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Review Paper

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

Violeta Medan [a,b,*], Thomas Preuss [c]

[a] Dept. de Fisiología y Biología Molecular y Celular, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Intendente Guiraldes 2160, Buenos Aires 1428, Argentina
[b] Instituto de Fisiología, Biología Molecular y Neurociencias, CONICET, Argentina
[c] Psychology Dept. Hunter College, City University of New York, 695 Park Ave., New York, NY 10065, USA

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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.

Contents

* Corresponding author at: Laboratorio de Fisiología y Biología Molecular y Celular, FBMC, FCEN, UBA, Intendente Guiraldes 2160, Buenos Aires 1428, Argentina. Tel.: +54 11 4576 3368.
E-mail addresses: violetamedan@fbmc.fcen.uba.ar (V. Medan), tpreuss@hunter.cuny.edu (T. Preuss).

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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 subjecťs 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