lead to the activation of OMA1 protease activity towards OPA1? Given previous work from the Langer lab, one model to potentially explain the results of Ehses *et al.* [6] would invoke the involvement of inner membrane lipid microdomains [14]. Prohibitins are inner membrane proteins thought to possess chaperone-like activity. These proteins are found in very large, megadalton complexes thought to function in the initiation of lipid microdomains, favouring the local assembly of functional platforms [15]. These functional platforms, which are enriched with prohibitin-binding partners, such as the m-AAA proteases, may sequester OMA1 to ensure its rapid cleavage and control the access of OMA1 to its substrates. Indeed, the bacterial homologues of OMA1 are highly catalytically active [16], suggesting that OMA1 must be kept under tight, yet reversible, control. It is then conceivable that the loss of the m-AAA proteases may disrupt these platforms, thereby allowing OMA1 to become available to process OPA1 (Figure 1B). This would couple inner membrane disorganization with the inhibition of mitochondrial fusion, resulting in the elimination of the fragmented, disorganized organelle.

Finally, the role of OMA1 in the regulated cleavage of OPA1 is an evolutionary twist on the simpler system in yeast for the cleavage of the OPA1 homologue Mgm1. In yeast, the rhomboid protease Rbd1/Pcp1 cleaves Mgm1 under conditions of high energy [17]. Under low ATP conditions, Mgm1 cannot be pulled across the import channel by the matrix chaperones and instead its translocation is arrested at the first hydrophobic domain, resulting in the accumulation of the long, uncleaved forms of Mgm1, thereby inactivating fusion. Rather than altering the topology of OPA1, it appears that the mammalian mitochondria survey their health through the altered topology and activity of the OMA1 protease. The integration of OMA1 into OPA1 cleavage appears to be missing in *Drosophila melanogaster* or *Caenorhabditis elegans*, suggesting that these organisms may regulate OPA1 processing in a manner homologous to yeast. Indeed, work in flies has shown a role for the rhomboid protease Rhomboid-7 in OPA1 cleavage [18]. It will be important in future work to uncover the functional implications for these different mechanistic pathways that regulate OPA1/Mgm1 cleavage.

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Behavioral Neurobiology: Leech Lust in the Lab

Animals typically will not exhibit reproductive behaviors during invasive experimental manipulations. The demonstration of courtship-related impulse activity in isolated leech ganglia promises new opportunities to elucidate the neural basis of mating.

Kevin M. Crisp

Charles Darwin suggested that one sign of the intelligence of earthworms is their apparent obliviousness to their surroundings during copulation. “Their sexual passion,” he wrote, “is strong enough to over come for a time their dread of light”, which they avoid instinctively at other times [1]. This single-minded focus during mating is not characteristic of most animals. Stereotypic courtship and mating behaviors are rarely elicited from

animals under conditions of restraint, partial dissection or other invasive laboratory techniques that are classically required to elucidate a mechanistic understanding of behavior. This is a great pity for the field of neuroethology, especially given the central importance of reproductive behaviors to a species' success. In this issue of *Current Biology*, Wagenaar *et al.* [2] demonstrate that leech ganglia can be impelled to produce mating-related motor neuron activity *in vitro* — 'fictive' mating — by treatment with exogenously applied reproductive hormones. This exciting discovery suggests a new model system for research into the neural substrates of hormone-activated reproductive behavior.

Annelids have long been appreciated as model systems for studies of the neural mechanisms underlying behavior due to, as prior authors have put it, "their availability, simplicity, phylogenetic position, learning capacity and tolerance of mutilation" [3]. The neurons and neural circuitry underlying several non-reproductive behaviors have been described to an unprecedented level of detail in the medicinal leeches, such as *Hirudo medicinalis* (Linnaeus, 1758). The leech has a relatively simple nervous system containing large, easily visualized neurons that can be uniquely identified from one individual to the next by their location in the nervous system, morphology, histochemistry, electrical properties and synaptic connections. Because these neurons are identifiable and amenable to modern electrophysiological recording techniques, the leech is exemplary even among annelids as a system in which behavior can be studied using preparations as reduced as single ion channel recordings or as complex as partially-dissected (semi-intact), behaving animals. In this way, the control of swimming, heart beat and simple forms of learning have been detailed in terms of identified cells, synapses and circuits [4].

Until recently, little was known about the neural mechanisms underlying reproductive behaviors in leeches. Breeding leeches in a colony proves challenging as leeches are especially easy to dissuade from mating by even the most subtle changes in environmental conditions. Thus, inducing reproductive behaviors under laboratory conditions that afford modern electrophysiological recording techniques has not previously been possible. The medicinal leeches are hermaphrodites that fertilize internally, requiring precise alignment of the male and female gonopores, which are on the ventral surface of adjacent segments. As leeches ambulate upon a substrate by crawling with their ventral surface down, such an alignment does not arise accidentally. Pre-copulatory behavior begins with a phase of partner exploration with the head and mouth parts, followed by a period of slow, rhythmic twisting movements that align the partners and permit copulation. Reproductive behavior terminates with a rhythmic thrusting and retracting of the anterior end during cocoon deposition.

Only relatively minor elements have been described within this complex behavioral sequence. For example, two pairs of motor neurons in sex ganglion M6 (the sixth mid-body ganglion) have been identified that, upon stimulation, elicit eversion of the normally internal penis [5]. Some nerve fibers leaving the sex ganglia (M5 and M6) contain leech excitatory peptide, bath application of which causes rhythmic contractions and increased tonus in isolated penile tissue [6]. Interestingly, during development, contact of growing axons with the male genitalia has been observed to trigger a second wave of central neurogenesis resulting in the birth of hundreds of peptide-expressing neurons in the sex ganglia [7–10]. These new neurons, suspected to play a role in reproductive behavior, express (among other things) an oxytocin-like peptide [11]. Members of the arginine-vasopressin/oxytocin superfamily of peptide hormones are highly conserved across the animal kingdom with respect to their involvement in reproductive behaviors [12,13]. Annetocin, for example, is an annelid-specific oxytocin-like peptide that induces egg laying in earthworms [14], and injections of oxytocin-like peptides cause egg-laying in the leech *Whitmania pigra* [15]. Interestingly, the leech *Theromyzon tessulaton* expresses an arginine-vasopressin-related receptor that is up-regulated after sexual maturation and down-regulated after egg-laying [16].

In their new study, Wagenaar *et al.* [2] elegantly demonstrated that injecting leeches with arginine-vasopressin/oxytocin-like peptides, especially conopressin G and the leech-specific hirudotocin, releases rhythmic movements that strongly resemble the stereotyped sequence of mating behaviors [17,18] normally only observed under ideal conditions in a breeding colony. Conopressin, for example, induced a sequence of rhythmic behaviors in isolated leeches that included movements resembling partner exploration and cocoon deposition ten and 50 minutes after injection, respectively. Through a series of experiments on increasingly reduced preparations, Wagenaar *et al.* [2] were able to demonstrate that bath-application of micromolar conopressin could elicit the neural correlate of partner exploration (fictive courtship) from isolated chains of just three ganglia (M4–M6). Interestingly, the resulting fictive motor activity is so slow in periodicity that it borders on episodic, with a cycle period of approximately five minutes. This places the rhythmic motor pattern elicited among the slowest behaviors in the animal kingdom, excluding circadian and annual activity patterns.

Because of its accessibility to experimental manipulation, the leech nervous system now stands as a promising model for studies of the neural circuits underlying hormone-triggered reproductive behaviors, such as courtship. Voltage-sensitive dyes, combined with intracellular electrophysiological recordings and staining of individual cells by intracellular injection of dyes, have been used with great success to identify neurons involved in the generation of leech behaviors [19]. Molecular-based approaches, such as RNA interference, are under development as tools in the leech to further elucidate the cellular and molecular basis of behavior [20]. In short, the stage is now set for experiments to determine the neural basis by which an evolutionarily-conserved hormone activates rhythmic behaviors critical for reproductive success in the leech.

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Vertebrate Vision: TRP Channels in the Spotlight

The recent discovery of the critical role of TRPM1 in retinal function in vertebrates has come as a surprise and has already provided important insights into a common cause of blindness.

Christophe Ribelayga

A fundamental feature of visual processing in vertebrates is the segregation of visual signals into ON and OFF channels that detect increases and decreases in light intensity, respectively [1]. This step originates at the first retinal synapse between photoreceptors and bipolar cells. Photoreceptors hyperpolarize in response to light and reduce the rate of glutamate release, which in turn causes depolarization of ON bipolar cells and hyperpolarization of OFF bipolar cells. The polarity of the light responses of bipolar cells is determined by the subtype of glutamate receptor expressed on their dendrites: ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)/kainate (KA) receptor channels on OFF bipolar cells and metabotropic glutamate receptor 6 (mGluR6) on ON bipolar cells [1,2] (Figure 1). The basic components of the signaling cascades in ON and OFF bipolar cells have been known for some time [1,2], but the molecular identity of the mGluR6-gated cation channel that produces the downstream depolarization in ON bipolar cells has been the subject of debate for about 20 years [2]. Most of the early claims were that this channel was a cyclic guanosine monophosphate (cGMP)-gated channel, similar to the one that generated the light response in photoreceptors [1,2]. This possibility was attractive because it suggested analogous transduction mechanisms for light in photoreceptors and glutamate in ON bipolar cells. However, it gradually became clear that cGMP had only a modulatory role in the mGluR6 transduction cascade and did not directly gate the cation channel [2], leaving the molecular nature of this channel an open question. Several independent studies now provide strong evidence that this channel is the type 1 melastatin-related transient receptor potential (TRP) channel TRPM1 [3–8]. This major breakthrough highlights the importance of TRP channels in vertebrate vision and makes an interesting story in the light of the serendipitous manner in which their role came to be discovered.

The first hint at the molecular identity of the channel came unexpectedly from studies on the genetic basis of coat color in the Appaloosa horse [9,10]. The Appaloosa coat spotting pattern in horses is caused by a single incomplete dominant gene (*LP*-for *Leopard complex*) [9]. Interestingly, Appaloosa horses homozygous for *LP* (*LP*/*LP*) have congenital stationary night blindness (CSNB) [9,10], a non-progressive scotopic, i.e. dark-adapted, visual deficit also found in humans [11]. CSNB is diagnosed by an abnormal scotopic electroretinogram (ERG): the a-wave (initial negative deflection), which reflects the light-induced reduction in dark current in photoreceptors, is normal but the b-wave (positive deflection), which mostly reflects electrical responses of ON bipolar cells, is absent, indicative of normal photoreceptor function but impaired ON bipolar cell function [9–11]. Genomic mapping of the *LP* locus identified a small region on chromosome ECA1 composed of five genes, of which one — *TRPM1* — was expressed at much lower levels in