showed that high diapause was associated with amino-acid-changing variation in two sites in the 3′ end of exon 5: one polymorphism changed alanine to valine and the other isoleucine to lysine. The strongest association was found with the latter polymorphism [6]. It is not clear how this amino-acid polymorphism might be related to the differences in *cpo* transcript abundance between the high and low diapausing recombinant inbred lines.

While the above results firmly establish a role for *cpo* in fly diapause, some important questions remain. For example, how does the *cpo* amino acid polymorphism translate to phenotypic variation in diapause? How do *tim*, *Dp110* and *cpo* interact to affect natural variation in diapause and its associated adaptive phenotypes, such as lifespan, fecundity, lipid levels and stress resistance?

The *cpo* gene was first identified through a screen for genes expressed in sensory organ precursor cells during peripheral nervous system development: *cpo* mutant flies exhibit a variety of behavioural phenotypes, including abnormal responses to light [7]. The *cpo* gene is expressed in the peripheral and central nervous systems of embryos, larvae and adults and in the midgut, glia, salivary glands and in the ring gland which is the primary endocrine structure of *Drosophila* [15]. This expression pattern is intriguing as diapause is known to be under neuroendocrine control [2]. Further studies addressing the temporal and spatial patterning of *cpo* required for natural variation in diapause are warranted.

The coordination of metabolism and reproduction with circadian cycles is found among yeast, worms, flies and mammals [16]. Synchronization of reproduction in spring time can occur as a result of mammalian embryonic diapause [17]. In human seasonal obesity, climatic factors alter the coordination of resource use and reproduction [18,19]. Future research on the mechanisms of diapause will not only expand our understanding of the function and evolution of this fascinating overwintering strategy in insects, it will also provide us with candidate genes and pathways modulating the diverse responses of a variety of organisms to seasonal changes.

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Neuronal Homeostasis: Does Form Follow Function or Vice Versa?

Nerve cells adjust their electrical excitability and the overall strength of synaptic connections to maintain their functional identity. A recent study suggests that they may also regulate dendritic branch patterns to compensate for the variability of synaptic contacts and help ensure appropriate connectivity in the brain.

Dirk Bucher

The elaborate morphology of neuronal dendrites and the complex spatial distribution of synapses they receive are cell-type specific and determine how signals are integrated, thereby lending considerable computational power to a single neuron [1]. However, even in the case of individually identified invertebrate neurons, which can unambiguously be compared across individuals, neuron morphology is variable [2,3]. Furthermore, the number and distribution of physical synaptic contact sites throughout the dendrites are variable. Despite this variability, nerve cells have to function in a consistent manner that is appropriate for their role in circuit activity (Figure 1). How does variability arise? During development, the precise branching patterns and the placement of synapses are

established in different steps [4,5]. In a complex temporal sequence involving both activity-dependent and activity-independent mechanisms, branches are added, eliminated, increased in size or retracted. Concurrently, synaptic contacts are formed or eliminated, strengthened or weakened, and the overall size of the neuron increases.

The interplay of synaptogenesis and dendritic growth has been studied extensively, but there is no consistent picture across different model systems and developmental stages. In some cases, the arrival of synaptic inputs stimulates dendritic elaboration, while in others it stops arbor growth and stabilizes existing branches. Either way, how is the functional identity of specific cell types maintained in the face of structural dynamics and variability? A recent paper by Tripodi *et al.* [6] suggests that some forms of dendritic structural plasticity can be homeostatic in the sense that they compensate for the variability of synaptic inputs.

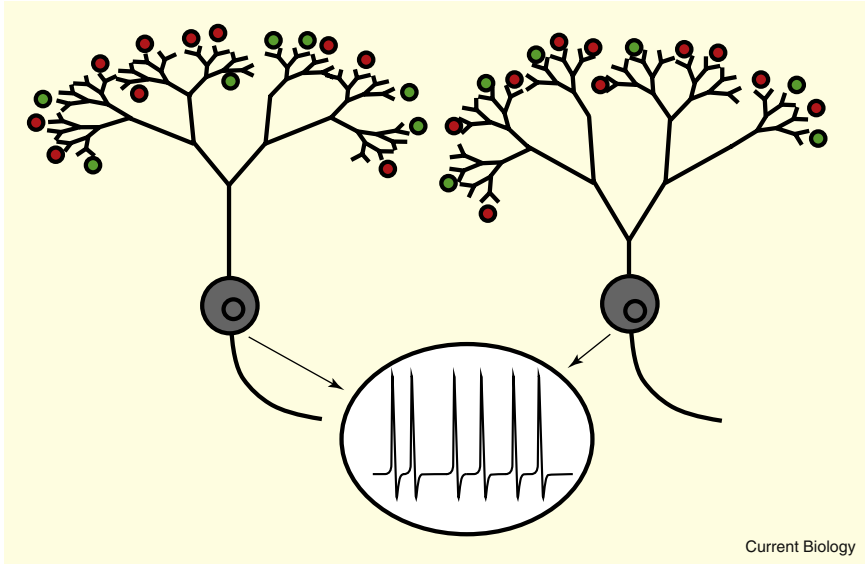

Figure 1. Neuronal homeostasis.

Nerve cells of the same type within and across individuals vary in their detailed dendritic morphology and in the number and distribution pattern of synaptic contacts that they receive from other neurons. Despite this variability, their physiological activity and functional identity within the circuit has to be consistent.

Homeostatic mechanisms balance plasticity and developmental changes in order to keep neuronal activity within functional boundaries [7,8]. Even though the detailed cellular mechanisms are elusive, the basic idea is that a target average electrical activity is as much part of neuronal identity as is its transmitter phenotype. In consequence, the abundance of different types of ion channels and the relative strengths of inhibitory and excitatory synaptic inputs can only change in a balanced manner that ensures stable overall electrical activity.

Neuronal homeostasis is conceptually intertwined with the observation that virtually all of the components that determine a neuron's function and identity to some degree vary quantitatively across individuals [9]. This variability is seen in the expression levels of receptors and ion channels, in the strength and distribution of synaptic contacts, and in the detailed dendritic morphology of neurons. Variability arises from different biological processes. Genetic differences, epigenetic factors and plasticity give rise to component variability, which is the *reason* compensatory mechanisms are needed in the first place. Conversely, homeostatic mechanisms themselves *result* in variability because there may be different solutions to the same problem — quantitatively different combinations of subcellular components may be found that give rise to consistent functional properties. Not surprisingly, it is not always easy to tell if some variable cellular property is the cause of homeostatic regulation or part of the regulatory mechanism in action.

Dendritic morphology is a good example of this predicament. Structural variability could be the consequence of developmental processes and may therefore need to be compensated by homeostatic changes in excitability and synaptic function. Alternatively, it could be the result of structural plasticity that itself compensates for variability of synaptic inputs. Tripodi *et al*. [6] argue the latter. They studied a motor neuron during *Drosophila* embryonic development. This choice came with a number of distinct experimental advantages. First of all, this motor neuron is an identified individual and can be unambiguously compared across individuals. Second, its dendritic arbors can be visualized in conjunction with all presynaptic contacts in transgenic flies. And finally, genetic manipulations allow studying the role of presynaptic contacts and activity in establishing dendritic morphology.

The findings of Tripodi *et al*. [6] are summarized schematically in Figure 2. There appear to be two sequential effects of forming a synaptic contact. Synaptic contacts act as a local stop-growing signal for the contacted branch. This process is activity-independent, as it is not affected by altered presynaptic activity. However, synaptic contacts also stop elongation in adjacent sister branches and this process does depend on synaptic activity: it is absent when synapses are formed but release no transmitter. The activity-dependent effect appears to be mediated by protein kinase A (PKA), as overexpressing constitutively active PKA rescues the effect of blocking transmitter release, and expression of a PKA inhibitor induces dendritic overgrowth. Consistent with these findings, synaptic overgrowth leads to reduced dendritic complexity and the absence of synapse formation leads to dendritic overgrowth.

These mechanisms have important implications. Forming a synaptic contact would very locally stabilize the branching pattern, whereas branches that receive no inputs will continue to parse the neuropil by elongating and branching. This can be viewed as a compensatory mechanism for variability in spatial synaptic input