Exciting guts with GABA

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A new study in this issue demonstrates that two GABAergic motor neurons in *C. elegans* are excitatory at target muscles because GABA activates a ligand-gated cation conductance, which is structurally similar to several other ligand-gated channels.

In this issue, Beg and Jorgensen[1] provide the first direct evidence for the existence of GABA-activated cation conductances that underlie excitatory actions of GABA in *C. elegans*. This finding will surprise many vertebrate neuroscientists who commonly assume that all GABA actions in the adult nervous system are inhibitory. It will surely please, but not necessarily surprise, invertebrate pharmacologists, who know of other reports of GABA-mediated excitation[2–5], and who know that in molluscs and arthropods many neurotransmitters activate several different kinds of ligand-gated channels, including both anion and cation conductances[6–8]. The Beg and Jorgensen[1] study reminds us once again that the sign of action of a neurotransmitter is not determined by its identity, but by the nature of the receptor that it activates.

There are 26 GABA-containing neurons in *C. elegans* [9,10], including the AVL and DVB neurons, which excite the two enteric muscles that control the final step of defecation. The early work raised the question of whether these GABAergic neurons contain another excitatory neurotransmitter, or whether GABA itself is responsible for the excitatory actions of the neurons[9,10]. Now, Beg and Jorgensen[1] answer this question, through a combination of genetic, anatomical and physiological experiments.

The authors exploited a mutant called *exp-1* that lacks enteric muscle contraction[11] but shows no other obvious behavioral deficits. Interestingly, the protein encoded by *exp-1* is found at the neuromuscular junctions on the anal depressor and intestinal muscles, which are innervated and excited by the AVL and DVB neurons. In a series of electrophysiological experiments, the authors show that *exp-1* codes for a novel GABA-activated cation conductance[1]. When EXP-1 is expressed in *Xenopus* oocytes and GABA is applied, a large inward current with a reversal potential near 0 mV is evoked. The reversal potential is affected by alterations in both the Na^+ and K^+ external concentrations, but not by manipulations of the external Cl^- concentration. These data suggest that GABA released from the AVL and DVB neurons is the excitatory neurotransmitter mediating depolarization of the anal depressor and intestinal muscles.

What does this new GABA-activated receptor look like? Beg and Jorgensen[1] cloned and sequenced the *exp-1* gene by standard methods, and then compared the sequence with those of other ligand-gated channels, including the *C. elegans* GABA-gated Cl^- channel gene, *unc-49*, isolated a few years ago[12]. Functional GABA receptors in vertebrates are thought to require residues found on both α and β subunits to form the GABA binding site. EXP-1 contains the GABA-interacting residues found in both α and β subunits in vertebrates. The authors suggest that EXP-1 could act as a homomeric receptor because a GABA-binding region could be formed at the interfaces between EXP-1 subunits. In contrast, it is thought that UNC-49B and UNC-49C subunits co-assemble to form the functional GABA receptor[12].

What determines the nature of the permeant ions through the EXP-1 channel? There is strong homology between the second transmembrane (M2) domain of the EXP-1 receptor and that of the vertebrate cationic nicotinic α7 acetylcholine (ACh) receptor, but little homology with the anionic GABA and glycine receptors. Previous work with the glycine receptor indicates that mutating only three amino acids could convert an anionic channel to a cationic channel[13]. Similarly, Beg and Jorgensen[1] suggest that the identity of three amino acid residues is crucial for making EXP-1 a cationic conductance.

The molecular identification of EXP-1 in *C. elegans* puts on firm footing several previous reports of the existence of depolarizing, cationic responses to GABA in other invertebrates, including arthropods and molluscs[3–5]. Therefore, many invertebrate species may express an EXP-1 like GABA receptor in addition to conventional Cl^- channels (**Fig. 1**). This indicates that researchers using other invertebrate species should avoid assuming that the presence of GABA-containing neurons implies inhibitory function.

What about vertebrates? Early in neuronal development, GABA is often excitatory because in many neurons the Cl^- equilibrium potential is very depolarized. Therefore, activation of conventional $GABA_A$ receptors results in large depolarizations that can bring the neuron to its firing threshold[14] (**Fig. 1**). Later in development, the Cl^- equilibrium potential drops closer to the resting potential. GABA acting at $GABA_A$ receptors then takes on its well-

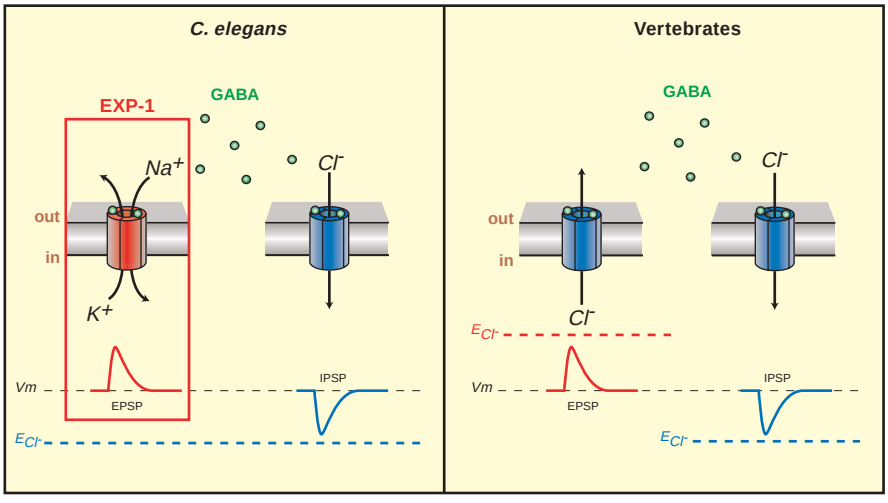

Figure 1 Mechanisms underlying the excitatory and inhibitory actions of GABA in *C. elegans* and in vertebrates. E_{Cl^-}, Cl^- equilibrium potential; EPSP, excitatory postsynaptic potential; IPSP, inhibitory postsynaptic potential; V_m, membrane voltage.

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known inhibitory action. Has a developmental regulation of the chloride equilibrium potential replaced some functions that could have been achieved with EXP-1?

GABA is not the first neurotransmitter known to gate both cation and Cl^- channels in invertebrates. Acetylcholine and glutamate activate both cation and Cl^- conductances in molluscs and arthropods[6–8], whereas in vertebrates these substances are thought to gate cation conductances exclusively. This raises the question of whether ACh- and glutamate-gated Cl^- channels and EXP-1 channels have disappeared during evolution. Perhaps hidden in the vertebrate genome are genes coding for molecules that are 'left over' from invertebrate species that may function only early in development, or in some restricted physiological settings until now relatively little studied by electrophysiologists. (For example, who knows what mysteries await us in the vertebrate enteric nervous system!) Resolving this question will require much more complete sequence information in both vertebrate and invertebrate species before the phylogenetic relationships among these channel genes become completely clear.

In addition to adding to our knowledge of the diversity of ion channel genes, this body of work on *C. elegans* achieves one of the major goals of neuroscience: to explain some of the mysteries of behavior in terms of their underlying cellular, circuit and molecular mechanisms. Beg and Jorgensen[1] started out trying to understand an apparent anatomical and physiological anomaly, and this ultimately led to the gene encoding a new GABA receptor. We look forward to the new insights into how nervous systems function that should result from the isolation and study of EXP-1 homologs in other species, perhaps both invertebrate and vertebrate.

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The acquisitive auditory cortex

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The auditory cortex, once thought to be a passive detector, is now caught in the act of reshaping the frequency sensitivity of its neurons to intercept target sounds that are significant for a behavioral task, suggesting tuning properties can change 'on-line'.

Early in the history of cortical neuroscience, the sensory cortex was regarded as a static field of neurons, each lying in wait for its particular 'adequate stimulus'. The only role of such a cortex seemed to be to pass the 'sensory' information upstairs to higher 'association' areas where the real action (perception? cognition?) took place. In the auditory system, for instance, the primary auditory cortex in anesthetized animals showed nicely ordered tonotopic maps that slavishly preserved the frequency map that is established in the cochlea[1]. Any deviation from a uniform representation of the audible frequency range could only be seen as a distortion of the sensory world.

Nowadays, those simplistic views of a static cortex are no longer tenable. A growing body of evidence indicates that the sensory cortex is dynamic, constantly reorganizing in response to experience and to the demands of sensory tasks so as to aggressively apprehend relevant stimuli. In the auditory cortex, regions of tonotopic maps expand to 'fill in' areas deprived of input by cochlear lesions[2]. When sound frequencies are paired with reward in an auditory task, the cortical representations of those frequencies expand[3]. Pairing a tone with electrical stimulation of the nucleus basalis also results in tonotopic map plasticity[4], as does intracortical microstimulation[5]. In this issue, Fritz and colleagues provide a compelling new demonstration of auditory cortical reorganization[6].

The authors recorded from neurons in the primary auditory cortex of ferrets while the animals performed an auditory discrimination task. The results of the study are novel in several regards: reshaping of neuronal frequency tuning could be observed essentially 'on-line' during performance of the task; the changes resulted from performance of a normal listening task rather than from electrical stimulation or pharmacological intervention; the changes were rapid (on the order of minutes); and details of both facilitation and suppression of neural sensitivity were measurable. One receives an impression of the auditory cortex actively reaching out, optimizing itself to grasp particular target frequencies.

In the experimental protocol, ferrets licked a water spout while they listened to repeated broadband reference sounds. The ferrets were trained to cease licking whenever they heard the sound change to a pure-tone target sound. The responses of auditory cortical neurons were recorded with microelectrodes during this behavioral task. Unbeknownst to the ferrets, it was the reference sounds that were of most interest to the investigators. The reference sounds were specially designed to probe efficiently the spectro-temporal response fields (STRF) of cortical neurons. The STRF is a far cry from a traditional frequency tuning curve in that it reveals the multiple frequency components that facilitate or suppress the response of a particular neuron, and it shows the optimal timing among such frequency components.

In the 'passive' condition before presentation of a particular target, the STRF of most neurons showed a single facilitatory frequency band and multiple suppressive bands. Fritz and colleagues then introduced target tones at frequencies selected with reference to a neuron's STRF. About two-thirds of neurons showed appreciable reshaping of their STRFs after a particular frequency was paired with reinforcement. Most often the changes

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