

receptor superfamily, which act in a relatively straightforward manner as transcription factors, as well as proteins not known to act in intracellular signalling pathways, such as the chloride channel CFTR and the enzyme nitric oxide synthase (Mayer and Bukau 1999). Furthermore, one of the kinases whose activity shows sensitivity to Hsp90 is the WEE1 protein, a regulator of cell division (Aligue *et al* 1994). Thus there is already evidence that signalling in processes which are not, strictly speaking, concerned with development, can be Hsp90-dependent. Hsp90 could, therefore, through its buffering action under “normal” conditions, mask genetic variation in such pathways as well. Though altered traits in features such as degradative and biosynthetic capacities may appear less dramatic than the morphological variations seen with decreased Hsp90 activity, the evolutionary significance of a “capacitor” for genetic variation affecting metabolic properties would be no less.

The central importance of the Rutherford and Lindquist finding is its implication for evolution. By masking genetic variation that would not be neutral when unmasked, and by making such variation visible to natural selection under stress conditions, Hsp90 could provide a mechanism for “storing” genetic variation. Environmental stress would make this variation available precisely under conditions in which selection has scope to act.

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Neural complexity underlying simple behaviour

A central problem in neurobiology has to do with how patterns of electrical activity convey meaningful information. That neurons and neuronal circuits of varying complexity determine behaviour is no longer in doubt. But identifying neural “networks” that control specific behaviour and the rules that these networks use to initiate and modulate appropriate responses remain difficult questions. Simple invertebrates exhibit a range of well studied behaviours and in many instances, all or most of the participating neurons have been identified. The knowledge gained from such studies can be applied to higher animals, including primates. We describe here some recent studies in invertebrate model systems that demonstrate the utility of the approach.

Spatial coding using neuronal firing rates (“Where is the neuron that fires best”) has been well studied in several areas of the brain such as the visuo-motor system and the somatosensory system.

However, temporal coding (“When does the neuron fire after the onset of the stimulus”) and its usefulness to the brain has been a matter of debate. A recent set of experiments in the olfactory system of the locust point to neural oscillations as possible reference frames in which temporal coding may occur (Stopfer *et al* 1997, reviewed by Singer 1999). An odour is represented in the brain by a unique firing pattern of olfactory neurons. Specificity in coding is thus achieved by allowing only a subset of neurons to respond to a given odour. Laurent and co-workers (Singer 1997 and references therein) found that neurons in the antennal lobe of the locust, *Schistocerca americana*, engage in highly synchronized oscillatory activity (around 40 Hz) when stimulated with odours. Such neural oscillations have been implicated as a kind of temporal coding for odour representation. Only certain spikes produced by a neuron in a specific time window (depending on the odour and the neuron) are found to become phase-locked to the field oscillations while the remainder are randomly distributed. If one takes into account only the rate code, a neuron may seem to respond to two different odours with the same firing rate across a broad window. However one odour may cause it to fire preferentially in a particular cycle while the other odour elicits the same response from the same neuron in another cycle of oscillations, and thus a clear temporal code emerges. Information about the odour is contained in the combination of spikes (action potentials) that are precisely synchronized with the oscillations. As shown above, this information cannot be retrieved by considering only changes in the average firing rate across a broad time window. In an experiment with honeybees, the oscillatory firing was desynchronized using picrotoxin – an inhibitor of GABAergic neurons, which are important for these oscillations. Desynchronizations clearly impaired the ability of the honeybee to distinguish between related (but not between un-related) odours as measured by behavioural tests (Stopfer *et al* 1997). The possible existence of a temporal neural code is behaviourally significant as it drastically increases the number of stimuli that a group of neurons can encode. Such a temporal code, operating in conjunction with a rate code, can also confer a greater degree of reliability on the representation of the stimulus upon which decisions will be based.

Can single neurons be shown to perform computations that may govern behaviour? Two sets of experiments using the locust and the leech indicate how firing rates could be used to perform the necessary mathematical operations. Intracellular recordings on two identified locust visual neurons – the lobula giant motion detector (LGMD) and its post-synaptic target, the descending contralateral motion detector (DCMD), have investigated the biophysical implementation of a multiplication operation (Gabbiani *et al* 1999). Objects approaching on a collision course with the animal vigorously excite the LGMD. The response of both the LGMD and the DCMD was found to be correlated with the visual angle subtended by the object on the locust’s retina. This angle represents the size of the object as well as its distance from the eye and is referred to as the “angular size”. The response was found to begin early during the approach of the object before it reached 10° in visual angle. The firing rate gradually increased as if the neurons were tracking the approaching object. The peak firing rate was achieved after the object had reached an angular size of 24° on the locust’s retina. The critical parameters on which the neuron’s firing rate was seen to depend were the angular size, and the angular velocity of the approaching object. Since the LGMD receives inputs from both size- and motion-sensitive neurons, the authors propose that a multiplication operation may be implemented by LGMD in order to compute its firing rate. DCMD, the post-synaptic target of LGMD, projects to thoracic motor centers involved in generation of jump and flight-manuevers that could lead to collision avoidance behaviour.

Yet another system that has been used profitably to understand the neuronal circuitry that governs behaviour is the medicinal leech, *Hirudo medicinalis*. The leech has a number of reflexes that can be studied. These include, among others, the swimming reflex and the bending reflex (Lewis and Kristan 1998). By means of intracellular recordings, it has been ascertained that the four P cells in one segment of the leech’s body control the bending reflex; they are thought to sense the location of the stimulus and generate an appropriate response. Furthermore, there are 17 interneurons that are driven by the P cells. These interneurons have specific tuning properties, in that they stimulate downstream motor neurons maximally in a particular direction. The final outcome is to define what is called a population code, where the responses of a number of participating neurons are integrated and processed before an output is generated. It is important to appreciate that this method of computing is different from one in

which the output depends directly on the cell that fires maximally (winner-take-all). The leech affords a tractable system where key questions regarding population coding can be successfully addressed.

A related but more complex question is whether "higher" functions like learning and memory can be attributed to specific patterns of neural activity. Investigators over the past few years have studied the marine slug *Aplysia californica* in sufficient detail to be able to assign a host of well-defined behaviours to this animal. The slug's feeding response has been minutely documented in terms of actual movements of the feeding organs, the odontophore and the radula. The pattern of electrical activity in the neurons that either sense the presence of food, initiate the feeding response, or modify it has also been identified. Monitoring concomitant activity in specific neurons has made it possible to identify firing patterns that characterize either the feeding or rejection response.

The strength of such approaches using invertebrate systems lies in the fact that simple behaviours and their cause can be studied in their entirety. The years to come are likely to witness an amalgamation of theories from research in invertebrate and vertebrate systems. A tenable explanation of information processing by the brain is likely to emerge from this.

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