex ones. As a result, the genes, molecular pathways, and neural circuits discovered to be regulating foraging, learning, and perhaps even social behaviors in worms and flies will be recapitulated in more complex forms of these behaviors. A fascinating example of this emerging insight is the paper by Wu et al. (2003) on neuropeptide Y (NPY) in this issue of *Neuron*.

NPY has been implicted in the regulation of a variety of behaviors in mammals, including feeding, anxiety, fear, and responsiveness to stress (Pedrazzini et al., 2003). However, results from the manipulation of NPY in transgenic mice do not always support these functions

(Thorsell and Heilig, 2002). Wu et al. studied the function of the *Drosophila* homolog of NPY, called dNPF (Brown et al., 1999), and its receptor dNPFR1 (Garczynski et al., 2002) in foraging and social behaviors exhibited by the larva. Their results reveal a striking developmentally regulated function for dNPF signaling in both behaviors.

Drosophila larvae basically do two things: forage for food and "wander" in search of a pupation site. Foraging larvae use their mouth hooks to feed on food while moving through the feeding substrate, which is typically rotting fruit (Figure 1). Once a larva surpasses a minimum size, it switches from foraging to wandering behavior. This switch is thought to involve a small surge in the steroid hormone ecdysone. Wu et al. define wandering behavior as an increase in locomotion and lack of feeding followed, in some cases, by the onset of burrowing behavior, which ends in pupation in the food substrate. Because the burrowing actually occurs only by larvae that are in groups, Wu et al. call it "social" behavior. Whether this is truly social behavior remains to be determined (Wilson, 1975).

Wu et al. predicted that because NPY is involved in food-related behavior in mammals, dNPF might play a role in the maintenance of foraging behavior in *Drosophila* larvae. They hypothesize that dNPF should be high in the foraging stage and reduced in the wandering stage larvae. By measuring the RNA expression of dNPF using in situ hybridizations to whole-mount larval CNS, they find this to be true. They also measured dNPF expression in fed and food-deprived foraging stage larvae and found similar high levels of expression in both cases, indicating that dNPF RNA levels in the CNS are not affected by the hunger state of foraging larvae. However, it would be informative to know if this is also the case in the gut and whether ecdysone plays a role in these dNPF-mediated behaviors.

Wu et al. went on to test the hypothesis that high dNPF in the CNS promotes feeding and downregulation induces the nonfeeding wandering state. They ablated the dNPFergic neurons with an attenuated diphtheria toxin (DTI) and regulated expression of the DTI using a *dnpf* promoter fragment. (Parallel experiments were also performed using *dnprf1*.) This caused a loss of the normal dNPF immunostaining pattern of four protocerebral neurons in the brain and, tellingly, the onset of premature wandering behavior in foraging aged larvae. Since cell ablation also affects all molecules in the dNPF-expressing neurons, not just dNPF, one caveat to this experiment is that it is difficult to conclude definitely that the ablation of dNPF specifically caused the change in behavior. In support of the authors model, overexpression of *dnpf* broadly in the nervous system in a pattern that included peptidergic neurons prolonged foraging in older larvae. Future experiments should overexpress wild-type *dnpf* in dNPF-expressing neurons on wild-type and *dnpf* mutant genetic backgrounds.

Another exciting aspect of this study is that the expression patterns of *dnpf* and *dnpfr1* suggest a potential circuit for *npf* signaling in the CNS. dNPF neurons extend their axons into the larval brain and along the midline of the ventral chord. Cells that express the nNPFR1 receptor are found in the dorsomedial surface of the subesophageal and abdominal ganglia. Wu et al. point out that dNPFR1 cells are in the right location to receive

Figure 1. *Drosophila* Larvae Feeding

dNPF in the segmented ventral ganglia which, in turn, may modulate the activities of the head and abdominal muscles involved in larval feeding and foraging behavior. Future morphological and neurophysiological analysis of this potential circuit and its relevance to behavior is of considerable interest.

Intriguingly, the ablation of dNPF neurons in foraging larvae only caused wandering behavior in response to solid but not liquid food. Wu et al. argue that solid, unlike liquid, food is aversive to foraging larvae and that the combination of an aversive food source and the ablation of dNPF cells caused the larvae to be less "motivated to feed." Invoking the idea of feeding motivation arises from the mammalian literature on NPY. Wu et al. attempt to address the difficult issue of analyzing motivational feeding in *Drosophila* larvae by suggesting that the rate of mouth hook movement can be used as a measure of motivation during feeding. They draw parallels between larval mouth hook movement and bar pressing in rodents. This analogy is wanting: larvae feed by shovelling food with their mouth hooks, so the movement of their mouth hooks is more similar to rodent chewing or gnawing at a food pellet. It is difficult to say if they have measured motivational feeding. An assay that measures how hard a larva might "work" to obtain food under various conditions of food deprivation, availability, and quality might better address the fascinating issue of dNPF's role in motivational feeding in *Drosophila*.

Wu et al. also propose that the normal downregulation of dNPF at wandering causes larvae to avoid food and increases the chance of group burrowing activity just prior to pupation. However, it is not clear whether wandering larvae show aversion to food or if they treat food and nonfood substrates indiscriminately or whether the presence of aversive food initiates burrowing. Their results, however are reminiscent of studies in the nematode worm *C. elegans*, where a naturally occurring genetic polymorphism in a neuropeptide Y-like receptor, *npr-1*, accounts for solitary and social foraging behavior (de Bono and Bargmann, 1998). Food-dependent aggregation in these worms is mediated by nociceptive neurons that detect pain or aversive conditions, suggesting that social foraging is a response to stress (de Bono et al., 2002). Future studies should determine if *dnpf* signaling in older *Drosophila* larvae arises through sen-

sory mechanisms that detect aversive stimuli. Wu et al. also observe that larvae congregate in groups prior to the initiation of group burrowing. They postulate that this initial congregating of larvae arises from olfactory signals. *Drosophila* mutants defective in olfaction, vision, and mechanosensation can be used to dissect the sensory cues involved in this social behavior.

What is the evolutionary significance of burrowing behavior prior to pupation? In humid conditions, pupating on the fruit can cause pupae to rot, whereas pupating off the fruit under desiccating conditions can decrease pupal survival (Sokolowski, 1985). So why burrow in groups and embed your pupae inside the food when there is an increased chance of rotting under humid conditions? Larvae that burrow in groups are more able to make holes in the solid substrate than single larvae. Embedding of pupae in the food may have arisen in response to *D. melanogaster* pupal parasitoids such as *Pachyerepoideus vindemniae* who may have difficulty parasitizing pupae that are embedded in the food substrate. If so, one might expect to find genetic variation for these behaviors in populations with and without this parasitoid; genetic variation for foraging behavior has already been reported (Osborne et al., 1997). Wu et al. have not investigated if dNPF contributes to interindividual variation in burrowing or embedding behavior.

This paper underscores the conservation of function in food-related behaviors in insects, worms, and mammals. The role of *npy* in *Drosophila* foraging differs from that of *npr-1* in *C. elegans*, whose natural genetic variation accounts for solitary or social foraging behavior. In *Drosophila*, the regulation occurs within the lifetime of the individual, whereas, in *C. elegans*, the existence of genetic variants suggests natural selection for behavioral subtypes on an evolutionary time scale. We have reported similar patterns of gene "reusage" for the *foraging* gene, a cGMP-dependent protein kinase (PKG) studied in *Drosophila* and honey bees. Akin to the *C. elegans* and *Drosophila* NPY systems, the PKG gene plays a role in natural genetic variation of behavior in the fly and the developmental regulation of behavior in the honey bee. The *for* gene in *Drosophila* accounts for naturally occurring allelic variation in rover and sitter food-related behaviors (Osborne et al., 1997). The honey bee foraging gene *Amfor* is upregulated when an individual young bee switches from working in the hive to foraging outside the hive, a job performed by older bees (Ben Shahar et al., 2002). These data enable us to postulate that the same molecules are used in different ways to find species-specific behavioral solutions to coping with variation in the environment. The question of whether PKG and NPY act in the same food-related behavior pathway in these organisms is as yet unresolved. Still, the discovery of a role for *Drosophila* NPY in group burrowing by Wu et al. lends credence to the notion that *npy* signaling is a key to social behavior in both simple and more complex organisms.

Drosophila NPY can provide an important entry point into understanding the genes, molecules, and neural circuits involved in the regulation of two developmentally regulated complex behaviors—foraging and the formation of social groupings. Rapid genetic screens for suppressors or enhancers of NPY in *Drosophila* can now be initiated that uncover novel genes of general importance to NPY signaling and food-related behaviors. Identification of gene function along with neural circuitry for complex behaviors is an undeniably important and compelling area for future investigation.

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