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Review Paper

The Mauthner-cell circuit of fish as a model system for startle plasticity

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ABSTRACT

The Mauthner-cell (M-cell) system of teleost fish has a long history as an experimental model for addressing a wide range of neurobiological questions. Principles derived from studies on this system have contributed significantly to our understanding at multiple levels, from mechanisms of synaptic transmission and synaptic plasticity to the concepts of a decision neuron that initiates key aspects of the startle behavior. Here we will review recent work that focuses on the neurophysiological and neuropharmacological basis for modifications in the M-cell circuit. After summarizing the main excitatory and inhibitory inputs to the M-cell, we review experiments showing startle response modulation by temperature, social status, and sensory filtering. Although very different in nature, actions of these three sources of modulation converge in the M-cell network. Mechanisms of modulation include altering the excitability of the M-cell itself as well as changes in excitatory and inhibitor drive, highlighting the role of balanced excitation and inhibition for escape decisions. One of the most extensively studied forms of startle plasticity in vertebrates is prepulse inhibition (PPI), a sensorimotor gating phenomenon, which is impaired in several information processing disorders. Finally, we review recent work in the M-cell system which focuses on the cellular mechanisms of PPI and its modulation by serotonin and dopamine.

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Contents

1. Introduction . . . 00
 1.1. Startle circuits of vertebrates . . . 00
  1.1.1. The Mauthner-cell startle circuit of fishes . . . 00
  1.1.2. The startle circuit of mammals . . . 00
 1.2. Significant M-cell inputs from the acoustico-lateralis system . . . 00
 1.3. Significant M-cell inputs from the visual system . . . 00
2. Plasticity in the startle circuit . . . 00
 2.1. Temperature modulation of startle response . . . 00
 2.2. Aminergic modulation of startle response. . . . 00
 2.3. Social modulation of startle responses . . . 00
3. Sensorimotor gating in fishes . . . 00
4. Modulation of auditory PPI . . . 00
5. Conclusions and future avenues . . . 00
Acknowledgements . . . 00
References . . . 00

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1. Introduction

All animals display some form of defensive reflexes to avoid potential injury. One prominent example is startle behavior. In addition to its vital importance, study of startle or other protective reflexes has contributed to fundamental advances in neuroscience. For example, study of the gill withdrawal reflex in *Aplysia* (Croll, 2003; Glanzman, 2009; Kandel, 1976), the tail flip in crayfish (Edwards et al., 1999), the eye blink response in humans (Graham, 1975), and the C-start in fishes (Eaton et al., 1991; Korn and Faber, 2005; Zottoli et al., 1999) provided critical insights to issues ranging from the behavioral and neural basis of habituation, sensitization, fear conditioning and sensorimotor gating (Koch, 1999) to the advancement of the command-neuron concept (Eaton et al., 2001; Edwards et al., 1999), the cellular and molecular basis of learning and memory (Glanzman, 2009), and the research on neural networks implementing decision-making (Edwards et al., 1999; Korn and Faber, 2005).

The startle response typically involves fast and massive activation of head and body muscles in response to threatening and intense sensory stimuli. As such, startle is a protective reflex that also constitutes often the initial phase of a more elaborate escape behavior that involves other motor systems, although the latter function is less clear in mammals (Yeomans and Frankland, 1995; Yeomans et al., 2002). Despite its vital role, frequent or unnecessary startles need to be avoided since they disrupt other important behaviors. These constrains are reflected in the structure of startle networks, which are typically centered around large, (i.e. high-threshold) 'decision' neuron/s that integrate vast excitatory and inhibitory inputs from multiple sense organ, and control the activation of large muscle areas (Eaton, 1984). Startle can be an all-or-none behavior mediated by a pair of bilateral decision neurons [e.g. crayfish (Edwards et al., 1999; Wine and Krasne, 1972), squid (Otis and Gilly, 1990), teleost fish (Eaton et al., 1977)], or a graded response mediated by the sequential recruitment of numerous (50–60) decision neurons in distinct brain nuclei [mammals (Lingenhöhl and Friauf, 1994; Yeomans and Frankland, 1995), see also below]. In that context, it is interesting to note that even all-or none startle systems are typically complemented by parallel multifiber pathways that modulate either the later parts of a startle response and/or produce graded yet flexible startle-like behaviors by themselves (Bhatt et al., 2007; Fetcho and Faber, 1988; Fetcho and O'Malley, 1995; Herberholz et al., 2004; Otis and Gilly, 1990; Preuss and Gilly, 2000; Wine and Krasne, 1972).

Startle behavior is distinct, relatively easy to quantify, and the large size and small number of startle circuit neurons allows in many cases their identification in the CNS for anatomical, electrophysiological and molecular studies (Cachope and Pereda, 2012; Curti and Pereda, 2010; Eaton, 1984; Korn and Faber, 2005; Pereda et al., 2004). Particularly important for this review however, is the fact that startle circuits provide an excellent preparation and readout for studying the sensory integration processes that underlie the initiation of startle behavior including its modification by environmental context and physiological state of an animal.

Indeed, startle plasticity is widespread and subject to intense research. Startle response can be increased by conditioned or unconditioned aversive manipulations as an electrical foot shock (Boulis and Davis, 1989; Davis, 1974), habituated by repeated presentation of the startling stimulus (Aljure et al., 1980; Davis et al., 1982; Typlt et al., 2013; Valsamis and Schmid, 2011) and it can be enhanced by fear, anxiety and related states [reviewed in Fendt and Koch (2013)]. Failure to adjust startle threshold levels has been connected to several fear and anxiety disorders (Dreissen et al., 2012; Ganser et al., 2013; Grillon, 2002, 2008) and startle testing is a well established assay to investigate anxiety-like behaviors in several species (Pittman and Lott, 2014).

One of the most intensively studied aspects in startle plasticity is prepulse inhibition (PPI) of the auditory startle response. In the PPI paradigm, the startle response to a strong stimulus is reduced when it is preceded by a weak prepulse of the same or a different modality by 30–500 ms (Campeau and Davis, 1995; Hoffman and Ison, 1980; Weber and Swerdlow, 2008). The difference on the intensity (or probability) of the startle response with or without a sensory prepulse provides an operational measure of the inhibition induced by the prepulse. This reduction is thought to reflect the subject's sensorimotor gating levels (Braff et al., 2001a). It has been proposed that the functional role of PPI is protection from a disruptive event such as startle at an early stage of stimulus information processing (Graham, 1975). Underlining its importance as a basic filtering mechanism, PPI of startle response has been extensively studied in rodents (Braff et al., 2001a; Swerdlow et al., 2008) but also in sea slugs (Frost et al., 2003; Lee et al., 2012; Mongeluzi et al., 1998), teleost fishes (Burgess and Granato, 2007; Kohashi and Oda, 2008; Neumeister et al., 2008) and birds (Schall et al., 1999). These studies suggest cross-species similarities for some of the mechanisms that regulate startle plasticity and PPI (Siegel et al., 2013). PPI has also attracted considerable attention from biomedical research as schizophrenia patients show deficits in PPI although these deficits are not unique of schizophrenia but are also present in bipolar mania, Huntington's disease, panic disorder and other sensory processing disorders (Braff et al., 2001b; van den Buuse, 2010; Siegel et al., 2013).

Given the biological and medical relevance of understanding startle and startle plasticity mechanisms, the importance of developing animal models to study startle behavior and PPI has been repeatedly acknowledged (Koch, 2013; Siegel et al., 2013). Great progress has been made in elucidating the circuits, neuropharmacology, and genetics of PPI in rodents and linking these findings to a range of information processing disorders (Braff et al., 2008; Swerdlow et al., 2008). However, some methodological limitations continue to constrain the field. For example, reliably accessing the startle circuitry relevant to PPI with *in vivo* electrophysiology remains difficult in rodents (Lingenhöhl and Friauf, 1994). *In vivo* experiments are critical, however, since they allow physiological stimulation of the inhibitory pathway/s active during PPI, a requirement to identify the effector mechanisms underlying PPI.

The thesis of the current review is that the startle system of teleost fishes, the Mauthner-cell (M-cell) is ideally suited to advance such mechanistic studies of startle plasticity.

Several recent reviews have focused on aspects of plasticity in the M-cell circuit (Cachope and Pereda, 2012; Curti and Pereda, 2010; Kano, 1995; Korn and Faber, 1996, 2005; Pereda et al., 2004; Zottoli and Faber, 2000; Zottoli et al., 1995) but here we will specifically focus on recent findings on cellular mechanisms regulating startle plasticity and particularly PPI in the primary auditory startle circuit of teleost fishes. We start describing the startle circuit in fishes and mammals to stress their common organizing principles, followed by an account of main sensory inputs to the Mauthner cell. Next we review environmental factors capable of modulating the startle response and the role of dopamine and serotonin in M-cell plasticity. A description of PPI and its modulation by dopamine follows, and we conclude with an overall discussion of the results presented and open questions for the future.

1.1. Startle circuits of vertebrates

Escape behaviors are critical for survival as they allow predator avoidance, and most vertebrates, including mammals, have highly

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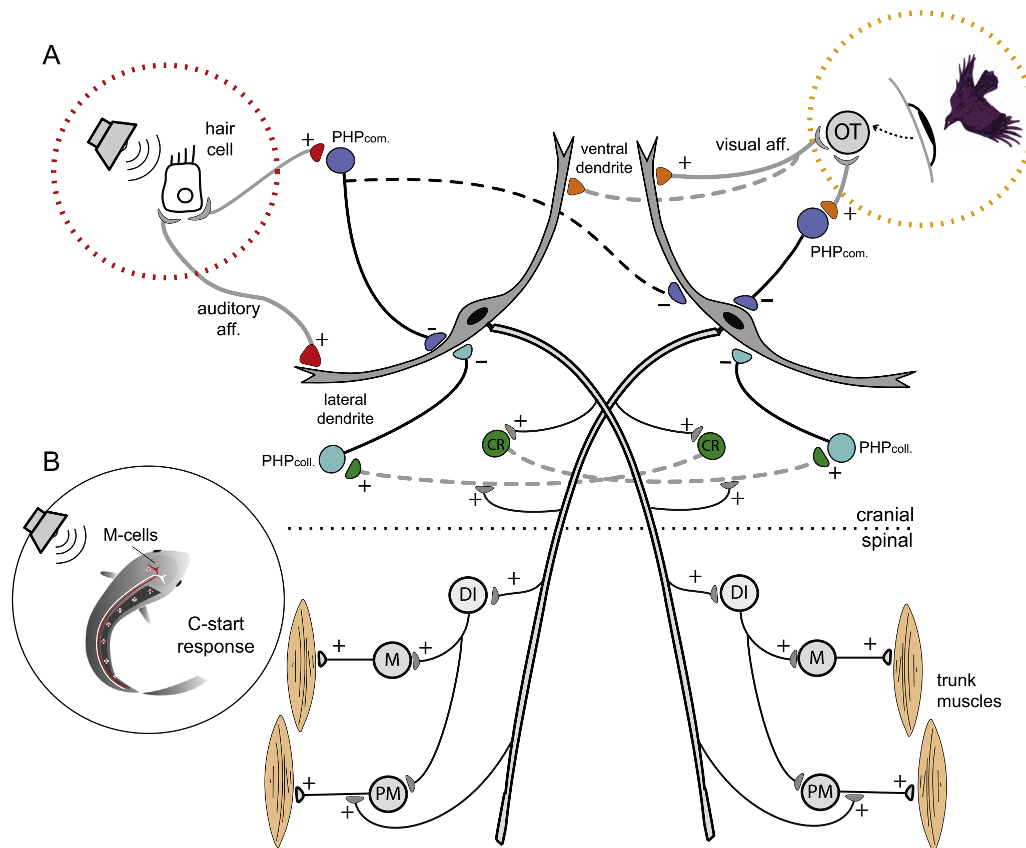

Fig. 1. The Mauthner cell circuit. Schematic shows the paired Mauthner cells (M-cells), their visual and statoacoustic inputs and cranial inhibitory networks. Each M-cell receives bilateral visual inputs and ipsilateral auditory inputs. The schematic shows only the left auditory afferents (red) and the right visual afferents (orange). The auditory pathway is direct, as hair cells activate auditory nerve afferents with synapses on the M-cell's lateral dendrite and also excite bilaterally-projecting feedforward inhibitory interneurons, the commissural PHP cells (blue). The collateral PHP neuron population (coll., light blue) mediates recurrent (feedback) inhibition triggered by firing of either ipsilateral or contralateral M-cells that is conveyed through the cranial relay neurons (CR, green). The polysynaptic visual pathway conveys information from the retina to the optic tectum (OT) which sends afferents that contact both M-cells ventral dendrite. M-cell axons exit the medulla through the spinal cord to make direct contact with primary motoneurons (PM) and indirect contanct with other motoneurons (M) through a set of interneurons (DI). Spinal inhibitory networks and cranial motoneurons are omitted to simplify the schematic. A single action potential in one of the M-cell produces contraction of contralateral trunk muscles producing the characteristic C-shape that initiates the startle response or C-start (B). Adapted from Faber et al. (1989) and Pfaff et al. (2012).

developed neural networks for detecting an approaching predator, deciding when to initiate the escape and the trajectory to follow.

1.1.1. The Mauthner-cell startle circuit of fishes

The startle response pattern is suggestive of a protective function against injury from potential threats and of a preparatory phase for the flight/fight response (Koch, 1999; Yeomans et al., 2002), however, its functional role in mammals is not always clear as startle itself does not necessarily imply an escape (Yeomans and Frankland, 1995; Yeomans et al., 2002). In many species of teleost fish, however, startle is part of a true escape behavior with a clear-cut function: interrupt all ongoing behaviors to follow a relatively stereotyped motor sequence resulting in an escape reaction to the threat (Batty, 1989; Dill, 1974; Eaton et al., 1991; Faber et al., 1989; Kohashi and Oda, 2008; Neumeister et al., 2010; Preuss and Faber, 2003; Whitaker et al., 2011). This escape sequence starts with a fast and massive unilateral contraction of trunk muscles resulting in the fish assuming a C-shape (stage 1) followed by a return stroke in the opposite direction ('return flip') where the tail straightens propelling the animal away from potential danger (stage 2) (Domenici and Blake, 1997; Eaton et al., 1977, 2001; Zottoli, 1977).

Stage one of the C-start is initiated by a pair of large brainstem neurons, the Mauthner cells (M-cells), which are prototypical integrate-and-fire neurons that receive massive sensory inputs from the acoustic-lateralis, vestibular, visual, and somatosensory systems (Canfield, 2003; Furukawa and Ishii, 1967; Korn and Faber, 2005; Mirjany and Faber, 2011; Preuss and Faber, 2003; Preuss et al., 2006; Szabo et al., 2006, 2007) (Fig. 1). A single action potential (AP) in one of the two M-cells is sufficient to activate motor networks on the contralateral trunk muscles and simultaneously inhibit those on the ipsilateral side (Eaton and Farley, 1975; Eaton et al., 2001; Faber et al., 1989; Fetcho and Faber, 1988; Nissanov et al., 1990; Weiss et al., 2006; Zottoli, 1977). Ablation of M-cells in goldfish or zebrafish (DiDomenico et al., 1988; Eaton et al., 1982; Issa et al., 2011; Liu and Fetcho, 1999; Zottoli et al., 1999) or evolutionary loss of M-cells (Greenwood et al., 2010) eliminates short latency C-start escapes.

Stage two of the C-start determines the final escape trajectory, which is influenced by for example, stimulus direction and obstructions in the environment (Eaton and Emberley, 1991; Eaton et al., 1988, 2001; Foreman and Eaton, 1993; Mirjany et al., 2011; Nissanov et al., 1990; Preuss and Faber, 2003). This flexibility depends at least partly on the activation of other reticulospinal neurons, such as the M-cell homologous that in conjunction with the M-cell are collectively known as the brainstem escape network (BEN) (Canfield, 2006; Eaton et al., 2001; Gahtan et al., 2002; Weiss et al., 2006).

Indeed, the Mauthner cell homologous are electrically connected with the M-cell (Neki et al., 2014), and receive auditory inputs although their firing thresholds and projection patterns are different from the M-cell (Nakayama and Oda, 2004). In addition to their putative role for stage 2, thay can also produce C-start

type behaviors, albeit with longer latencies when the M-cell is eliminated from the circuit (Kohashi and Oda, 2008; Kohashi et al., 2012; Liu and Fetcho, 1999).

In summary, activity in either of the two M-cells decide the likelihood, latency, and initial turn direction of the response (Hatta and Korn, 1999; Korn and Faber, 2005; Preuss and Faber, 2003; Preuss et al., 2006; Zottoli et al., 1999), with other neurons in the BEN adding necessary plasticity to the expression of the behavior.

The M-cell dendritic morphology is relatively simple (Fig. 1): two primary dendrites, one lateral and one ventral, each extending up to 500 μm from the soma (Korn and Faber, 2005; Faber and Korn, 1978). Because of its size, morphology, and electrophysiological signature (an unusually large extracellular field potential), it is possible to record reliably from the M-cell soma and its dendrites *in vivo* (Faber and Korn, 1978; Furshpan and Furukawa, 1962; Korn and Faber, 2005; Preuss et al., 2006). The excitatory sensory inputs to the M-cell include afferent inputs from the auditory (Furshpan and Furukawa, 1962; Preuss and Faber, 2003; Szabo et al., 2006), vestibular (Zottoli and Faber, 1979), visual (Preuss et al., 2006; Zottoli et al., 1987), somatosensory systems (Chang et al., 1987) and lateral line (Faber and Korn, 1975; Mirjany and Faber, 2011). However, the two sensory systems that most often have been shown to trigger a startle response with physiological stimuli are an intense sound or a gradually increasing visual or auditory loom stimuli (Eaton et al., 1988; Preuss et al., 2006; Weiss et al., 2006; Zottoli, 1977). The fact that subthreshold LED flashes can bias the direction of an escape evoked by an abrupt sound highlights multimodal aspects of sensory processing in the M-cell (Canfield, 2003, 2006). Similar modulatory functions have been shown for lateral line inputs to the M-cell, which by themselves are insufficient to evoke an action potential in the M-cell (Faber and Korn, 1975; Mirjany and Faber, 2011). Moreover, the relative efficacy of a given sensory modality in the M-cell can change during development. Zebrafish shows a transition from somatosensory to statoacoustic nerve as the preferred input for the M-cell during development (Kohashi et al., 2012).

The sensory input to the M-cell studied in most detail is mediated by the monosynaptic connection from a group of large afferents of the posterior branch of the eight (auditory) nerve (Furshpan, 1964; Nakajima, 1974; Tuttle et al., 1986). These saccular fibers terminate on the lateral dendrite as single club endings, 10–15 μm in diameter, and they have mixed electrotonic and chemical synapses with the dendrite (Pereda et al., 2003, 2004). This constitutes a rapid pathway with a latency of 1–2 ms when using acoustic stimuli in air (Canfield, 2003; Casagrand et al., 1999; Preuss and Faber, 2003; Szabo et al., 2006), contrasting with the slower polysynaptic visual pathway coming from the retina through the optic tectum and contacting the M-cell in its ventral dendrite, which has a latency of 12–22 ms when using short (10–20 ms) visual pulses (Canfield, 2003, 2006; Weiss et al., 2006).

Inhibition has been shown to serve two major roles in the M-cell. Feedforward inhibition sets the threshold for escape, regulating M-cell excitability in response to sensory stimuli, to ensure that only sufficiently strong and abrupt stimuli trigger the M-cell (Faber and Korn, 1978). Feedforward inhibition is also involved in information processing by restricting the spatial spread of excitation and its duration, favoring the detection of temporal changes in a signal (Faber et al., 1991; Preuss and Faber, 2003; Preuss et al., 2006). For the auditory pathway this is attained by commissural passive hyperpolarizing potential (PHP) exhibiting neurons, which receive mixed electric and synaptic inputs from primary afferents and provide chemical inhibition to the lateral dendrite and M-cell soma within a synaptic delay (Fig. 1). Interestingly, the same pathway also mediates an instantaneous electrical field (ephaptic) inhibition coincident with presynaptic action potentials at the M-cell axon hillock (Furukawa and Furshpan, 1963; Furukawa et al., 1963; Takahashi et al., 2002; Weiss et al., 2008) (Fig. 1). Another source of inhibition is a recurrent pathway triggered by the M-cell spike that avoids repetitive firing of the activated M-cell as well as firing of the contralateral M-cell (reciprocal inhibition) (Faber et al., 1989; Takahashi et al., 2002). This feedback pathway involves cranial relay neurons (CR, Fig. 1), which in turn bilaterally activate inhibitory PHP neurons, but also cranial motor neurons that evoke startle-related opercular, ocular, jaw and pectoral fin movements (Auerbach and Bennett, 1969; Diamond, 1971; Hackett and Buchheim, 1984; Hackett and Faber, 1983).

In summary, in the M-cell startle network, threshold to startling stimuli is determined ultimately by the balance between excitatory and inhibitory mechanisms acting in the startle "decision-making" circuit (Faber et al., 1989). The downstream network of the M-cell includes interneurons and motorneurons forming cranial and spinal networks that ultimately mediate the execution of the escape response (Bhatt et al., 2007; Faber et al., 1989; Fetcho and Faber, 1988; Fetcho and McLean, 2010). Plasticity in the M-cell output synapses or in the downstream elements could be translated to behavioral plasticity of startle behavior (Aljure et al., 1980; Gelman et al., 2011) but here we will concentrate on plasticity affecting the 'decision making' process (e.g. plasticity affecting the firing probability of the M-cell).

1.1.2. The startle circuit of mammals

The circuit for the mammalian startle reflex shares many organizing principles with those for fast escape responses in lower vertebrates and invertebrates. In mammals, the primary acoustic startle circuit encompasses two central relay stations between the sensory periphery (cochlea) and the motor and premotor neurons that execute the motor response. Auditory input enters the cochlear nuclei where the cochlear root neurons are, which in turn excite a small cluster of about 60 giant neurons (PnC neurons) from the caudal pontine reticular formation that innervate cranial and spinal motoneurons (Lingenhöhl and Friauf, 1992, 1994). The graded nature of the escape mammalian startle responses is partially a consequence of startle being the result of the activation of a population of neurons (and not a single neuron).

Similarly to M-cells, PnC neurons are activated by high-intensity acoustic stimulation at latencies of 3–8 ms (Lingenhöhl and Friauf, 1992) and have a relatively low resistance and large membrane time constant (Faber et al., 1989; Wagner and Mack, 1998). Lessions of the PnC neurons block the startle response elicited by acoustic or air-puff stimuli (Koch et al., 1992; Lee et al., 1996). Trigeminal or auditory stimuli reach the PnC neurons through large-diameter, myelinated axons projecting directly from the cochlear, vestibular and spinal trigeminal nuclei of rats (Lee et al., 1996; Lingenhöhl and Friauf, 1994). In turn, PnC giant neurons project directly and indirectly to motoneurons in the brain stem and spinal cord via a large and fast-conducting axon (Wu et al., 1988). One of the major difference between the M-cell circuit and the PnC circuit is that whereas only one M-cell is activated producing unilateral contraction of the trunk muscles, the mammalian response is bilateral, with reticulospinal neurons (PnC neurons) on both sides of the midline being excited (Lee et al., 1996). Besides this fact, the mammalian startle networks parallels the fish auditory startle network at every stage, the properties of this circuit performing a very fast response minimizing the number of synapses between the sensory input and the motor output and using large caliber myelinated fibers, electrical synapses and establishing direct contacts with motoneurons.

1.2. Significant M-cell inputs from the acoustico-lateralis system

Up to 100 eight nerve (auditory) afferent inputs impinge onto the mid distal M-cell lateral dendrite and provide massive

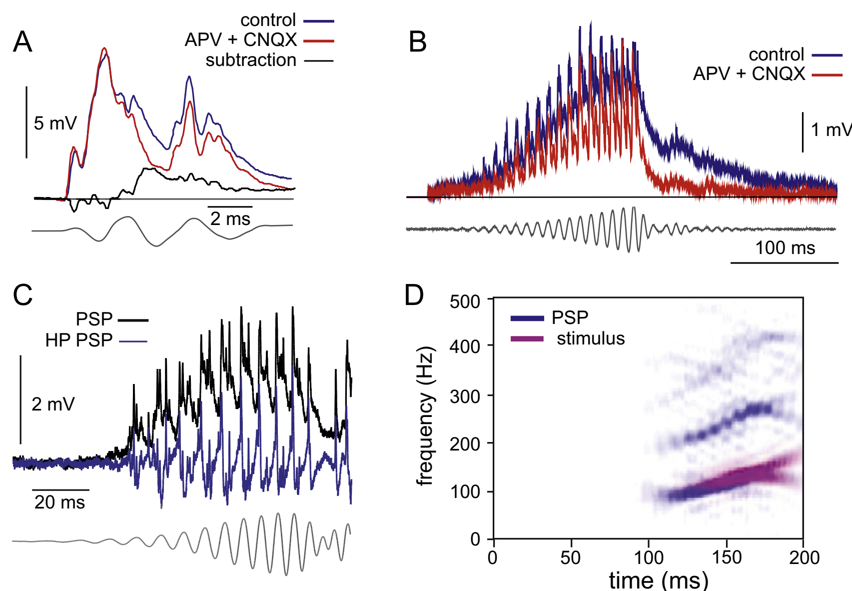

Fig. 2. Auditory representation in the M-cell. (A) Example traces of postsynaptic potentials (PSPs) recorded in the M-cell proximal lateral dendrite in response to sound pip (200 Hz, 147 dB re. 1 μPa in water, lower trace) before (blue) and after (red) superfusion with ionotropic glutamate receptor antagonists cocktail (APV 100 μM, CNQX 100 μM) and subtraction of both traces (black). The gray line indicates the RMP baseline. Note that while part of the slow component of the PSP is insensitive to glutamate blockers, the subtraction trace reveals a significant glutamate blockers-sensitive component. (B) Somatically recorded M-cell PSPs in response to an AM stimulus (200 Hz, 0–90 dB in 100 ms, lower trace) before (blue) and after (red) superfusion with ionotropic glutamatergic antagonist cocktail (same as in A). The gray line indicates the RMP baseline. Note the marked decrease in the underlying envelope of the PSP as compared to A. (C) Somatically recorded M-cell PSPs (black) in response to FM/AM stimulus (50 Hz initial frequency, 109 dB; 200 ms, lower trace) and its high-pass filtered representation (blue). All recordings (A–C) were obtained with KAc-filled electrodes. (D) Superimposed joint time–frequency spectrograms of the high-pass filtered response (blue, fundamental and two harmonics) and the sound stimulus (red). The high frequency component follows the changing sound frequency. Adapted from Szabo et al. (2006).

excitatory input via mixed electrical and chemical synapses (Lin and Faber, 1988; Pereda et al., 2004). The size of these primary afferent terminals (up to 15 μm) and the M-cell dendrite allows for simultaneous pre- and postsynaptic recordings and the characterization of their role in sensory processing of acoustic stimuli. Interestingly, paired recordings suggest that >80% of the chemical connections are silent (Lin and Faber, 1988), i.e. a presynaptic AP produces a postsynaptic electrotonic potential but no chemically mediated excitatory postsynaptic potential (EPSP). The chemical component seems to be recruited only when a large fraction of the afferent fibers is simultaneously activated as with direct electrical stimulation to the eight nerve fibers (Pereda et al., 1992, 1994). Accordingly, M-cell EPSPs evoked by short sound pips (single sine waves, Fig. 2A) and longer lasting frequency (FM) or amplitude (AM) modulated tone bursts (Fig. 2B) show two components namely, one that is phasic and phase locked to stimulus frequency and its first harmonic (Fig. 2C and D), and a sustained underlying depolarization with a slower onset that tracks the amplitude of the stimulus (Szabo et al., 2006). Blocking of the chemical synaptic transmission revealed that the fast components are essentially electrotonic coupling potentials (Fig. 2B) of eight nerve APs, whereas the underlying slow EPSP is largely glutamatergic (Szabo et al., 2006). Together with the demonstration of silent synapses (see above) these results suggest that the chemical component of the mixed synapse is weak or functionally silent when single sound pips or short tone bursts are used (Szabo et al., 2006). Chemical transmission becomes more prominent with longer lasting stimuli and with repetitive stimulation (Cachope et al., 2007; Curti and Pereda, 2004).

The M-cell also receives input from the anterior and posterior lateral line nerves (Faber and Korn, 1975). These fibers contact the M-cell proximal lateral dendrite and soma with mixed (chemical and electrical) synapses and provide weak but essential modulatory information for the left–right directionality of goldfish startle response (Mirjany and Faber, 2011; Mirjany et al., 2011).

1.3. Significant M-cell inputs from the visual system

Each M-cell receives binocular visual input from both ipsi and contralateral optic tectum projections that end in the distal ventral dendrite (Zottoli et al., 1987). In goldfish, brief visual stimuli produced by a flash or a black disk projected on top of the animal typically do not elicit startles but do produce subthreshold EPSPs in the M-cell (Fig. 3A and B). As noted, similar stimuli are capable of modulating the auditory startle response in the African cichlid fish *Astatotilapia burtoni* (Canfield, 2003, 2006).

Startle responses however, can be reliably evoked in goldfish by visual loom stimuli, i.e., by motion stimuli that stimulate an approaching object on collision course (Batty, 1989; Dill, 1974; Preuss et al., 2006; Webb, 1986). Intracellular *in vivo* M-cell recordings show graded depolarizing EPSPs (Fig. 3C), and chronic recordings in freely moving animals confirmed that these escapes are initiated by a M-cell AP (Preuss et al., 2006; Weiss et al., 2006).

As noted, acoustic and visual information converge in the M-cell and both modalities and most predator strikes will typically involve visual and mechanosensory components, e.g. a diving bird breaking the water surface. Indeed, the M-cell has been shown to integrate visual, statoacoustical and somatosensory inputs for an appropriate startle behavior (Canfield, 2003; Mirjany et al., 2011 and Medan and Preuss unpublished results).

2. Plasticity in the startle circuit

The M-cell network has a vital function (i.e. escape from predation) but on the other hand unnecessary escapes would be non-adaptive. Therefore, it becomes apparent the necessity of a very robust and reliable response on one hand, but of an adaptable and plastic response on the other (Pfaff et al., 2012). In the startle network specifically, thresholds to startling stimuli will be determined ultimately by the balance between excitatory and inhibitory

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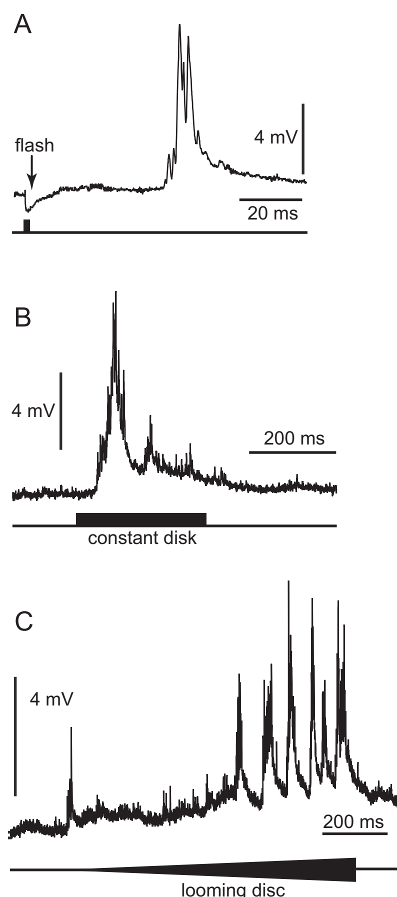

Fig. 3. Visual representation in the M-cell. (A) Visual response recorded in the M-cell ventral dendrite to a 1 ms flash recorded *in vivo*. Note increased latency compared to auditory stimuli (Fig. 2). (B) Visual response recorded in the ventral dendrite to the image of a black disc projected on a white screen on top of the animal subtending a view angle of about 50° in the animal's retina. Note the response decays before the stimulus offset. (C) Response to a visual loom stimulus (subtending retinal view angles from 0° to 113° in 900 ms) recorded in the ventral dendrite of the same M-cell as in B. All recordings (A–C) were obtained with KAc-filled electrodes. Note that the response peaks before the stimulus reaches its maximum expansion and persists throughout the rest of the stimulus duration. (Medan and Preuss, unpublished).

mechanisms acting on the startle "decision-making" circuit along with changes occurring in the M-cell excitability itself (Faber et al., 1989).

2.1. Temperature modulation of startle response

Fishes are poikilotherm animals that maintain a coordinated behavior over a range of naturally occurring temperature changes. Thermal plasticity of the startle circuit is critical for temperature tolerance and determines the temperature-dependent effects on performance (Montgomery and Macdonald, 1990; Schulte et al., 2011).

In goldfish, an acute 10 °C temperature drop profoundly affects auditory evoked C-starts: the response is delayed by about 20 ms, the angular velocity and acceleration of the head turn is diminished (Fig. 4A1 and A2) and the total distance traveled within the first 100 ms after stimulus onset is significantly reduced (Fig. 4A3). Interestingly however, the likelihood for an escape increases significantly after cooling (see Fig. 6 in Preuss and Faber, 2003) due to an increase in M-cell excitability. The latter is mediated by an increase in M-cell input resistance (Fig. 4A5) and a reduced and delayed onset of feedforward inhibition to the M-cell (Preuss and Faber, 2003). In a natural context, such an increase in M-cell excitability will increase the distance at which a fish responds to an approaching predator and thus might compensate for the decremental effects of cooling on the motor system.

Another critical aspect of the C-start is its directionality and the ability of the fish to avoid obstacles (Eaton and Emberley, 1991). Cooling doubles the frequency of inappropriate turns toward the stimulus and increases escapes "into the wall" of the aquarium (Fig. 4A4) which would be detrimental in natural conditions. In order to explain the sensitivity of response directionality to acute cooling one has to consider that startle stimuli typically bring both M-cell close to threshold and only small differences in the excitatory/inhibitory balance within both M-cells 'decide' which reaches threshold first. Accordingly, the observed overall increase in M-cell excitability and decrease in inhibition is a likely cause for the directional deficits after acute cooling. Further evidence for this notion comes from a study by Szabo and colleagues (Szabo et al., 2008), which showed that acclimating animals to cold temperatures predominantly restores M-cell inhibition and directionality.

2.2. Aminergic modulation of startle response

Dopaminergic modulation of startle behavior has been reported decades ago in rodents (Mansbach et al., 1988) although the locus or loci of action of dopamine are still unclear. The synaptic bed of the M-cell lateral dendrite is innervated by thin fibers containing small dopamine-positive varicosities that project from forebrain nuclei (O'Connell et al., 2011; Pereda et al., 1992). Dopamine enhances the synaptic EPSPs in the M-cell lateral dendrite in response to electrical stimulation of the auditory afferents (8th nerve). This modulation affects both components of the mixed synapse, i.e. enhances the coupling potential of electrical synapses and the glutamatergic chemical transmission (Pereda et al., 1992). Dopamine action is mediated through the cAMP and PKA second messenger pathway affecting glutamate ionotropic receptors expressed in the chemical excitatory synapse (Pereda et al., 1994). Dopamine can affect startle also upstream of the primary startle circuit. Experiments in larval zebrafish using a cross-modal paradigm in which a preceding flash enhanced a sound-evoked startle response showed that the visual enhancement of the auditory startle reflex required light-responsive dopaminergic neurons of the caudal hypothalamus and D1 dopamine receptor activation. The enhancement is produced by an increase in the auditory-evoked response in the M-cell accounted for by an increase in the signal-to noise ratio of the auditory afferents and the efficacy of the auditory nerve to M-cell synapse (Mu et al., 2012).

The M-cells are also innervated by 5-HT projections (Gotow et al., 1990; Whitaker et al., 2011) which have their highest densities in the ventral dendrite, although 5HT afferents are also present in the soma (Petrov et al., 1991). Mintz and Korn (1991) demonstrated a serotonergic modulation of the inhibitory glycinergic afferents as well as postsynaptic modulation of a voltage-dependent inward rectifier in the M-cell. Recently, it has been shown that only 5-HT5A and 5-HT6 receptors are expressed in the M-cell (Whitaker et al., 2011) and that specific antagonists of 5-HT5A receptor decrease startle probability (Curtin et al., 2013) (Fig. 4B1).

Consistent with this notion Curtin et al. (2013) showed that a 5-HT5A receptor antagonist attenuated the M-cell synaptic response to acoustic stimuli (Fig. 4B2, B3). This effect is mediated by a decrease in the input resistance of the M-cell itself (i.e. a postsynaptic mechanism) reflected as a decrease in the voltage vs. current curve of the M-cell as well as in a reduction of the antidromic AP amplitude (Fig. 4B4, B5). Blocking 5-HT5A receptor decreases M-cell membrane resistance both close to resting membrane potential and close to firing threshold, suggesting that the affected con-

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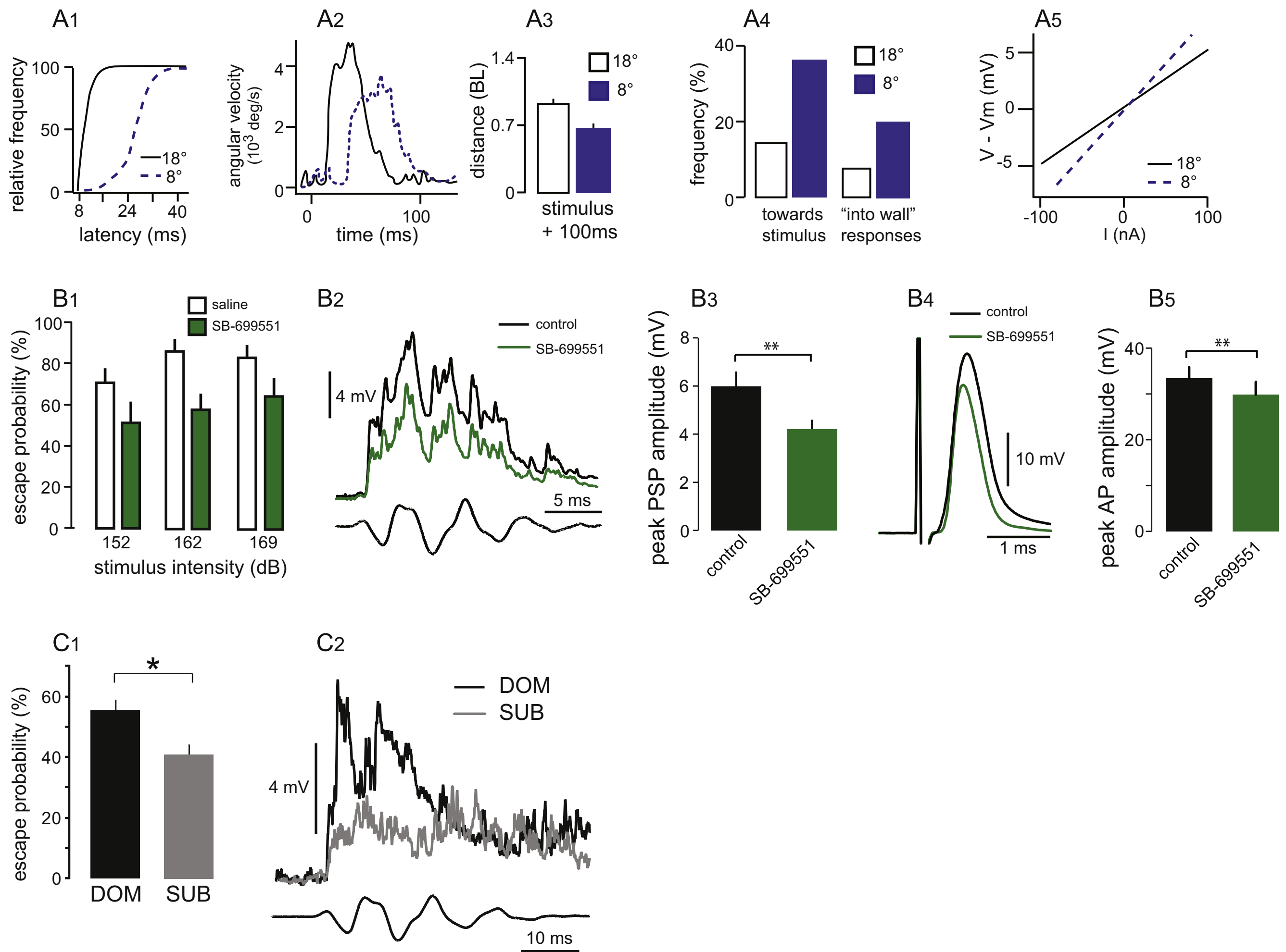

Fig. 4. Mechanisms of startle plasticity in the M-cell. (A) Effects of cooling on sound evoked C-starts (200 Hz pips). *A1*, cumulative distribution of response latency at 18 °C ($N = 27$, $n = 53$, solid black) and 8 °C ($N = 33$, $n = 48$, dashed blue). This measure increases significantly after cooling from a mean (±SEM) of 11.5 ± 0.3 ms at 18 °C to 27.3 ± 0.8 ms at 8 °C ($F = 202.66$; df = 1.74; $p < 0.001$). Similarly, cooling decreases the angular velocity of the fish center of mass (*A2*), kinematics correspond to two escapes performed by the same animal at 18 °C (solid black) and 8 °C (dashed blue). Cooling also decreases significantly the mean distance traveled in the first 100 ms after stimulus onset (*A3*, in body length, BL, $F = 12.66$, df = 1, 33; $^{*}p < 0.002$; 18 °C: $N = 6$, $n = 18$ and 8 °C: $N = 6$, $n = 17$). *A4*, lower temperature increases the frequency of inappropriate responses ($p < 0.01$, X^2 test), i.e. escapes toward the stimulus from 14% at 18 °C ($N = 24$; $n = 66$) to 36% at 8 °C ($N = 27$; $n = 62$) and turning into the wall (6% at 18 °C vs. 20% at 8 °C). *A5*, current–voltage relationship obtained by injecting square current pulses in the dendrite and recording in the soma at 8 °C and 18 °C. The transfer resistance ($V_{soma}/I_{dendrite}$) shows an increase from 53 kΩ at 18 °C to 85 kΩ at 8 °C ($N = 2$). *N*: number of animals, *n*: number of escapes. Adapted from Preuss and Faber (2003). (B) Serotonergic modulation in the M-cell system. *B1*, Plots of mean startle response rates (±SEM) in response to acoustic stimuli of different intensities (dB re. to 1 μPa in water), before (open bars) and after blockade of 5HT receptor 5A with SB-699551. *B2*, Representative example of a somatic M-cell PSP (KAc electrodes) in response to sound before (black) and after (green) SB-699551 systemic injection (0.9 mg/kg body weight). Bottom trace indicates sound stimulus (200 Hz pip at 147 dB re. 11 μPa in water). *B3*, Plots of mean peak amplitudes (±SEM) of sound-evoked PSPs for control and SB-699551 conditions ($N = 14$, paired *t* test, $^{**}p = 0.0011$). *B4*, Example trace of antidromically evoked APs recorded in the soma before (black) and after (green) injection of SB-699551 with KAc filled electrodes. *B5*, mean peak amplitude (±SEM) of the antidromically evoked APs in the two conditions ($N = 6$, paired *t* test, $^{**}p = 0.0154$). The decrease in the AP amplitude is indicative of a reduction in M-cell input resistance. Adapted from Curtin et al. (2013). (C) Social modulation of the M-cell system of African cichlid fish. *C1*, Plots of mean escape rates (±SEM in dominant [DOM] and subordinate [SUB] males (DOM: 58.3 ± 2.9, $N = 14$; SUB: 41.7 ± 2.0, $N = 18$, bootstrap analysis, $^{*}p < 0.01$). *C2*, example traces of somatically recorded M-cell PSPs (KAc electrodes) in response to a sound pip in a dominant (black) and a subordinate (gray) cichlid male. Bottom trace indicates sound stimulus (133 dB re. 1 μPa in water). Adapted from Neumeister et al. (2010).

ductance shows no voltage dependence within the physiological range of membrane depolarization. Previous studies by Mintz and Korn (1991) showed that 5-HT modulates a voltage-dependent conductance in the M-cell. However, the voltage-dependent effect was only evident at somewhat unphysiological membrane potentials (∼-100 mV) with the author themselves questioning the biological significance of this conductance (Mintz and Korn, 1991).

Finally, studies on zebrafish larvae found no effect of the serotonin reuptake inhibitor fluoxetine on startle (Griffiths et al., 2012). They did find however an interaction between serotonin and glucocorticoids: in mutants with non-functional glucocortocoids receptors fluoxetine increased spontaneous locomotion and decreased startle (Griffiths et al., 2012). As the net effect of fluoxetine is a general increase of 5HT, all its receptors might be potentially affected, which potentially obscured the interpretation of these results and underlines the use of specific agonists/antagonist to determine the serotoninergic modulation of startle response.

2.3. Social modulation of startle responses

Many fish species establish social ranks which correlate with breeding status, differences in coloration and behavioral displays. In African cichlids fish (*A. burtoni*) dominant (DOMs) males have bright body coloration and display courtship behaviors to attract females to their territory which they vigorously defend against other males (Huntingford, 2012; Maruska and Fernald, 2013; O'Connell and Hofmann, 2012). At the same time, coloration and behavioral activity makes DOMs likely also more conspicuous for predators (Fernald and Hirata, 1977; Maan et al., 2008). Interestingly, this tradeoff is compensated by an increased startle

probability and lower escape threshold when compared to less conspicuous subordinate (SUBs) males (Neumeister et al., 2010) (Fig. 4C1). The behavioral differences are paralleled by a larger auditory evoked EPSP to a given sound stimulus (Fig. 4C2) and a reduction on inhibitory drive impinging on the M-cell in DOMs (Neumeister et al., 2010). Serotonin is one of the prime candidates for mediating this socially controlled plasticity in the M-cell since ketanserin, a 5-HT2A receptor antagonist differentially affects the inhibitory tone in DOMs and SUBs (Whitaker et al., 2011).

3. Sensorimotor gating in fishes

In larval zebrafish or adult goldfish behavioral PPI is observed as a reduction on the all-or-none probability of eliciting an auditory evoked C-start when it is preceded by a non-startling sound (Burgess and Granato, 2007; Neumeister et al., 2008) (Fig. 5A, left). The effective lead times between the non-startling prepulse and the pulse (20–500 ms) are comparable with the effective lead times in mammals (Davis and Gendelman, 1977; Swerdlow et al., 2006) (Fig. 5A, right).

PPI is observed shortly after zebrafish hatches, implying that PPI of startle is a ontogenetically basic mode of startle plasticity (Bhandiwad et al., 2013; Burgess and Granato, 2007). *In vivo* recordings from the M-cell revealed that an auditory prepulse significantly attenuates the synaptic response to a subsequent sound pulse in the M-cell, thus providing a synaptic correlate for PPI evoked by physiological stimuli (Fig. 5B). This attenuation is maximal at short lead times (20 ms) but it is still present with an interstimulus interval (ISI) of 500 ms (Curtin et al., 2013; Medan and Preuss, 2011; Neumeister et al., 2008) (Fig. 5C). The synaptic PPI is largely mediated by a prepulse-induced reduction in input resistance that is particularly apparent in the depolarized M-cell, i.e., close to firing threshold (Fig. 5D, black vs. red trace). Specifically, an auditory prepulse eliminates a membrane nonlinearity (linked to an inward rectifier) that under control conditions (no prepulse) dynamically increases M-cell input resistance during depolarization (Faber and Korn, 1986; Medan and Preuss, 2011; Neumeister et al., 2008) (Fig. 5D, black trace, compared to dashed line, i.e. to a linear response). In addition, auditory prepulses also decrease M-cell input resistance in the non-depolarized membrane which further reduces M-cell excitably during PPI (Curtin et al., 2013; Medan and Preuss, 2011; Neumeister et al., 2008). The combination of these two postsynaptic inhibitory mechanisms can largely account for the time course of PPI, although presynaptic components of PPI cannot be excluded (Frost et al., 2003). Interestingly, prepulse induced changes in input resistance have also been shown in the mammalian startle circuit (Fendt et al., 2001; Yeomans et al., 2010). Taken together, these findings are in line with the view that PPI is mediated within the elementary startle pathway in vertebrates (Fendt et al., 2001; Gómez-Nieto et al., 2013; Li et al., 2009). The existence of a zebrafish mutant with an apparently specific deficit in sensorimotor gating opens the possibility of additional studies on the neural circuit underlying normal and altered PPI of startle (Burgess and Granato, 2007; Hirata et al., 2005).

Importantly, these results also demonstrate that the unique experimental accessibility of the M-cell system for *in vivo* electrophysiology, makes it a particularly well-suited and a promising preparation for studying PPI at the molecular, cellular, and network levels.

4. Modulation of auditory PPI

Decades ago, deficits in auditory PPI were observed in schizophrenic patients; these deficits were partially compensated by

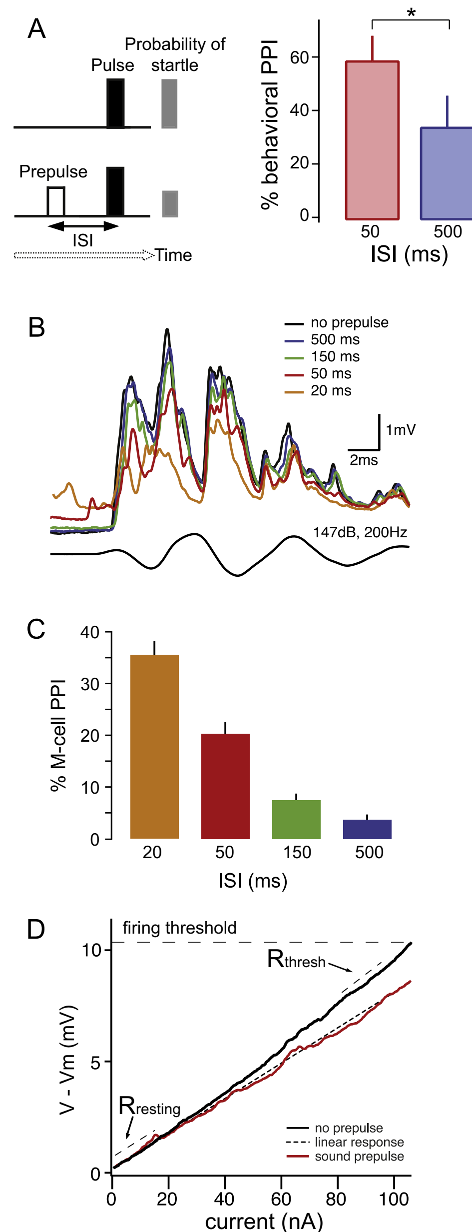

Fig. 5. Prepulse inhibition effect on startle response and in the Mauthner cell. (A) Left: schematic showing the prepulse inhibition (PPI) experimental paradigm. When the Pulse is preceded by a lower intensity Prepulse with an interstimulus interval (ISI) ranging from 20 to 500 ms the startle probability decreases. In behavioral experiments, PPI is typically expressed as PPI effect = 100 − (startle probability with prepulse–pulse/startle probability with pulse) × 100 (Neumeister et al., 2008; Zhang et al., 2000). Right: example of behavioral PPI effect (see text) at two different ISI, 50 and 500 ms. An ISI of 50 ms produces a mean (±SEM) drop of 56.9 ± 9.2% in the startle probability while 500 ms has a significantly smaller effect (25.6 ± 10.9%, $N = 10$, paired t test, $^{*}p < 0.05$) Adapted from Curtin et al. (2013). (B) Effect of the prepulse/pulse interstimulus interval (ISI) on PPI of sound evoked PSPs at the M-cell. Recordings of M-cell PSPs to a sound pip without (black trace) or with a prepulse at 4 distinct ISIs (KAc electrodes). Bottom trace shows sound stimulus (200 Hz, 147 dB re. 1 μPa in water). (C) Quantification of ISI dependence on peak PSP amplitudes (mean ± SEM; $N = 20$) showing a progressive increase in PPI as the ISI diminishes. (D) Postsynaptic effects of a sound prepulse on the M-cell membrane properties. Representative example of the voltage–current (V–I) plots for the M-cell with (red) or without (black) a sound prepulse (50 ms ISI). Note that without a prepulse, the M-cell has initially a linear V–I relationship that becomes increasingly nonlinear for depolarizations above 4–5 mV, compare $R_{resting}$ with $R_{threshold}$ slopes. (Mean ± SEM for no prepulse $R_{resting} = 101 \pm 12$ kΩ and for no sound $R_{threshold} = 116 \pm 16$ kΩ, $N = 15$) A sound prepulse attenuates the nonlinear behavior of the membrane (red, mean ± SEM for 50 ms sound prepulse $R_{resting} = 85 \pm 9$ kΩ and for 50 ms sound prepulse $R_{threshold} = 89 \pm 14$ kΩ, $N = 15$). The hypothetical linear response is showed in dotted line. Adapted from Medan and Preuss (2011).

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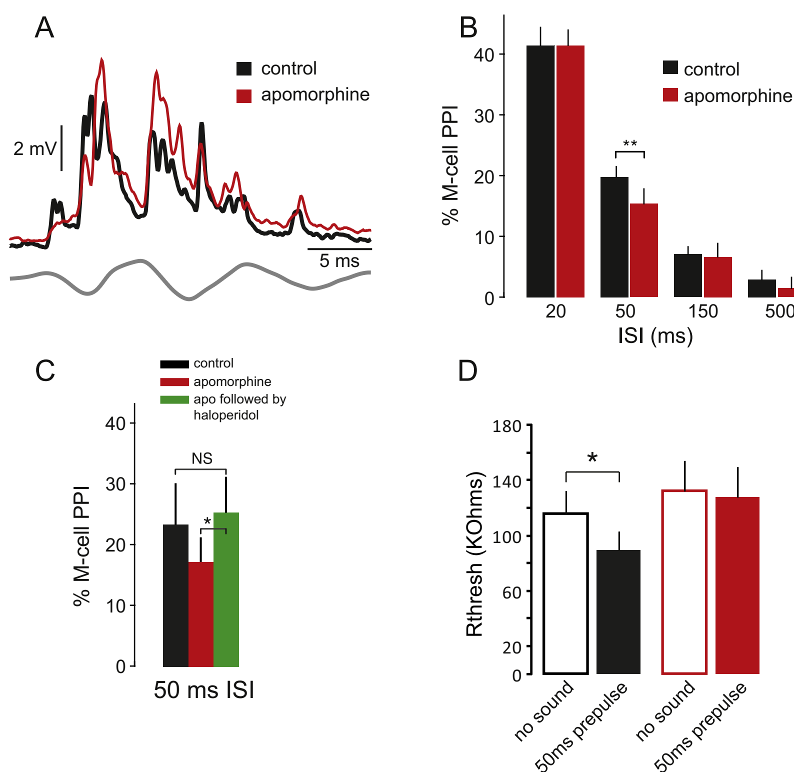

Fig. 6. Dopaminergic modulation of PPI in the Mauthner cell. (A) Somatically recorded M-cell PSPs in response to a sound pip (with a preceding sound prepulse of ISI 50 ms) before (black) and after (red) systemic apomorphine injection (2 mg/kg body weight). Note the increased synaptic response after drug application indicating a decrease in PPI. Bottom trace (gray) shows the sound stimulus (200 Hz, 147 dB re. 1 μPa in water). (B) Plots of the mean PPI effect on the M-cell PSPs (±SEM; $N = 18$) before and after apomorphine. Note the time dependence of PPI disruption by apomorphine: PPI levels are smaller only for 50 ms ISI ($^{*}p < 0.01$). (C) Plots of the mean PPI effect (ISI 50 ms) on the M-cell PSPs (±SEM) before (black) and after (red) apomorphine injection and after subsequent injection of haloperidol (0.6 mg/kg i.m., green). Haloperidol restores PPI levels to control levels ($^{*}p < 0.05$, $N = 4$). NS: not significant. (D) Left two bars: mean (±SEM) input resistance in the depolarized M-cell membrane (R_{thresh}, see text) without (open black bar) and with a preceding prepulse (ISI 50 ms; black bar) indicating a decrease in R_{thresh} with a prepulse ($^{*}p < 0.05$). Apomorphine abolishes this effect increasing R_{thresh} reversing the effect of the auditory prepulse (right two bars). Adapted from Medan and Preuss (2011).

dopamine D2 receptor antagonists (Braff et al., 1978, 2001b). In rodent models, similar deficits in PPI could be pharmacologically reproduced by a dopaminergic agonist (apomorphine) injection (Mansbach et al., 1988). These findings originated a research model centered on the dopaminergic effects on PPI, which has been extended to other neurotransmitters systems, namely glutamate (Brody et al., 2004; Duncan et al., 2006), GABA (Yeomans et al., 2010), serotonin (Dulawa et al., 2000) and acetylcholine (Bosch and Schmid, 2006, 2008; Javitt, 2009; Powell et al., 2009).

Indeed, teleost fishes and mammals exhibit similar pharmacological responses to dopamine and glutamate with respect to PPI. For example, the dopaminergic agonist apomorphine disrupts behavioral PPI in zebrafish which can be restored by haloperidol, a dopamine D2 receptor antagonist (Burgess and Granato, 2007). Recordings in goldfish M-cells showed that apomorphine indeed disrupts the M-cell PPI, what is indicated by an increase of the sound evoked (pulse) M-cell PSP after drug application (Fig. 6A, black vs. red trace). Interestingly, this effect is restricted to a specific prepulse/pulse interstimulus interval of 50 ms (Fig. 6B, Medan and Preuss, 2011). Consistently, we found that haloperidol had no general effect on PPI (indicating that there is no tonic release of dopamine in the circuit), but does restore the apomorphine-induced effects on M-cell PPI at the 50 ms ISI (Fig. 6C). The effect of apomorphine operates by restoring the nonlinear behavior of the M-cell membrane upon depolarization (Fig. 5D), acting specifically on the resistance near the firing threshold [R_{thresh}, see above]. In control conditions, a 50 ms sound prepulse induces a significant drop in resistance (Fig. 6D, left bars) (Medan and Preuss, 2011; Neumeister et al., 2008) while after apomorphine injection the same auditory prepulse fails to reduce the M-cell membrane resistance and hence its nonlinear behavior is restored. In other words, the M-cell becomes insensitive to the prepulse only when it precedes the pulse by 50 ms (Fig. 6D, right bars).

The fact that *in vivo* M-cell recording provides the entire inhibitory PPI time course in a single trial offers a significant experimental advantage. Interestingly, schizophrenia patients show PPI deficits of the eye-blink reflex only at a 60 ms prepulse-pulse interval (Braff et al., 1978, 2001a; Ludewig and Vollenweider, 2002; Swerdlow et al., 2006) emphasizing the importance of studying the time dependency of PPI mechanisms.

5. Conclusions and future avenues

The teleost M-cell system has proven an ideal model for a multi-level analysis of fundamental questions, such as (i) what are the central mechanisms underlying the adaptive modifications of a relatively stereotyped sensorimotor reflex, (ii) what is the role of inhibition in sensory information processing, beyond the classical concept of lateral inhibition and more recently and (iii) for the inhibitory mechanism mediating sensorimotor gating (PPI) in the vertebrate startle circuit.

The experimental accessibility of the M-cell lateral and ventral dendrites for intracellular *in vivo* recordings will continue to provide unique opportunities for understanding multimodal integration and its role in decision-making. The emerging prospects

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of *in vivo* imaging, computational modeling, and genetic or optical manipulation of specific elements of the M-cell startle circuit makes for an exciting and bright future, indeed.

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