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The Mauthner Cell Half a Century Later: A Neurobiological Model for Decision-Making?

Review

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The Mauthner (M) cell is a critical element in a vital escape "reflex" triggered by abrupt or threatening events. Its properties at the molecular and synaptic levels, their various forms of plasticity, and the design of its networks, are all well adapted for this survival function. They guarantee that this behavior is appropriately unilateral, variable, and unpredictable. The M cell sets the behavioral threshold, and, acting in concert with other elements of the brainstem escape network, determines when, where, and how the escape is executed.

The Mauthner (M) cell is a critical element in a vital escape "reflex" that can be triggered by abrupt or threatening events, and this neuron determines whether or not there will be a response.

The modern era of M cell studies began about 50 years ago. The initial tone was set on electrophysiological (Furshpan and Furukawa, 1962) and behavioral (Wilson, 1959) grounds. Since then, studies of this neuron and its networks have often opened new directions for work in the more popular model systems of today. This privileged role derives from its morphological and electrophysiological identifiability in fish and amphibia, particularly teleosts, and from the fact that most of this research has been carried out with in vivo preparations.

The many investigations dealing with this complex system made it possible to gradually reconstruct the wiring diagram of the underlying neuronal networks (Figure 1) and to appreciate their functional properties, including their remarkable plasticity and adaptability to a continuously varying environment. Thus, even though a large number of studies were concerned with basic aspects of synaptic transmission and excitability, they now converge on higher-order issues related to the mechanisms and information processing, or decision-making operations involved in the choice of a behavior and its subsequent execution.

Brief Historical Reminder

Several structural features made the M cell ideal for morphological studies (Cajal, 1908; Bodian, 1937; see Zottoli, 1978). These include its large size, limited number (two per individual), and a stereotyped gross morphology with two major dendrites, a large crossed axon that descends in the spinal cord, and an initial segment surrounded by a particularly dense neuropil called the axon cap. Authoritative descriptions of synaptic structure were obtained at light and electron microscopic levels, including the defining features of mixed electrical and chemical excitatory synapses and of various types of inhibitory terminals and the soma-dendritic distribution of their endings (Nakajima, 1974). The M cell has also been a privileged model for developmental investigations (see Kimmel and Model, 1978). Particular attention was paid to factors and cues influencing cellular determination (Detwiler, 1933; Stefanelli, 1951), guidance and orientation (Oppenheimer, 1942; Swisher and Hibbard, 1967), and neuronal differentiation (Leghissa, 1941). For some of these experiments, prospective hindbrain regions were transplanted in the belly (Stefanelli, 1951) or midbrain (Model, 1978; Swisher and Hibbard, 1967) of several embryonic species, thus serving as some of the earliest examples of grafts in the nervous system.

Synaptic Functions

Study of the M cell system has contributed to fundamental descriptions of the primary forms of communication between neurons that are conserved throughout metazoan phylogeny, particularly the basic properties of electrical and chemical interactions. Its accessibility for a wide range of experimental approaches, including simultaneous recordings from the presynaptic and postsynaptic sides of identified connections with intracellular staining, or from different regions of the M cell, stems from one striking feature. Specifically, when the M cell is activated, the extracellular currents associated with its action potential produce a negative field potential that can be as large as 20–40 mV close to the axon hillock. This discovery by Furshpan and Furukawa (1962) signaled the beginning of the modern era of M cell research. Remarkably, these currents also underlie a class of neuronal interactions that still tend to be overlooked in other preparations, despite their potential functional relevance.

Field Effects

Nonsynaptically mediated electrical inhibition was demonstrated beautifully by Furukawa and Furshpan (1963). They found that activation of the M cell's recurrent collateral network causes an immediate inhibition of this cell. This early inhibition is correlated with an extracellular positive field, called the extrinsic hyperpolarizing potential (EHP), in the central core of the axon cap. It is due to outward currents generated by nearby axons that flow inward across the M cell axon hillock and hyperpolarize it. The EHP and its effect on excitability are monophasic because the presynaptic action potentials fail to propagate actively to the axonal terminals. These presynaptic cells constitute a defined population of inhibitory interneurons with processes that terminate on

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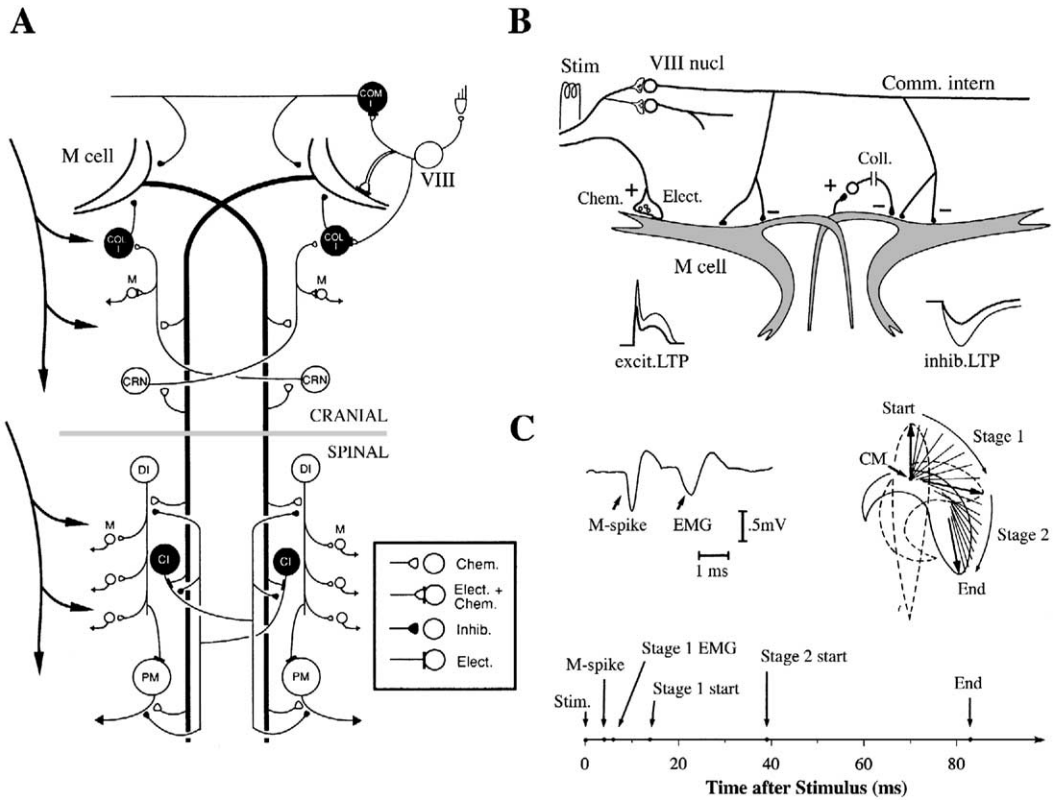

Figure 1. M Cell-Associated Circuits and Escape Reaction

(A) Horizontal view of the excitatory and inhibitory networks involved in the generation and control of the teleost escape reflex. One sensory system is shown from the eighth (VIII) nerve fibers, which are activated by hair cells in the ear and terminate on the lateral dendrite of the M cell. Excitatory and inhibitory neurons are empty and filled, respectively. M cell output to supraspinal motoneurons (M) is relayed through cranial relay neurons (CRN), which are excited by both M axons (thicker lines). At the spinal level there is a monosynaptic unilateral activation of primary motoneurons (PM). Several classes of inhibitory cells, the feed-forward commissural (COM I), the recurrent collateral (COL I), the crossed (CI), and the descending (DI) interneurons are shown. Note that COM I and COL I also mediate electrical inhibition of the M cell. Alternative reticulospinal pathways are indicated by thick lines to the left of the figure. (Inset) Symbols for chemical and electrotonic synapses (modified from Faber et al., 1989, used with permission from the New York Academy of Sciences USA).

(B) Sagittal view of the midbrain networks that manifest long-term changes (LTP) in synaptic strength at the ipsi- and contralateral M cells following tetanization (Stim) of an VIIIth nerve and control the unaffected collateral (Coll.) circuit. Symbols + and – refer to the corresponding synaptic function, i.e., excitation and inhibition (modified from Korn et al., 1992).

(C) (Upper left) Temporal relationship between activation of the M cell and the C-start. (Upper right) Superimposed silhouettes and anterior midlines, monitored every 4 ms, with the initial stage 1, or C-start (CM, center of mass), and the subsequent propulsive stage 2. (Below). Time sequence of the same events as above (reprinted from Eaton et al., 2001, with permission from Elsevier).

the soma and proximal dendrites of the M cell (Faber and Korn, 1973; Korn and Faber, 1975). Conversely, and also a consequence of the high resistance of the axon cap that channels current intracellularly, when the M cell fires, its field hyperpolarizes these interneurons, producing a passive hyperpolarizing potential (PHP). Discovery of the PHP was essential for a number of subsequent studies, because it allowed reliable identification of axons presynaptic to the M cell.

Field effects, also known as ephaptic interactions (Faber and Korn, 1989), represent a powerful mechanism for synchronizing neuronal populations, such as cerebellar interneurons (Korn and Axelrad, 1980) and hippocampal pyramidal cells in mammals (Dudek et al., 1998), including during seizures.

Electrical Connections via Gap Junctions

Throughout the first half of the twentieth century, a controversy raged over whether synaptic transmission in the vertebrate central nervous system is electrical or chemical, as described in detail by Eccles (1964). It seemed that the issue was resolved in favor of the latter hypothesis with the advent of motoneuron intracellular recordings in the early 1950s. However, the question of electrical transmission reappeared shortly thereafter. The issue was provoked by electron microscopic evidence in a few systems (Bennett et al., 1963; Robertson, 1961) of what are now called gap junctions. A notable example is the gap junction between a large myelinated club ending of an eighth nerve afferent and the lateral dendrite of the M cell, which was interpreted by Robertson et al. (1963) as being suggestive of electrical transmission.

Separate intracellular recordings from the pre- and postsynaptic elements demonstrated the electrotonic flow of current in both directions across M cell gap junctions (Furshpan, 1964). Furthermore, EM data suggested that these junctions are, in fact, mixed, i.e., they have both electrical and chemical transmission (Naka-

jima, 1974). Since then, electrical coupling has been found in an increasing number of central structures, with morphologically mixed synapses in some (inferior olive, cortex, lateral vestibular nucleus, retina, and hippocampus; see Pereda et al., 2003). However, the combined morphological and electrophysiological accessibility of the M cell, and of its auditory afferents, allowed in-depth study of their properties. For example, such recordings proved the hypothesis of dual transmission at single terminals (Lin and Faber, 1988a) and demonstrated that electrical transmission is amplified by a subthreshold voltage-dependent sodium current in the presynaptic endings, a mechanism that could be important in cases of weak coupling between dendrites (Curti and Pereda, 2004).

Recently, connexin35, the fish ortholog of the neuron-specific human and mouse connexin36, was localized to these junctions and to others in the goldfish brain, using a combination of confocal microscopy and freeze-fracture replica immunogold labeling (Pereda et al., 2003). A subunit of the NMDA glutamate receptor is in postsynaptic densities quite close to the gap junction plaques, providing a potential substrate for various forms of activity-dependent synaptic plasticity at these contacts (see below).

Chemically Mediated Inhibition and Excitation

Excitatory inputs diverge to the M cell and its inhibitory interneurons. Graded afferent stimulations revealed one of the operative rules postulated to link inhibition to excitation: the disynaptic inhibition produced by the bilateral feed-forward (or commissural) glycinergic pathway dominates for the weak strengths, and, only when it is saturated, can excitation bring the cell to threshold; (although the inhibition is disynaptic, it occurs without time lag relative to excitation, because all of the elements across the pathway have an electrical component). This parallel inhibitory pathway controls the effectiveness of the M cell's excitatory inputs. The output circuit includes a powerful Renshaw-like (or collateral) feedback loop, and these interneurons can also be activated by sensory afferents. The same basic design, i.e., convergence of feedforward and feedback inhibitory connections onto common targets, pertains to a number of central circuits in vertebrates, including those in the mammalian brain.

The M cell is also a prototype for understanding targeting and integration of inputs to specific local postsynaptic domains. Visual and statoacoustic inputs to this neuron are segregated to separate dendrites. Furthermore, different components of the latter pathway (auditory and vestibular otoliths, lateral line) are localized to specific regions of the lateral dendrite (Faber and Korn, 1978). The chemical map of transmitter systems along this dendrite, determined with iontophoresis (Diamond, 1963; Diamond and Huxley, 1968), pharmacology (Wolszon et al., 1997), and immunocytochemistry (Sur et al., 1994), also indicated regional specialization: AMPA, glycine, and GABA receptors are distributed throughout, while NMDA receptors and dopaminergic inputs are restricted to the distal dendritic region (with colocalization of somatostatin and GABA or glutamate in some terminals) (Sur et al., 1994). Serotonergic inputs are excluded from the dendrite (Figure 2, see also Korn et al., 1990).

The ability to record intradendritically from the M cell and its small membrane time constant were essential for quantifying the strength of the two forms that synaptic inhibition can manifest (Fukami et al., 1965) depending upon the Cl^- equilibrium potential (Furukawa and Furshpan, 1963, Furukawa et al., 1963). That is, it can appear as a shunt of an excitatory input, as initially demonstrated in crayfish muscle (Fatt and Katz, 1953), and as a frank and prolonged change in membrane potential. These properties also made it possible to establish the reality and specificity of dendritic, or "remote," inhibition (Diamond and Huxley, 1968), as first postulated by Frank (1959) and subsequently observed by Llinas and Terzuolo (1965). Thus, in some cases inhibition can be purely shunting due to an increased conductance, and its effectiveness can be highly localized and restricted to a distance of $\sim$50 μm along the large primary lateral dendrite. This conclusion was validated with predictions based on an equivalent circuit model of the M cell implemented by Furukawa (Furukawa, 1966) and by Huxley (Diamond and Huxley, 1968), with results that matched experimental observations. Furthermore, these issues have resurfaced, as in vitro patch-clamp and imaging techniques allowed them to be addressed in a wide range of mammalian neurons (Andersen, 1990, Fregnac et al., 2003).

The physical separation between adjacent synaptic units in the CNS might appear to preclude crosstalk between them. However, the postsynaptic conductance changes evoked by two separate inhibitory inputs with adjacent terminals summate supralinearly when they are co-activated. Kinetic modeling of quantal currents, based on biophysical and morphological parameters and patterned after pioneering models of the neuromuscular junction (Land et al., 1980), indicated that this effect is due to lateral diffusion of transmitter (Faber and Korn, 1988). This type of facilitation depends on rapid diffusion of glycine from one synapse to the next (0.5–1.0 μm in 300 μsec) and on the requirement that glycine receptors be at least doubly liganded to open. Previously described for the snake neuromuscular junction after cholinesterase inhibition (Hartzell et al., 1975), but unrecognized in the CNS, this phenomenon, later referred to as "spillover" (Kullmann et al., 1999), is important in various forms of synaptic plasticity.

Analysis of the kinetics of M cell responses to iontophoretic application of glycine and GABA suggested the presence of distinct receptors for the two amino acids, with their effects being primarily diffusion-limited (Diamond and Roper, 1973). When fluctuation analysis, first developed for isolated preparations (Anderson and Stevens, 1973), was used in the M cell, the mean open time of both glycine- and GABA-activated channels corresponded to the decay time constant of unitary IPSPs, suggesting that diffusion is quite rapid and channel kinetics are rate-limiting in physiological conditions (Faber and Korn, 1980). Interestingly, Werman in Mazliah (described in Faber and Korn, 1978) had obtained reliable steady-state dose-response curves for GABA and glycine receptor interactions at the M cell's lateral dendrite, as required theoretically (Werman, 1969). Furthermore, their results indicated that GABA can allo-

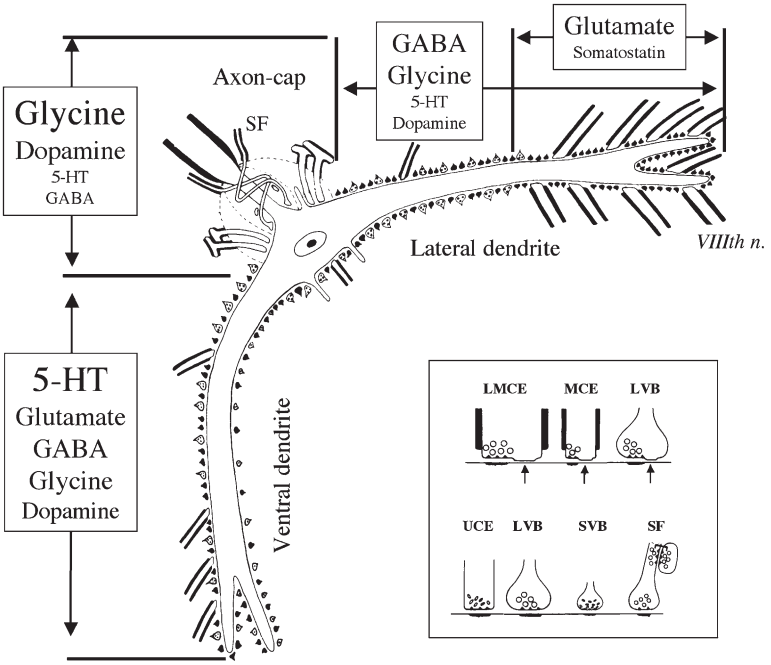

Figure 2. Schematic Representation and "Transmitter Network" of the M Cell

Diagram of the cell and of the distribution of its afferent synaptic endings, some of which are localized in discrete regions, particularly around the soma, the initial part of the axon, and the distal lateral dendrite. The cell is subdivided according to regions defined by the dominance of a given transmitter, rather than by common morphological boundaries. For each area, the relative weights of the indicated substances, are proportional to the character size (modified from Korn et al., 1990, used with permission from Elsevier). (Inset) Junctions recognized by electron microscopy, which carry gap junctions (arrows), chemical, or mixed synapses. They are excitatory (LMCE, large myelinated club endings; MCE, small myelinated club endings; LVB, large vesicle boutons) or inhibitory (UCE, unmyelinated club endings; SVB, small vesicle boutons). Terminals of the thin fibers that spiral around the M axon (SF) are excitatory, according to Scott et al. (Scott et al., 1994) (modified from Nakajima, 1974, used with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.).

sterically modify the glycine receptor, thereby increasing the affinity of glycine to its binding site (see Faber and Korn, 1978). The still unresolved problem of whether the M cell glycine receptor could be activated by GABA acquired functional relevance when it emerged that the two inhibitory transmitters are colocalized in the same presynaptic terminals in the M cell system and in mammals (Triller et al., 1987; Ottersen et al., 1988; Todd and Sullivan, 1990). Furthermore, GABAergic terminals can be apposed to postsynaptic GlyRs (Triller et al., 1987), and, in rat spinal cord both transmitters can be coreleased from individual vesicles (Jonas et al., 1998). A novel subunit of the glycine receptor, αZ1, with a high degree of homology with mammalian α subunits, was cloned from zebrafish brain (David-Watine et al., 1999). It is present in the M cell (Imboden et al., 2001), and the homomeric receptor that it forms can be activated by both transmitters, albeit with different kinetics and EC_{50}s (Fucile et al., 1999), as is also the case for human α1 and α2 homomeric receptors (De Saint Jan et al., 2001).

The Probabilistic Nature of Synaptic Transmission

Quantal Release. The discovery that the presynaptic interneurons that can be identified by the presence of a PHP (see above) mediate glycinergic inhibition of the M cell (Korn and Faber, 1976) allowed paired recordings from these connected neurons. This advance enabled a series of experiments designed to ask 1) if the quantal model of transmission, developed by Katz and his collaborators (Katz, 1969) for the neuromuscular junction, is pertinent to central synapses, and 2) if structural correlates could be determined for its statistical parameters. Such investigations were timely since both issues were being widely debated and there were alternative and conflicting speculations about the nature of transmitter release in the CNS (see McLachlan, 1978; Redman, 1990). As expected, the postsynaptic responses recorded in the soma fluctuated in size. Their amplitude distributions, whether peaky or not, were adequately fit with a simple binomial release model (Korn et al., 1981) convolved with a statistical description of the background noise.

Normally the variable driving force for Cl^-, which is determined by intracellular injections of this ion, makes it impossible to compare quantitative measurements of inhibitory responses between different experiments. However, a major advantage of the M cell system is that this limitation can be overcome by adopting a normalization procedure, based on the finding that the conductance change underlying the collateral inhibition is approximately equivalent to the cell's input conductance (Faber and Korn, 1982). This was an important step because the collateral IPSP could be used to calculate the IPSP driving force and convert quantal size to a conductance measure. This procedure made it possible to confirm subsequently the derived quantal size with that obtained using direct measurements of miniature (m) IPSPs recorded in the soma in the presence of TTX (Korn et al., 1987).

The quantal conductance was the basis for estimating the number of glycine-activated receptor channels open at the peak of the quantum. Initial estimates of 1000 channels or more, based on a putative single-channel conductance of 25 pS (Neher and Stevens, 1977) were subsequently revised downwards (Korn et al., 1994), after outside-out recordings in the M cell of the zebrafish embryo showed higher single-channel conductances (Legendre and Korn, 1994).

In individual experiments, the finding that the binomial parameter n was equivalent to, or close to, the number of boutons, which, in turn, contain only one release site or active zone (Triller and Korn, 1982), led to the hypothesis that each of them independently releases the contents of at most one vesicle, with an average probability p (Korn et al., 1982; Korn and Faber, 1991). That is, n corresponds to the number of release

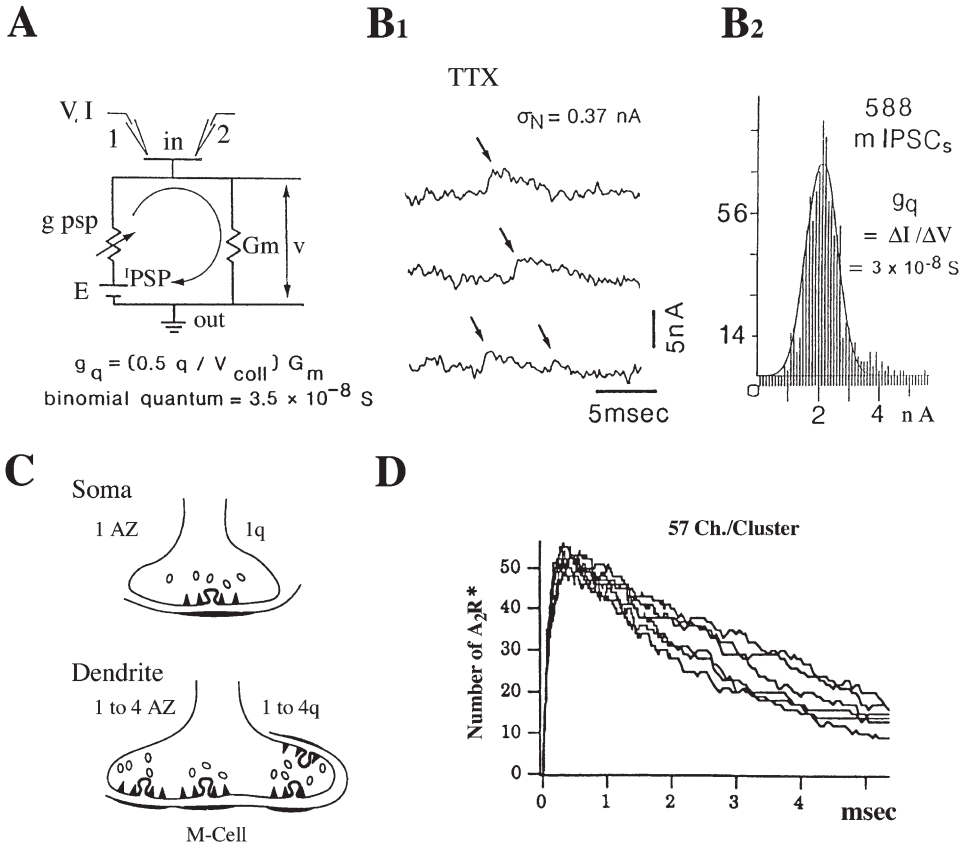

Figure 3. The One-Vesicle Hypothesis

(A, B1, and B2) Experimental verification of the quantal size predicted from the binomial analysis. (A) Equivalent circuit of the M cell membrane with two microelectrodes used to measure the membrane conductance Gm, the chloride driving force E, and the amplitude of the full-sized inhibitory postsynaptic potential Vcoll. The equation for estimating the quantal conductance g_q, derived from the statistical analysis of fluctuating IPSPs, predicts a value of 35 nS (modified from Faber and Korn, 1982, used with permission from the American Physiological Society). (B1 and B2) Unimodal distribution of spontaneous miniature inhibitory currents. (B1) Examples of quanta (arrows) recorded in the M cell in voltage clamp and in presence of TTX, with the smallest one almost obscured by the instrumental noise, σ_N. (B2) Amplitude histogram of a population of quanta, with a mean quantal size close to the predicted one and a variance larger than σ_N (modified from Korn et al., 1987). (C) Extension of the one-vesicle hypothesis, as formulated for the M cell soma (above), to the synchronized "multivesicular" release in the case of more complex dendritic synapses (reprinted from Korn et al., 1994, with permission from Lippincott, Williams, & Wilkins).

(D) Superimposed simulated quantal responses (n = 6) obtained with a cluster of 57 channels after the "release" of 10,000 molecules of glycine. The fluctuations of the peak amplitude and of the decay phase are accounted for by the unpredictable behavior of the activated channel population (reprinted from Faber et al., 1992).

sites at each terminal, rather than to the number of synaptic vesicles, as initially proposed (del Castillo and Katz, 1954). Precedence for this concept came from statistical studies of transmission at peripheral junctions, suggesting that the calculated binomial n corresponded to the number of release sites presumably detected by an extracellular microelectrode (Wernig, 1972, 1975; Zucker, 1973). According to Martin (1977), who endorsed this view, the "growing inclination to assign n to a finite number of release sites rather than to a number of available quanta as first assumed" was nevertheless based more on "intuition, than on experimental evidence." Furthermore, in contrast to the soma, inhibitory terminals impinging on the M cell dendrite have from one to four active zones (Sur et al., 1995) and the size and shape of the receptor matrices increase regularly from the soma to the tip of the dendrite (Triller et al., 1990). Histograms of mIPSP amplitudes recorded there after blocking evoked transmission have a similar number of classes with comparable proportions (Korn et al., 1994; Korn, 1998). This result implies that an ending that contains several release sites might at the same time release multiple quanta corresponding, again, to the number of active zones (Figure 3).

Data compatible with the one-vesicle hypothesis, which has sparked a great deal of related studies, have been obtained in a number of systems, while in others release may instead be multivesicular. A more cautious interpretation is that each active zone releases a quantum (Korn et al., 1994), which "most likely could be one vesicle, but perhaps a group" (Silver et al., 2003).

Related Synaptic Properties. During this work, immunocytochemical labeling of the glycine receptors showed that in contrast with the neuromuscular junction, central receptors are localized in discrete postsynaptic clusters facing the active zone (Triller et al., 1985). Thus, it was proposed that the active zone and its postsynaptic receptor counterpart, including some "extrasynaptic" receptors found just beyond this region

(Faber et al., 1985), represent a distinct building block of the connections between nerve cells. It is characterized both morphologically and as a functional entity (Korn et al., 1990), it corresponds to the synaptic complex (Palay, 1958; Peters et al., 1991), and it is equivalent to the synaptic unit as first defined at the neuromuscular junction by anatomists and physiologists (Zucker, 1973; Wernig, 1975). This definition avoids potential confusion when the term "synapse" is indiscriminately used in reference to a single contact or to a connection having as many as 10,000 release sites, as in squid (Heuser and Reese, 1977). In this way the "synaptic connection" that an afferent input establishes with its target can be weighted quantitatively, according to the number of its constituent units.

A related issue, that of saturation of receptors by a quantum and the apparent invariance of the postsynaptic response (Jack et al., 1981; Edwards et al., 1990), was refined by studies at these inhibitory units in adult goldfish and embryonic zebrafish M cells, using whole-cell patch-clamp recordings in the latter (Legendre and Korn, 1994) and Monte Carlo simulations (Faber et al., 1992; Kruk et al., 1997). A single quantum fluctuates in size and time course due to intrinsic factors, particularly the stochastic properties of receptors. As predicted, this variability is greatest at junctions with the fewest number of receptors.

The simulations also showed that the peak quantal amplitude is relatively insensitive to the amount of transmitter in a vesicle such that two exocytoses give larger responses than one alone only if the ratio of molecules released to the number of receptors is no more than 3:1. An increase in quantal size, attributed to either the release of more transmitter or to the presence of more receptors, can also follow changes in morphology, e.g., an expansion of the contact zone between the pre- and postsynaptic membranes. This structural modification can be enough to slow diffusion of transmitter out of the synaptic cleft and is one more potential substrate for dynamic changes in synaptic strength.

Synaptic Plasticity

Studies of short- and long-term plasticity at M cell synapses have complemented work in other systems. The novelty of activity-dependent changes, both in vivo and at the first stages of sensory processing, is particularly noteworthy. That is, not only do the inhibitory and excitatory connections onto the M cell exhibit heterosynaptic facilitations induced by endogenous modulators, namely, serotonin and dopamine, respectively, but they also undergo homosynaptic potentiations.

Effects of Neuromodulators

A brief application of serotonin (5-HT) in the axon cap, or of its uptake blockers, produced increases in inhibitory currents evoked by activation of presynaptic networks that lasted tens of minutes, while the mean size of the spontaneous mIPSCs remained unaffected (Mintz et al., 1989). In the M cell, synaptic noise is predominantly inhibitory. Its quantal composition can be resolved, provided the isolated quanta can be distinguished, because they either are so numerous within synaptic noise or are isolated in the presence of TTX. Therefore, synaptic noise was used to determine the locus of the 5-HT action. Evidence of a presynaptic action was obtained (Mintz and Korn, 1991). First, the amine is found in a profuse network of varicose fibers in the M cell's synaptic bed (Gotow et al., 1990), with invaginations within the inhibitory terminals themselves. Second, 5-HT acts by increasing the probability of glycine release. The presumed mechanism, a block of voltage-dependent K^+ channels in the axon terminals, is similar to that partially responsible for sensitization of sensorimotor synapses in *Aplysia* (Kandel and Schwartz, 1982).

Dopamine is stored in thin varicosities that are found in the synaptic bed of the lateral dendrite only and do not make contacts with postsynaptic elements (Pereda et al., 1992). When applied locally, dopamine increases the amplitudes of both the electrical and glutamatergic components of the eighth nerve-evoked responses. This action is mediated by activation of a postsynaptic D2 receptor coupled via a G protein to a cyclic AMP-dependent cascade, as demonstrated pharmacologically, in part, by intracellular injections of compounds targeted to specific steps in the pathway (Pereda et al., 1994).

Opposing effects of these modulations on the behavioral threshold of the escape response are likely, particularly in light of the consequences of long-term potentiation (LTP) in the M cell system.

LTP of Chemical and Electrotonic Synapses

Teleosts, notably goldfish, are hearing specialists, and strikingly, both the excitatory and inhibitory premotor synapses in the auditory pathway to the M cell undergo an activity-dependent LTP (Figure 4). Similarly to the LTP described first in hippocampal area CA1 (Collingridge and Bliss, 1995), these potentiations can be induced by repetitive presynaptic bursts of spikes, evoked by stimulation of the eighth nerve at frequencies matching their auditory sensitivity (~500Hz). They are independent of the modulations described above.

The discovery of LTP at gap junctions in the club-ending synapses was quite surprising, as electrical synapses were not commonly considered to be modifiable. Yet, this LTP is due to a true increase in junctional conductance rather than to a nonspecific change in M cell membrane properties (Yang et al., 1990). It presumably involves modifications of existing gap junction channels, rather than changes in rates of insertion or removal, given that a small fraction of the channels are open in normal conditions. This enhancement, along with that of the associated chemical synapses, results from a postsynaptic increase of Ca^{2+}, which leads to activation of Ca^{2+}/calmodulin-dependent kinase II (Pereda et al., 1998). The potentiation is highly specific, with the Ca^{2+} action being restricted to the local domain of single contacts (Smith and Pereda, 2003).

Finally, both the chemical and electrical components of the mixed synapses can undergo long-term depression (LTD) in specific conditions (Yang and Faber, 1991).

LTP of Inhibitory Junctions

Although the neuronal firing threshold is determined in all neurons by the balance between excitation and inhibition, studies of plasticity were almost exclusively concerned with the former, until definitive evidence for inhibitory LTP was provided with the M cell system (Korn et al., 1992; Oda et al., 1995). Several other examples followed shortly in mammalian hippocampus, cerebellum, and cortex (Marty and Llano, 1995).

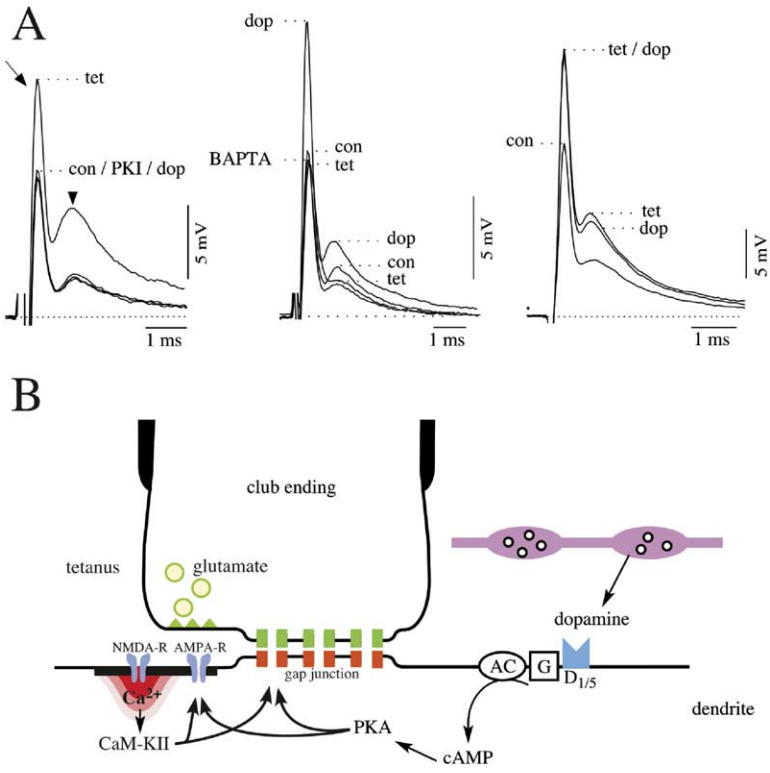

Figure 4. Convergent Cellular Mechanisms in LTP and Dopamine-Evoked Potentiation of Mixed Synapses between the Club Endings and the M Cell Dendrite

(A) Superimposed intracellular recordings of mixed electrical (arrow) and chemical (arrowhead) excitatory responses to ipsilateral eighth nerve stimulations. (Left) Intracellular injections of the protein kinase A inhibitor (PKI) block the subsequent attempt to evoke a dopamine (dop)-mediated enhancement, but tetanus (tet) still produces LTP. (Middle) Conversely, chelation of Ca^{2+} with BAPTA blocks LTP, but not the dopamine action. (Right) LTP occludes the effects of dopamine. (modified from Figures 4C1, 5B1, and 2B1 in Kumar and Faber, 1999, used with permission of the Society for Neuroscience). (B) Schematic model illustrating the distinct intracellular postsynaptic cascades that initiate tetanus-induced LTP (Ca^{2+} entry through the NMDA-R activates CaM-KII) and the dopamine-evoked potentiation (D1/D5 receptor binding increases cAMP levels and activates PKA), although they converge on common targets, AMPA-Rs, and gap junction connexins (modified from Figure 7F in Pereda et al., 2004, used with permission from Elsevier).

As noted already, the feed-forward glycinergic inhibitory pathway counters excitation of the two M cells by auditory afferents (see Figure 1). Stimuli with the same patterns as those used to potentiate excitatory junctions, but weaker and below threshold for firing the M cell, produce LTP of the inhibitory connections (Figure 5). This phenomenon was confirmed with paired pre- and postsynaptic recordings. As at excitatory junctions, the induction is synapse specific and is blocked by postsynaptic Ca^{2+} chelation. However, quantal analysis indicated that the locus of LTP expression is presynaptic. Furthermore, the enhanced postsynaptic conductance is boosted by an additional LTP at the initial excitatory relay between primary afferents and the interneurons themselves.

Repetitive sounds also induce inhibitory LTP and, remarkably, the same protocol has clear behavioral correlates in free-swimming fish. It is associated with a marked reduction in the probability of initiating an escape response due to a sudden stimulus, such as dropping a ball into the aquarium (Oda et al., 1998). This increased inhibition may thus be a mechanism for desensitization or habituation (Kandel et al., 1983), expressed as a shift in the behavioral threshold (cf. below).

Silent Connections: Substrate for Gain Control

A compound binomial model of transmitter release suggested that some of the terminal boutons in the connection between an Ia spinal afferent and an α-motoneuron (Redman and Walmsley, 1983), or between a group I afferent and a dorsal spinocerebellar tract neuron (Walmsley et al., 1988), could be ineffective. That is, although presynaptic conduction in an afferent is normal, some terminals seem to exhibit a zero or near-zero release probability. Yet studies of M cell inputs were the first to show that, in fact, a significant fraction of a neuron's afferent connections constitute a hidden population of silent chemical synaptic connections that can become functional in certain conditions. Since then, it has been recognized that chemical synapses can be switched on and off, and this phenomenon is now a mechanism commonly implicated in different forms of LTP (Malinow and Malenka, 2002) and LTD. A corollary of this notion of a labile fraction of cells is that it allows a rapid reorganization of neural networks. In practice, this also means that the failure to obtain a postsynaptic response in paired recordings does not necessarily imply the lack of anatomical contacts.

Approximately 80% of individual club ending connections with the M cell are chemically silent following a presynaptic spike, and they become functional with small increases ($\sim$100 μs) in spike width produced by blocking voltage-dependent K^+ channels with intraaxonal injections of Cs^+ or 4-AP (Lin and Faber, 1988b; Faber et al., 1991a). Thus, in the case of these afferents, each of which has multiple release sites, transmission may be gated at the level of the full connections. Moreover, the ratio of the chemical to the electrical EPSPs increases as more afferents are stimulated, reflecting the fact that the silent connections can be converted into functional ones when a significant population is coactivated (Pereda et al., 2004).

Impulses in at least 25% of the glycineric inhibitory interneurons produce no response in the M cell, although their pattern of connectivity is similar to that of functional interneurons and may involve as many as tens of release sites. Furthermore, intraaxonal injections of 4-AP or Ca^{2+} do not unmask transmission,

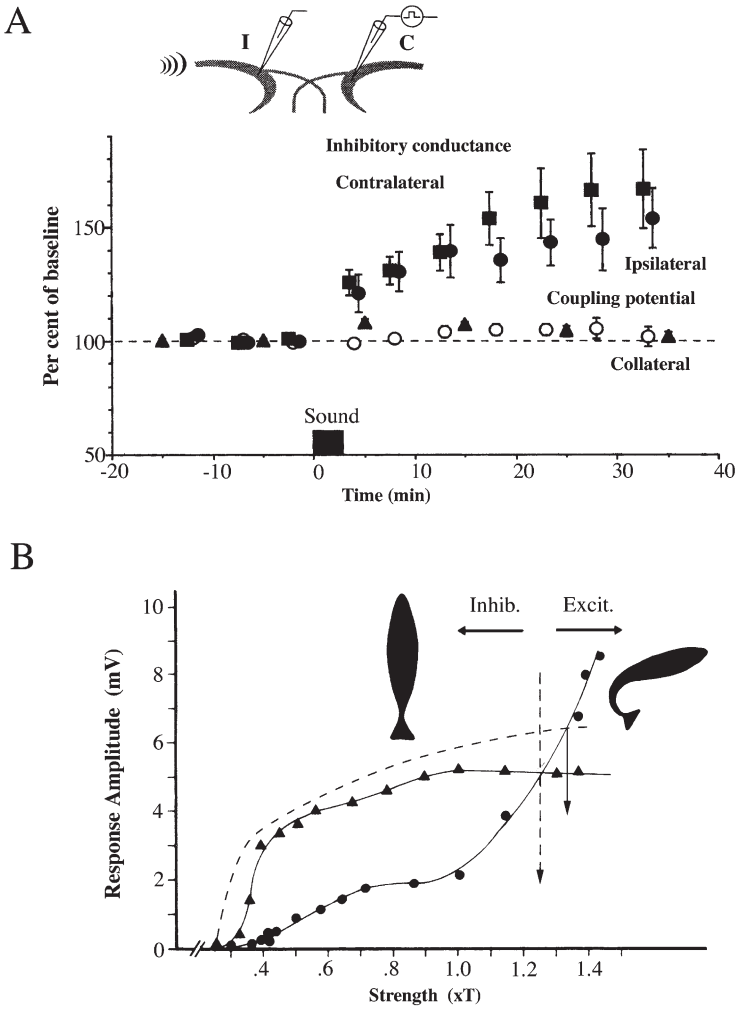

Figure 5. Sound-Evoked LTP of Inhibition and Consequent Modifications of the Behavioral Threshold

(A) (Above) Experimental arrangement for simultaneous intracellular recording of synaptic events produced in the ipsi-I (I) and contralateral (C) M cells by stimulation of the ipsilateral VIIIth nerve (not shown). (Below) Amplitude and time course of inhibitory LTP induced in both M cells by a conditioning protocol using repeated brief (500 Hz) tone bursts (black rectangles). Note that given the weak strength of VIIIth nerve stimulations, the ipsilateral excitatory inputs (coupling potential) and the contralateral feedback inhibition (Collateral) remain constant throughout the experiment (Oda et al., 1998, reprinted with permission from *Nature*).

(B) (Below) Plots of the amplitude of excitation (●) and of inhibition (▲) versus the strength of stimulation of the posterior branch of the eighth nerve, expressed as a fraction of that necessary to bring the M cell to its firing threshold (vertical dashed line) (reprinted from Faber and Korn, 1978, with permission from Lippincott, Williams, & Wilkins). This threshold can be shifted to the left or to the right by an increased strength of inhibition or excitation, for example, by prior experience that produces inhibitory LTP (dashed line). (Above) Fish silhouettes. Behavioral consequences of the physiological relationship illustrated in the graphs below. In a low-intensity sound environment, swimming is undisturbed, but a C-start is triggered when the sound level is increased (from Oda et al., 1995, used with permission of the American Physiological Society).

which is only exposed with inhibitory LTP. The potentiation is expressed primarily by these silent connections as well as by those that are weaker than "normal" ones. These two groups thus constitute a reserve pool with an overall enhancement at least 5-fold greater than that of the otherwise dominant population of potent inhibitory cells (Charpier et al., 1995). Hence, the distribution of synaptic strengths in a population of neurons may be discontinuous and subject to dynamic shifts between two distinct states.

A Nonrandom Component in Synaptic Noise

Neuronal membrane potentials vary continuously, due largely to background synaptic noise produced by ongoing discharges in presynaptic afferents and by the spontaneous release of transmitter that produces miniature quantal currents. These fluctuations influence the input-output function of neurons (reviewed in Burnod and Korn, 1989). They have most often been qualified as stochastic, on the sole basis of Poisson-like interevent histograms. Yet, this conclusion has been challenged when the same data, or recordings, were subjected to nonlinear analysis with the methods and concepts used to characterize a form of determinism called "chaos." Among others, these include return (or Poincaré) maps, which can reveal temporal structures that remain hidden in more conventional histograms, and the results of adequate measures (Faure and Korn, 2001). These measures were essential for unmasking determinism in the firing patterns of pacemaker cells, paired coupled neurons, central pattern generators, and several cortical assemblies (Elbert et al., 1994; Korn and Faure, 2003), thus raising the possibility that these activities can be controlled by external perturbations. A critical issue is whether intrinsic variability, which is considered to be an essential factor of successful behavior and survival in living systems (see below), reflects true randomness or if there is an underlying temporal order, and, if so, how it is shaped.

When the temporal structure of the dendritic inhibitory synaptic noise of the M cell was analyzed (Faure and Korn, 1997, 1998; Faure et al., 2000), previously undetected features of this signal were revealed. Until that time, due to well-known uncertainties, attempts to accurately distinguish the fine structure of synaptic noise using automated procedures were limited by available algorithms (Ankri et al., 1994; Ankri and Korn, 1999). However, return maps constructed with subsets of IPSPs selected according to different threshold am-

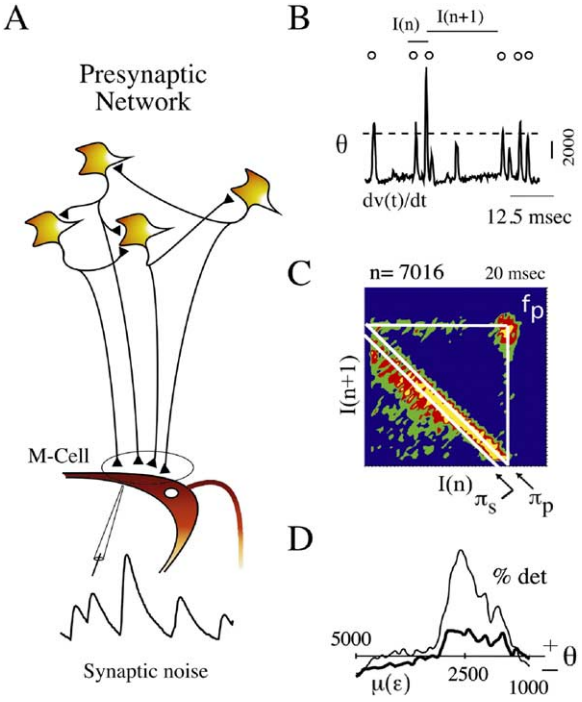

Figure 6. Evidence for Dynamic Patterns Compatible with the Notion of Chaos in Synaptic Noise

(A) Schematic representation of the presynaptic inhibitory network afferent to the M cell and, below, a fragment of the synaptic noise generated by this network's spontaneous activity. IPSPs are depolarizing due to intracellular injections of Cl^-.

(B) Derivative of a segment of actual synaptic noise. IPSPS are selected according to a given size by a threshold θ. Intervals, in ms, between consecutive events are labeled In and I(n+1), respectively. (Reprinted from Faure et al., 2000, used with permission of the American Physiological Society).

(C) Return (Poincaré) map constructed with these intervals. Note the striking signal-flag pattern, at the base of which the highest density of points reveals principal (π_p) and secondary (π_s) frequencies, with intervals equal to 13.3 and 14.4 ms, respectively (see text). Repeating this protocol after removing the related IPSPs and lowering the threshold would uncover a second, hidden triangle, with different underlying frequencies (not shown). (Reprinted from Faure et al., 2000, used with permission of the American Physiological Society).

(D) Variations of the significance level of two measures of nonrandomness, the percentage of determinism (% det.) and the Kolmogorov-Sinai entropy ($\mu(\epsilon)$), as functions of θ. The horizontal line indicates the confidence level after comparison with surrogates (modified from Faure and Korn, 2003, used with permission from the MIT Press).

plitudes as well as nonlinear measures disclosed several striking periodicities, centered around frequencies within the γ range that were observed in the brain activity of higher vertebrates (Figure 6). Furthermore, mutual interactions and the phase relationship between the IPSPs associated with the extracted frequencies were consistent with the notion that this signal is generated by presynaptic interneurons behaving as weakly coupled oscillators, as opposed to independent ones. In confirmation, auditory-evoked LTP, which increases some of the inhibitory synaptic strengths (Oda et al., 1998), permits complex presynaptic oscillating firing patterns to be transmitted more effectively to their postsynaptic target.

A model of the M cell system indicated that the state of the pool of afferent interneurons is recapitulated in the temporal structure of synaptic noise only if the mean quantal content varies between the simulated "connections," as observed experimentally (Korn et al., 1986). In this context, the probabilistic nature of neurotransmission becomes a functional advantage rather than a limitation, since it allows the transmission of information to be modulated by environmental factors without modifying the behavior of the synaptic networks (Faure et al., 2000).

Sensory Motor Behavior and the M Cell

Is the M Cell a Command Neuron?

The most common fast-start escape behavior is the C-start (Figure 1 C), so named on the basis of the shape of the fish at the end of the first stage of this reflex, before forward propulsion (stage 2) begins (Weihs, 1973; Webb, 1976; Eaton et al., 1977). Typically, in the goldfish, one of the M cells fires a single spike about 3 to 5 ms after the onset of an aversive acoustic stimulus (Zottoli, 1977; Eaton et al., 1988), and the first detected movement is a deviation of the head in the direction opposite to the activated M cell about 8 ms after the spike (Eaton et al., 1991). The C-start also occurs during prey capture and feeding (Canfield and Rose, 1993), probably during hatching (Eaton and Nissanov, 1985), and most likely in response to the disruption of an established social order (Fernald, 1975). Finally, the amphibian M cells apparently can trigger a different type of avoidance behavior, as they fire during the bilateral hindlimb contraction associated with the diving escape of the frog (Will, 1991).

These features suggested that the M cell might be the prototype of a "command neuron" (Kupfermann and Weiss, 1978), i.e., a neural decision-making cell whose firing could be "necessary and sufficient" to trigger a complete behavioral act, such as the crayfish escape. This concept was challenged in a series of particularly thoughtful experiments that showed that M cell ablations (Eaton et al., 1982; Di Domenico et al., 1988) do not abolish the behavior, but rather delay its onset by a few ms, and although M cell activation alone can trigger stage 1, the resultant behavior is less variable than is normal behavior (Nissanov et al., 1990; Eaton et al., 2001). Yet, the C-start almost never occurs without firing of the M cell, and this neuron always fires first, before all other brainstem neurons (Casagrand et al., 1999; Eaton et al., 2001). Consequently, the M cell is a "command-like" neuron (Eaton et al., 2001), even though it participates in a parallel "brainstem escape network" that finely regulates the escape trajectory.

The network comprises the M cell homologs MiD2cm and MiD3cm and other descending reticulospinal neurons (Figure 7). The homologs can fire bursts of action potentials, in contrast to the M cell (Nakayama and Oda, 2004), and they also activate spinal circuits that cause the trunk musculature to contract (Fetcho, 1991). These cells contribute to the normal behavior, but they are activated with a longer latency by auditory inputs and they have a higher firing threshold than the M cell

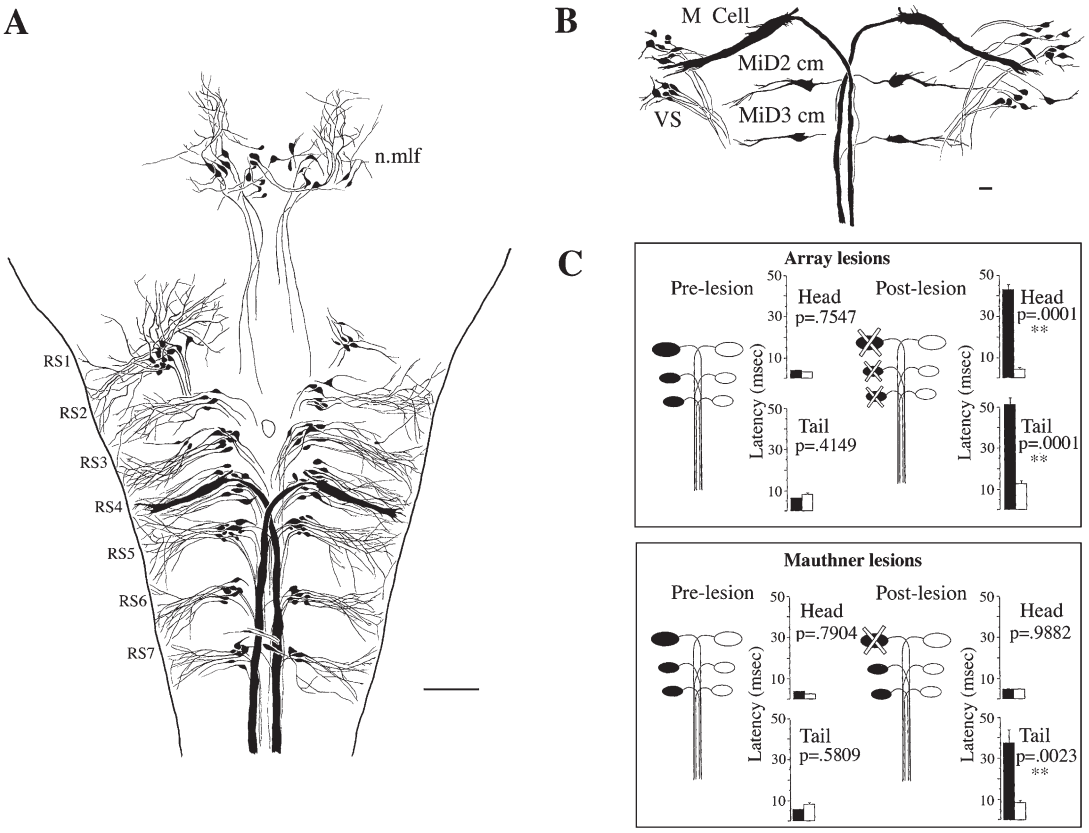

Figure 7. Segmental Arrangement and Functional Relationships of Reticulospinal Neurons

(A) Reconstruction, from horizontal sections, of the seven rhombomeres RS1–RS7 of a goldfish. Note the large M cells' somata and decussating axons; neurons are not symmetrical due to incomplete labeling by HRP. n.mlf, nucleus of the medial longitudinal fasciculus.

(B) Horizontal view of the segmentally homologous neurons. The M cell and the MiD2 and MiD3 cells occupy segments RS4, RS5, and RS6 segments, respectively. VS, vestibular nucleus. Calibration bars = 200 μm in (A) and 50 μm in (B) (from Lee et al., 1993, reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.).

(C) Effects of laser-induced ablations of the M cell array (above) and of the M cell alone (below) on the latency of the escape response. As indicated, the left side of each panel shows the control mean latency of the response evoked by stimuli on the head or on the tail; the black bars pertain to the side to be lesioned. Killing all three cells eliminated short-latency responses to both head- and tail-directed stimuli, while eliminating the M cell alone affected only the tail-evoked activity (from Liu and Fetcho, 1999, reprinted with permission from Elsevier).

(Nakayama and Oda, 2004). Thus, there is a longer delay when they compensate for the absence of the latter (Eaton et al., 2001).

Subsequently, these issues were elegantly addressed using imaging techniques that allowed the activity of neurons in the brain and spinal cord to be visualized in real time, in vivo, by taking advantage of the transparency of larval zebrafish (Fetcho and O'Malley, 1995). This approach confirmed predictions (Foreman and Eaton, 1993) that the serial Mauthner homologs are involved in escapes and that the combination of neurons activated depends upon stimulus features (O'Malley et al., 1996). In particular, the M cell alone fires when the stimulus is to the tail, but the homologs are also active when it is to the head, and causality was then demonstrated with photoablation of these neurons (Liu and Fetcho, 1999).

Single-cell imaging during behavior complements and/or forces reconsideration of concepts drawn from electrophysiology: (1) the brainstem escape network, including those neurons active during subsequent swimming, involves >80% of the neurons projecting to the spinal cord (Gahtan et al., 2001), and (2) spinal circuits involved in swimming and escape behaviors are overlapping, but not identical (Ritter et al., 2001).

To Escape: Yes or No?

In the case of an auditory stimulus, the speed of the escape reaction is attributed to the gap junctions at sensory synapses, the small time constant of the M cell's membrane, a rapidly conducting axon that monosynaptically excites primary motoneurons at the spike-initiating site, and the activation of fast muscles (Fetcho, 1991). On the other hand, the cellular properties and the network design guarantee that a large number of afferents are active before the M cell reaches its threshold for spike initiation (Faber et al., 1991b).

At the level of the neuron itself, these properties are a low input resistance, a short time constant, and a high resting potential, which guarantee that only strong and synchronized inputs reach the firing level. In addition, the effects of the sensory-evoked feed-forward inhibitory network and of the spontaneous background in-

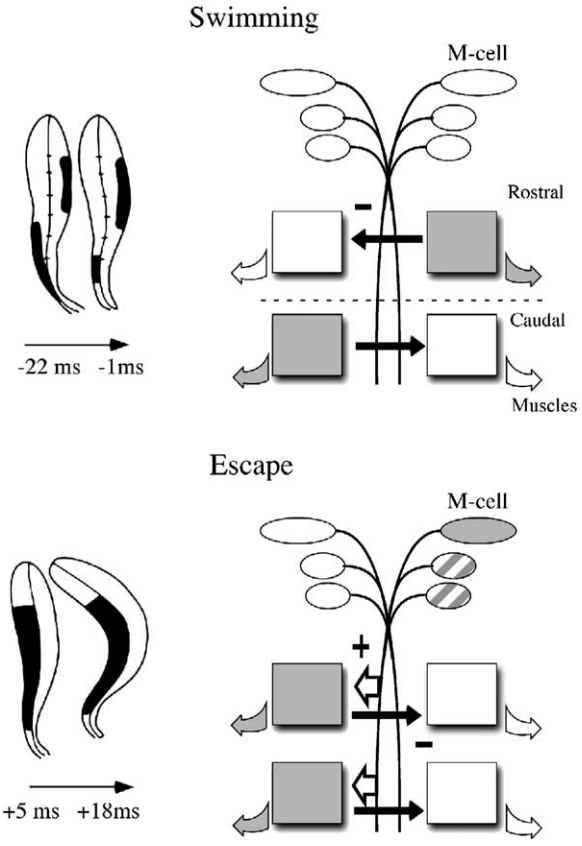

Figure 8. Diagram of the Spinal Circuits Shared by Different Motor Behaviors and Reconfiguration of Spinal Network Activity by Reticulospinal Commands as Escape Overrides Swimming

(Left) Fish silhouettes at indicated times, during swimming (above) and during the first stage of escape triggered by a sudden threat (below). The darkened areas represent the dominant muscular activity. (Right) Note that two spinal segments, represented by one box on each side of the spinal cord, are sequentially activated during swimming (signified by a horizontal dashed line). Neurons and connections in each box (not shown) are the same as detailed in Figure 1A. Escape priority is imparted by the M cell's activation of excitatory synapses (empty arrows, + signs) and of crossed inhibitory interneurons (thick black arrows), which guarantee that only one side of the spinal cord will be activated in all segments (lower diagram). Shading designates the activated hemisegments. Note that one M cell alone (shaded), or the cell with its homologs (hatched), is excited depending upon whether the stimulus is to the head or tail, respectively (modified from Korn and Faber, 1996, used with permission from Elsevier).

hibitory noise (Hatta and Korn, 1999) are maximized near threshold by the voltage-dependent open time of the Cl^- channels (Faber and Korn, 1987; Legendre and Korn, 1995). The other property that maximizes inhibition is the synergistic interaction between adjacent nonsaturated postsynaptic receptors that is due to lateral diffusion of the transmitter glycine (cf. above), which results in a greater inhibition than that expected from the simple summation of their individual effects. Thus, subcellular and channel properties must be included among the factors that determine the likelihood of an escape response.

Conversely, a number of nonlinearities can boost excitation at the time that inhibition is saturated and can be more easily overcome. For example, input resistance of the M cell is enhanced by depolarization (Faber and Korn, 1986).

At the network level, a bilateral feedback inhibition prevents activation of both M cells (Furukawa and Furshpan, 1963; Hackett and Faber, 1983), which would cause bilateral muscle contractions and result in minimal displacements of the fish. Asymmetric tonic inhibition of the two M cells may also bias the system in favor of activating one of them (Hatta and Korn, 1999). If, however, the two M cells are coactivated, a spinal inhibitory pathway suppresses the excitatory effect of the trailing action potential for intervals greater than 150 μs (Yasargil and Diamond, 1968). The midbrain inhibitory system, along with the role of a unique M cell dendrotoxin-I-voltage-gated potassium conductance (Nakayama and Oda, 2004), avoids repetitive firing that would result in multiple and ineffective body bends. Finally (Figure 8), there is a priority of the escape reaction over other motor behaviors (Svoboda and Fetcho, 1996) such as swimming, due to a high safety factor at all connections downstream from the M cell (Fetcho, 1991).

To Escape: Where and How?

During a typical acoustically triggered C-start, the animal changes its orientation away from the startling stimulus. The extent of this escape, as well as its variations, is controlled by the parallel network, including interactions between the activated M cell and its homologs (Eaton et al., 1984; Di Domenico et al., 1988; Casagrand et al., 1999).

Contrary to initial claims that the C-start trajectory is stereotypic, the stage 1 and stage 2 phases are highly variable in duration, angular displacement, and the distance moved (Nissanov and Eaton, 1989). The variability of these phases is the consequence of differences between the size of the initial agonist muscle contraction and that of the later antagonistic contraction, as well as the timing between the two contractions (Eaton et al., 2001). The resulting unpredictability of the escape path is in marked contrast to the direction taken by a predator aiming at its prey, and it is an important feature of the M cell-triggered behavior that makes it difficult for a predator to adapt, or to learn, a successful strategy for prey capture (Domenici, 2002).

This variability has been analyzed by defining escape trajectories in circular coordinates, with the references being the stimulus orientations at rest, and by measuring the angles characterizing the fish's orientation at the end of phases 1 and 2 (Domenici and Blake, 1993, 1997). Statistical measures indicate that variations in trajectories are not due to randomness, and they reveal multimodal adaptive patterns that remain hidden in classical linear plots based on a fixed origin. The variability of the C-start responses of solitary fish disappears in schooling, which produces a single trajectory presumably to avoid collisions (Domenici and Batty, 1997).

Despite these variations, the acoustically triggered escape is appropriately directional when the fish are in open field (Eaton and Emberley, 1991; Domenici and Blake, 1993), although this directionality can be reversed without apparent reason or by a nearby physical

barrier or visual cues. Furthermore, in 10% to 20% of the trials with an unobstructed path, the relationship between the trajectory of the escape and the stimulus angle is reversed and the fish turns toward the threat. This "tactical error" may be corrected by an aversive second away movement that starts at the end of stage1, which is the right timing for sensory feedback to influence steering (Domenici and Blake, 1993), although other authors (Di Domenico et al., 1988; Eaton et al., 1988) believe that it is preprogrammed.

In addition to auditory inputs, several constituents of the octavolateralis system (lateral line, vestibular; reviewed in Faber and Korn, 1978) also activate the M cells. It is likely that, as shown for the afferents from the swimbladder (Canfield and Eaton, 1990), they, along with parallel inhibitory projections, influence the directionality of the escape by differentially biasing the excitability of the two M cells. In conjunction with visual inputs, they also provide the substrate for the directional override that occurs when a fish, close to a wall, turns away from it (Eaton and Emberley, 1991; Preuss and Faber, 2003). The long latency of visually evoked excitatory potentials in the M cell suggests that vision can modify response direction before, rather than during, a predator's strike (Canfield, 2003).

"Decision" and the Escape Behavior

Studies of the M cell, long ago termed a "miniature brain" by Steve Kuffler, illustrate some of the difficulties encountered when trying to understand the relationship between brain and behavior. Initially, the escape reaction was simply viewed as a classical sensory-to-motor "reflex." Consequently, it was believed that this behavior could be explained by reducing it to the sum of its smallest possible components, or building blocks. However, it turns out that a rather complex system is actually involved.

The case of the M cell-triggered escape reactions illustrates several basic principles. First, even if the anatomical design of a motor behavior seems well adapted to a given function, other behaviors can utilize or build on that basic circuitry. It follows that "it is appropriate to define the goal that an organism has to reach before examining the mechanism (and the hardware) in which it is embodied" (D. Marr, quoted by Glimcher, 2003). This guideline was at the core of investigations that revealed the role of reticulospinal neurons other than the M cell and their hierarchical organization within the brain stem (Figure 8). Second, the role of the nervous system is to maximize the chances of achieving a specific aim, which in the case of the M cell-triggered reaction is most often equivalent to survival. This requires that the neural networks actively encode and decode recent and external ongoing events in order to deal with the uncertainties of the outside world (Oda et al., 1998; Preuss and Faber, 2003), while simultaneously introducing sources of variability such as synaptic noise, which act as internal randomizers (see above).

The decision by the M cell to trigger a specific motor reaction can be viewed as a process that shifts the balance between inhibition and excitation and favors the latter. In other words, as suggested by Schall and Thompson (1999), there is a "decisional threshold" that the rising activity has to cross in order for a movement to be produced. In this perspective, the decisional level for the escape is equivalent to the firing threshold of one neuron, and the likelihood that it is reached depends upon external conditions. Overall, the M cell system, with its various forms of plasticity, exemplifies the notion that "the environmental problems animals face shape not only behavior but also the neural hardware that generates that behavior" (Glimcher, 2002).

Future Avenues

The M cell continues to be an invaluable model for interdisciplinary research. Recent investigations of their morphological and electrophysiological properties indicate that M cells and their networks have the same properties in the zebrafish as in the more familiar goldfish (Hatta and Korn, 1998; Hatta et al., 2001) and that they share a common developmental and segmentation pattern (Metcalfe et al., 1986; Lee et al., 1993). Thus, the wealth of information generated over decades about these systems can be extrapolated to each other. Also, the transparency of the hindbrain has made single cells accessible in whole-brain preparations at early stages of development. Consequently, patch-clamp recordings at early stages at the M cell level have helped to clarify single-channel and synaptic properties at the M cell inhibitory synapses and to correlate them with some of the behavioral features (Legendre and Korn, 1994; Legendre, 1997; Triller et al., 1997). The same techniques should allow experimental manipulation of specific proteins in models of nervous system disorders, for example, mutating M cell glycine receptors, to address issues related to severe forms of spasticity in humans called hyperekplexia, or startle disease (Rajendra and Schofield, 1995).

Newly available powerful optical approaches such as noninvasive calcium imaging, laser photoablation, and genetic manipulation using transgenic lines or mutants are less difficult technically than electrophysiological approaches. They should make it possible to elucidate the causal links between neurons and behavior using the zebrafish as a vertebrate model (Fetcho and Liu, 1999). Hopes were raised when the Nusslein-Volhard group began to screen for mutants defective for touch responsiveness and locomotor behavior (Mullins and Nusslein-Volhard, 1993; Granato et al., 1996). However, a number of the mutants are lethal. Another issue, related to the mechanisms that guarantee that there is only one pair of M cells in the r4 segment of each fish, is whether the same segmentation rules apply to the reticulospinal neurons of mammals. Recent investigations indicate the involvement of the Notch-Delta pathway in singling out the M cell and controlling its development (Haddon et al., 1998; Gray et al., 2001) and the role of Hox genes in specifying the cell (Hale et al., 2004). Mutations of both pathways demonstrate a remarkable plasticity and adaptability of the M cell system to duplication (Liu et al., 2003) and to misallocation.

All of these results highlight the potential of the M cell system to link molecular biology and genetics with development and behavior, particularly since the zebrafish genome is known today.

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