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A review of the neural basis underlying the acoustic startle response with a focus on recent developments in mammals

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ABSTRACT

The startle response consists of whole-body muscle contractions, eye-blink, accelerated heart rate, and freezing in response to a strong, sudden stimulus. It is evolutionarily preserved and can be observed in any animal that can perceive sensory signals, indicating the important protective function of startle. Startle response measurements and its alterations have become a valuable tool for exploring sensorimotor processes and sensory gating, especially in the context of pathologies of psychiatric disorders. The last reviews on the neural substrates underlying acoustic startle were published around 20 years ago. Advancements in methods and techniques have since allowed new insights into acoustic startle mechanisms. This review is focused on the neural circuitry that drives the primary acoustic startle response in mammals. However, there have also been very successful efforts to identify the acoustic startle pathway in other vertebrates and invertebrates in the past decades, so at the end we briefly summarize these studies and comment on the similarities and differences between species.

1. Introduction

The startle response is a protective mechanism in response to strong, sudden stimuli, whereby an involuntary whole-body response is evoked by a startling stimulus. Physiological indications of the startle response include muscle contractions, blinking, accelerated heart rate, and freezing (Koch, 1999; Yeomans et al., 2002). The startle response is evolutionarily highly preserved and startle responses can be observed in essentially any animal that can perceive sensory signals, indicating the important protective function of startle. It is also not a conditioned behaviour because animals will startle upon the first presentation of a startling stimulus. The most common form of startle studied in clinical or experimental settings is the acoustic startle response (ASR) in response to a sudden loud noise or tone. The ASR can be observed from the onset of hearing after the opening of the auditory meatus, for example at around postnatal day 13 in rats (Kungel et al., 1996; Sheets et al., 1988).

In general, the ASR has a short latency of 6- to 8-ms after the onset of sound presentation (Ison et al., 1973), indicating that the primary neural circuit must be short and contains relatively few serial synapses. The precise measurements for latency and magnitude of the ASR are dependent on many factors, including background noise, stimulus rise/fall time, stimulus duration, and sound intensity. For example, sounds with fast rise/fall times are more effective in eliciting a startle response than sounds with gradual onsets. In mammals, ASR magnitude increases and latency decreases as sound intensity increases above the threshold of around 80 dB sound pressure level (SPL; Pilz et al., 1987, 1988).

Considering the many experimental manipulations that can be conducted, ASR has become an excellent and widely used tool for studying behavioural and neural plasticity. The ASR can be modulated by variations in the environment or affective state of the animal, which can lead to habituation, prepulse inhibition, prepulse facilitation, or fear-potentiation of startle. Prepulse inhibition is a measure of sensorimotor gating, habituation is a measure of learning and sensory filtering, and arousal states like fear and anxiety can be measured through conditioning paradigms involving the startle response. Additionally, ASR and/or its modulations have been shown to be altered in disorders such as schizophrenia, autism spectrum disorder, Alzheimer's disease, and panic disorder (Favaron et al., 2010; Sichler et al., 2019; Takahashi and Kamio, 2018), making it a useful behavioural paradigm to study the underlying neural mechanisms of neurological disorders. In brief, the neural basis of short-term habituation is assumed to be intrinsic within the primary ASR pathway, mediated through synaptic plasticity (Davis et al., 1982; Davis and Gendelman, 1977; Simons-Weidenmaier et al.,

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2006; Weber et al., 2002). The neural mechanisms underlying the other startle modulations are extrinsic, presumably through projections from higher brain regions to mainly the PnC, such as from the pedunculopontine tegmental nucleus and the amygdala (for review, see Davis et al., 2003; Gómez-Nieto et al., 2020). However, in order to fully understand the changes in sensorimotor processing associated with various neurological disorders, it is first imperative to understand the neural circuitry underlying the ASR itself.

This review is focused on what is known about the neural circuitry that drives the primary acoustic startle response. The last reviews on the neural substrates underlying ASR were published around 20 years ago (Koch, 1999; Yeomans et al., 2002). Due to advancements in methods and techniques, new insights on startle mechanisms have since been gained, which we summarize in this review. While most of this work has been done in rodents, there have also been very successful efforts to identify the ASR pathway in other vertebrates and invertebrates in the past decades. At the end of this review, we briefly summarize these studies and comment on the similarities and differences between species.

2. Methods

A literature search was conducted on PubMed, Scopus, MEDLINE, Web of Science, Cochrane, and Embase. Based off a preliminary search, search phrases were designed to encompass literature relevant to the neural basis of startle in response to acoustic stimuli. The search phrases "startl* AND (sound* OR acoustic* OR auditory*)" were combined with the search phrases "((neural OR brain*) AND (region* OR structur* OR mechanis* OR circuit* OR pathway* OR basis)) OR neurobiolog* OR neurophysiolog* OR neuron* OR synap* ". Titles and abstracts were screened by 3 independent reviewers using the following inclusion criteria:

1) Startle in response to acoustic stimuli
2) Investigated neural mechanisms for the startle response
3) Available in English

Papers were excluded based on the titles and abstracts if they addressed the following topics:

1) Only investigated startle in response to visual or tactile stimuli, but not acoustic
2) Used startle as a behavioural measure and did not investigate neural mechanisms underlying startle
3) Only investigated neural mechanisms for the modulation of the startle response (e.g., prepulse inhibition, habituation, fear-modulated startle), without interrogating the pathway underlying the primary startle response

Full texts were screened to extract relevant information for the review. Papers were excluded based on the full-text screening if results were not relevant to the primary ASR neural circuit, for example if the testing paradigms were only for modulation of startle or if the animals were only presented with non-acoustic stimuli. All animal models were included. Any date of publication was included.

3. Results

3.1. Search results

In total 3683 articles were retrieved through the literature search and screened for contributions to elucidate the primary acoustic startle response pathway (Fig. 1). 146 articles were included after title and abstract screening, of which 59 articles remained after full-text screening. The final number of articles included in the review is higher than the articles included after full-text screening because additional articles were found from the citations in the included articles and a supplemental search was conducted for necessary background knowledge for the introduction and results sections.

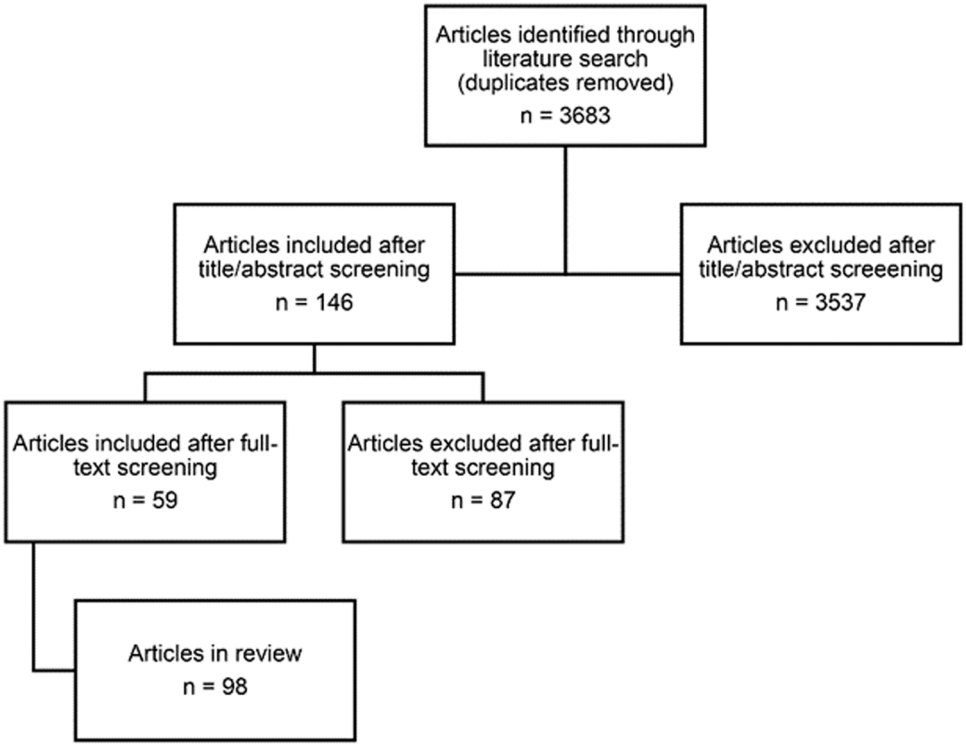

Fig. 1. Flowchart of the number of articles included after each step of the literature review process. Steps included literature search, title and abstract screening, and full-text screening.

3.2. Neural basis of ASR in mammals

3.2.1. Establishing a brainstem acoustic startle pathway

From early studies using decerebrate animals, it was evident that the cerebrum is not necessary for ASR as decerebrate animals were still able to startle in response to acoustic stimuli (Davis and Gendelman, 1977; Forbes and Sherrington, 1914; Wright and Barnes, 1972). Even for the auditory cortex, a study by Hunter and Willott (1993) found that lesions in the auditory cortex only temporarily affected ASR and only at certain sound levels. Thus, it is clear that acoustic startle is mediated entirely by structures in the brainstem.

It was initially thought that the inferior colliculus (IC) mediated ASR. Wright and Barnes (1972) observed that the superior colliculi, the red nuclei, and the vestibular nuclei are not needed for ASR, but bilateral lesions in the IC abolished startle. Another study found that lesions in the IC abolished startle in response to 110 dB startle pulses 24–48 h after surgery (Fox, 1979). Willott et al. (1979) concluded that specific subnuclei within the IC mediate ASR. The authors observed that neurons in the pericentral nucleus of the IC and the external nucleus of the IC were sensitive to parameters that are known to influence ASR (Willott et al., 1979).

However, later studies contradicted the idea that the IC mediates ASR. A study by Groves et al. (1974) lesioned the IC in rats and observed that, although ASR was abolished for 2–3 days after the surgery, the rats re-gained startle responses after 3–4 days. Other studies also found that IC lesions did not affect ASR magnitude 1 week after surgery (Chen et al., 2000; Li et al., 1998). One study found that lesions in the IC actually increased ASR amplitude 2 weeks after surgery (Leitner and Cohen, 1985). These contradictory studies on whether or not the IC mediates startle appear to stem from differences in how soon after surgery the animals were tested. With shorter recovery times, startle is reduced. However, with longer recovery times, IC lesions did not affect startle magnitude or even increased it. This was also seen in a study by Parham and Willott (1990) where lesions in the IC led to decreased ASR 1 day after surgery and increased ASR 1 week after surgery. These findings indicate that the IC plays a role in modulating startle rather than mediating the primary startle response.

Aside from the IC and the caudal pontine reticular nucleus (PnC; see Section 3.2.2), there have been a few other brainstem structures that were investigated in the context of ASR. Some regions that have been eliminated as part of the primary ASR circuit include the inferior olivary nucleus/inferior olive (de'Sperati et al., 1989), the central gray (Fendt et al., 1994), the laterodorsal tegmental nucleus (Jones and Shannon, 2004), and the pedunculopontine tegmental nucleus (MacLaren et al., 2014). A study by Wagner et al. (2000) concluded that the superior olivary complex was necessary for ASR, but this was later contradicted by Schmid and Weber (2002), in which the authors observed no excitatory glutamatergic projections from the superior olivary complex to the PnC. A recent study found that inhibition of glutamatergic neurons in the reticulotegmental nucleus (RtTg) decreased ASR, optogenetic activation of RtTg neurons elicited startle, there were direct projections from the cochlear nucleus to the RtTg, and there were direct projections from the RtTg to spinal cord motor neurons (Guo et al., 2021). Thus, the RtTg may be important for acoustic startle, but future studies are needed to further validate the RtTg as a brain region that mediates ASR.

3.2.2. Early studies on the complete ASR circuit and the PnC as the sensorimotor interface of the startle pathway

The caudal pontine reticular nucleus (PnC) is currently acknowledged as the brain region that mediates ASR, as described in older reviews (Koch, 1999; Koch and Schnitzler, 1997; Yeomans et al., 2002; Yeomans and Frankland, 1995). One of the first papers that proposed a complete ASR neural circuit including the PnC was by Davis et al. (1982). The authors made lesions in various regions of the reticular formation, including the oral pontine reticular nucleus, reticularis gigantocellularis, and dorsal or ventral PnC. Lesions in the ventral PnC decreased startle, while lesions in the other regions did not (Davis et al., 1982). When electrodes were placed in those different brain regions, only stimulation of the ventral PnC elicited startle-like electromyographic (EMG) responses with a latency of 5-ms when recording EMG potentials from the hindlimb (Davis et al., 1982). Lee et al. (1996) also made lesions in the ventrolateral part of the PnC, which significantly decreased startle amplitude, essentially abolishing ASR. In particular, N-methyl-D-aspartate (NMDA) lesions abolished startle when they affected the PnC area between the superior olivary complex and motor trigeminal nucleus (Lee et al., 1996). Thus, neurons in the ventrolateral PnC specifically appear to mediate ASR.

Davis et al. (1982) found that lesions in the dorsal and ventral nuclei of the lateral lemniscus decreased startle. Additionally, the authors investigated different regions in the cochlear nucleus and found that lesions in the ventral cochlear nucleus (VCN) decreased ASR, but lesions in the dorsal cochlear nucleus (DCN) did not (Davis et al., 1982). When electrodes placed in the VCN were stimulated, a startle-like EMG response with latency of 7-ms was elicited, indicating that the VCN precedes the PnC in the primary ASR circuit. Finally, electrical stimulation of the lumbar spinal cord elicited a startle-like EMG response with latency 2.5-ms. From these experiments, Davis et al. (1982) concluded that the primary ASR circuit consists of the auditory nerve, VCN, lateral lemniscus, PnC, and spinal cord motor neurons.

Using horseradish peroxidase (HRP) and intracellular recordings, Lingenhöhl and Friauf (1992) found that acoustically activated neurons in the PnC had a mean soma diameter of 44 μm, and the smallest soma diameter was 32 μm. Hence, these neurons were referred to as "giant neurons". Other details about giant neuron morphology that the authors observed include having 4–8 primary dendrites that branched considerably, spineless dendrites, and axons that initially project dorsomedially and then continue in a caudal direction (Lingenhöhl and Friauf, 1992). The authors also found that the mean excitatory postsynaptic potential (EPSP) latency of these giant neurons was 2.6-ms in response to an 80 dB SPL stimulus (Lingenhöhl and Friauf, 1992). This very short latency supports that PnC giant neurons mediate the short-latency ASR.

Lingenhöhl and Friauf (1994) subsequently conducted a series of experiments that demonstrated the similarities between properties of PnC giant neurons and behavioural ASR. Spike thresholds were over 80 dB SPL for around half of the PnC giant neurons (Lingenhöhl and Friauf, 1994), which corresponds to the high threshold for eliciting behavioural startle. The authors once again found that mean EPSP latency was 2.6-ms for PnC giant neurons and also found that mean spike latency was 5.2-ms in response to 80 dB SPL stimuli (Lingenhöhl and Friauf, 1994). These findings align with the short latency of the ASR. A later study by Gómez-Nieto et al. (2014) also conducted electrophysiological recordings in the PnC, and the authors found a mean spike latency of 4.39-ms in response to 90 dB SPL stimuli, indicating that the spike latency decreases as the intensity of the startling stimulus increases. Another parameter that influenced giant neuron responsivity that also affects ASR was stimulus rise time; longer rise times increased EPSP onset latencies and spike latencies (Lingenhöhl and Friauf, 1994). Additionally, PnC giant neurons were sensitive to paradigms of prepulse inhibition and habituation (Lingenhöhl and Friauf, 1994). Overall, the authors demonstrated many parallels between PnC giant neuron response properties and behavioural acoustic startle.

The study by Lingenhöhl and Friauf (1994) also investigated PnC projections and inputs. *Phaseolus vulguris* leucoagglutinin injected into the PnC anterogradely labelled ipsilateral axons in the cervical and thoracic ventral spinal cord, and these axons looked similar to giant neuron axons that were characterized with HRP. Additionally, PnC giant neurons could be antidromically stimulated with a latency of 1.2-ms when motor neurons in the thoracic spinal cord were stimulated (Lingenhöhl and Friauf, 1994), indicating that PnC giant neurons project directly to the spinal cord. Fluorogold injections into the PnC labelled neurons in the cochlear root nucleus, the DCN, and the VCN, mostly contralaterally (Lingenhöhl and Friauf, 1994). Thus, considering that

the PnC receives projections from the cochlear nuclear complex and giant neurons directly project to motor neurons in the spinal cord, this brain region serves as a sensorimotor interface of the acoustic startle pathway. Lingenhöhl and Friauf (1994) proposed that the primary ASR circuit consists of neurons in the cochlear nuclear complex, specifically cochlear root neurons (CRNs), PnC giant neurons, and spinal cord motor neurons.

Koch et al. (1992) made both large and small lesions in the PnC. Large lesions abolished ASR without impairing general locomotion (Koch et al., 1992), again indicating the importance of the PnC in mediating ASR. Small lesions showed that startle amplitude was correlated to the number of giant neurons, but not correlated to the total number of all types of PnC neurons (Koch et al., 1992), further supporting that giant neurons are the population of neurons in the PnC that mediate ASR.

3.2.3. *Afferent input into PnC*

The generally accepted ASR pathway includes a synapse between PnC giant neurons and spinal cord motor neurons. PnC neurons project mostly ipsilaterally to spinal cord motor neurons (Nodal and López, 2003). Even prior to investigating the PnC in the context of ASR, studies found that spinal cord motor neurons directly receive inputs from PnC neurons (Peterson et al., 1979; Tohyama et al., 1979). However, there was contradictory evidence with regards to which brain region the PnC giant neurons received inputs from. In the circuit proposed by Davis et al. (1982), the PnC received input from the auditory nerve through the lateral lemniscus. However, later tracing studies did not find projections from the lateral lemniscus to the PnC (Lingenhöhl and Friauf, 1994; Shammah-Lagnado et al., 1987), indicating that this brain region is not part of the primary ASR circuit. Davis et al. (1982) also proposed that the ASR was mediated by the PnC receiving input from the VCN, and a study by Meloni and Davis (1998) concluded that the DCN mediates ASR at high intensities of 110 dB SPL and louder. The PnC does indeed receive projections from the VCN and DCN (Kandler and Herbert, 1991). However, due to the relatively long response latencies of 4–14 ms in the DCN, it is unlikely that the DCN mediates ASR via projections to the PnC, since PnC giant neurons have a shorter latency of 2.6-ms (Lingenhöhl and Friauf, 1994). It is also unlikely that the VCN mediates startle because injection of an anterograde tracer into the VCN showed that there were very few VCN axons in the PnC (Lingenhöhl and Friauf, 1994). This was further demonstrated by a more recent study that conducted BDA injections into the DCN and VCN, which revealed that fibers from these areas do not innervate PnC giant neurons (Gómez-Nieto et al., 2014).

Lee et al. (1996) made lesions in the ventrolateral lemniscus (VLL), the paralemniscal zone (PL)/ventrolateral tegmental area (VLTg), the rostral part of the ventral nucleus of the trapezoid body (rVNTB), and CRNs. Lesions of the VLL, PL/VLTg, and rVNTB did not affect startle magnitude, but lesions of CRNs significantly decreased startle amplitude, essentially abolishing ASR. From these results, the authors proposed that the primary ASR circuit consisted of CRNs projecting to the PnC (Lee et al., 1996). The VLL lesion results also contradicted Davis et al. (1982), where lateral lemniscus lesions abolished startle. Lee et al. (1996) suggested that, in the previous paper, VLL lesions destroyed axons of CRNs or, considering how close the VLL and PnC are, the VLL lesions encroached into the PnC which is why startle was abolished.

To recapitulate the papers that attempted to elucidate the complete primary ASR neural circuit, Davis et al. (1982) initially proposed that the ASR pathway includes synapses between the VCN, lateral lemniscus, PnC, and spinal cord motor neurons. However, Lingenhöhl and Friauf (1994) found negligible auditory input from the lateral lemniscus to the PnC and observed that few axons from the VCN projected into the PnC, and they discussed that DCN response latencies were too long to mediate the primary ASR. Thus, the authors proposed that the primary ASR circuit consists of CRNs, the PnC, and cranial and spinal cord motor neurons (Lingenhöhl and Friauf, 1994). Lee et al. (1996) found that lesions of CRNs abolished ASR whereas lesions of the lateral lemniscus did not, and also concluded that the ASR circuit consists of CRNs, PnC neurons, and spinal cord motor neurons. Overall, the circuit for ASR is likely as follows: CRNs project to PnC giant neurons, which project to spinal cord motor neurons, which elicit the muscle contractions of the startle response (Fig. 2). Additionally, Nodal and López (2003) proposed that CRN projections to the lateral paragigantocellular nucleus mediate the rapid autonomic responses associated with startle.

Recent papers have more extensively studied the connection between CRNs and PnC giant neurons. López et al. (1999) confirmed that CRNs project contralaterally to the PnC. The authors also observed that one CRN has multiple postsynaptic projections to PnC neurons (López et al., 1999), making them the most likely input to the PnC that mediates ASR. CRNs projecting to the PnC have large diameter axons, indicating fast conduction, and their axon arbors terminate near PnC giant neurons (Lingenhöhl and Friauf, 1994). Sinex et al. (2001) recorded various electrophysiological properties of CRNs. The authors found that CRNs have first-spike latencies of 2.2 ms (Sinex et al., 2001), which fits well in context of the ASR neural circuit considering that PnC giant neuron EPSP latencies are 2.6 ms (Lingenhöhl and Friauf, 1994). Meanwhile, first-spike latencies of VCN neurons were longer than 2.6 ms (Sinex et al., 2001), further indicating that VCN neurons do not mediate ASR. Nodal and López (2003) found that CRNs project bilaterally to PnC giant neurons, but there are more contralateral than ipsilateral projections. Additionally, CRN axons are myelinated, another indication of fast conduction which is necessary for the short latency ASR, and CRN axon terminals make contact with PnC neurons (Nodal and López, 2003). Finally, CRNs were shown to receive inputs from the auditory nerve (Gómez-Nieto et al., 2014). HRP injections into the cochlea showed that there were inputs from the auditory nerve to the cochlear nucleus, including CRNs (Gómez-Nieto et al., 2014). Auditory nerve afferents were immunopositive for vesicular glutamate transporter 1, indicating excitatory transmission, and these endings were close to CRN cell bodies and dendrites (Gómez-Nieto et al., 2014). The authors also investigated the projections from CRNs to the PnC and found that 75.6% projected contralaterally while 24.4% projected ipsilaterally. Retrogradely labelled axons of CRNs that projected to PnC giant neurons were found in the trapezoid body (Gómez-Nieto et al., 2014). A previous study by Leaton and Kelso (2000) observed that bilateral lesions in the nucleus of the trapezoid body abolished the startle response. This result was likely due to those lesions affecting CRN axons (Gómez-Nieto et al., 2014; López et al., 1999).

3.2.4. *Neurotransmitters involved in the primary startle pathway*

In terms of the neurotransmitters that mediate ASR, many studies have indicated that glutamate is the main neurotransmitter for PnC giant neurons. Ebert and Koch (1992) iontophoretically applied different antagonists to PnC neurons with short latency and high threshold for acoustic stimuli, likely giant neurons, and concluded that α-amino-3--hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate glutamate receptors on PnC giant neurons mediate ASR. Krase et al. (1993) found that both AMPA receptor (6-cyano-7-nitroquinoxaline-2, 3-dione; CNQX) and NMDA receptor (dl-2-amino-5-phosphonopentanoic acid; AP-5) antagonists decreased ASR when injected bilaterally into the PnC. A similar study conducted by Miserendino and Davis (1993) infused γ-D-glutamylglycine, AP-5, or CNQX into the PnC and observed decreased startle in all groups. Schmid and Weber (2002) found that evoked EPSPs in PnC giant neurons were blocked by administration of an AMPA receptor antagonist, again indicating that glutamate is a key excitatory neurotransmitter in the ASR neural circuitry. Steidl et al. (2004) infused kynurenate, a non-selective glutamate antagonist, into the PnC and observed that startle was inhibited in particular when the antagonist was administered to the ventrocaudal PnC.

Using glutamate AMPA receptor subunit 4 (GluA4) knockout mice and wildtype littermates, a recent study by García-Hernández and Rubio (2022) found that deletion of GluA4 decreased ASR magnitude and

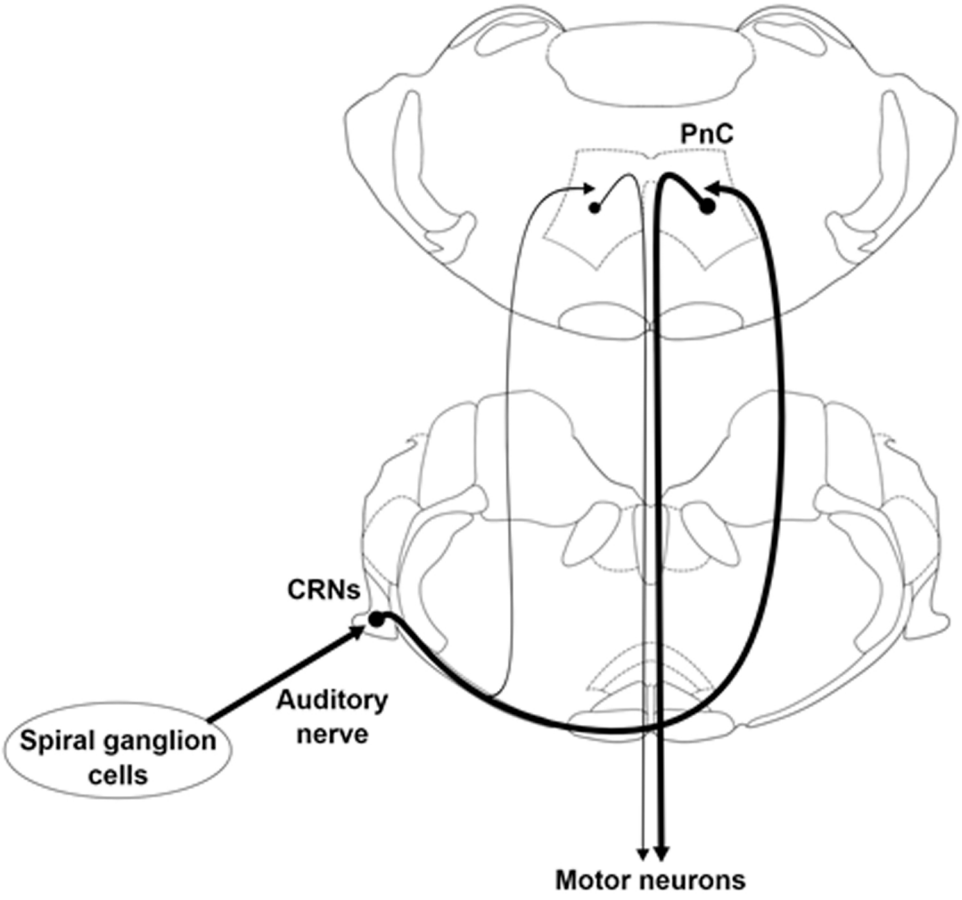

Fig. 2. The primary acoustic startle response neural circuit in rats. Spiral ganglion cells receive information from hair cells in the cochlea and innervate cochlear root neurons (CRNs). CRNs project bilaterally to the caudal pontine reticular nucleus (PnC), but predominantly project contralaterally. Giant neurons in the PnC project ipsilaterally to motor neurons in the spinal cord, which subsequently activate muscle cells to produce the behavioural startle response.
Brain sections modified from Paxinos and Watson (2007).

probability, essentially abolishing the startle response. Auditory brainstem response recordings were not different between genotypes, indicating that GluA4 knockout mice did not have hearing loss (García-Hernández and Rubio, 2022). Additionally, GluA4 was immunolocalized on PnC giant neurons, further supporting the idea that glutamate acting on PnC giant neurons mediates ASR (García-Hernández and Rubio, 2022). The authors acknowledged that GluA4 could potentially be expressed in the synapse between PnC giant neuron axons and spinal cord motor neurons, which was not investigated in this study.

Some neurotransmitters and receptors have been eliminated as candidates participating in the primary ASR circuit, but likely play a role in modulating ASR. Koch and Friauf (1995) found that injecting glycine antagonist or agonist into the PnC did not affect startle. In contrast, a patch-clamp study by Geis and Schmid (2011) found that glycine inhibits PnC giant neurons. The difference may be due to the fact that Geis and Schmid (2011) applied glycine as the agonist whereas Koch and Friauf (1995) applied the agonist β-alanine, which also binds to gamma-aminobutyric acid (GABA) transporters, NMDA receptors, and some GABA receptors. GABA agonists also inhibit PnC giant neuron excitatory postsynaptic currents (Yeomans et al., 2010), indicating that both glycine and GABA receptors play a role in inhibiting startle, but not in mediating startle. Furthermore, Schmid et al. (2010) found that activation of group III metabotropic glutamate receptors inhibits neurotransmission to PnC giant neurons and reduces startle responses, indicating that these receptors play a role in modulating startle, but not mediating. In summary, GABA, glycine, and metabotropic glutamate receptors, and likely others, can modulate startle responses but are not involved in eliciting the primary acoustic startle response. These receptors might rather be involved in neural mechanisms underlying startle modulation through prepulse inhibition, fear conditioning, habituation, etc.

In summary, the current literature proposes a short primary ASR pathway in mammals that includes spiral ganglion cells forming the auditory nerve and synapsing on CRNs, which in turn innervate the ventrolateral PnC with large caliber axons that mostly cross to the contralateral side (Fig. 2). PnC giant neurons in turn project to the spinal cord where they ipsilaterally innervate motor neurons. The spiral ganglion cells, CRNs, and PnC giant neurons presumably all use fast glutamatergic neurotransmission.

3.3. *Neural basis of ASR in fish*

The ASR in fish is all-or-none (Medan and Preuss, 2014), in contrast to the graded response seen in mammals. The ASR in fish has a slightly longer latency of 11–12 ms than the mammalian latency of 6–8 ms, and it varies slightly depending on the species. For example, latency is 12-ms after sound onset in goldfish (Weiss et al., 2008), 11-ms in pufferfish (Greenwood et al., 2010), and 11-ms in surface fish larvae (Paz et al., 2020). The slightly longer response latency might be due to the fact that fish have a lower body temperature as poikilotherms. Another characteristic of the ASR in fish is that the response is directional, guiding the fish away from the startling stimulus in an open field (Eaton et al., 1981) and away from obstacles if obstacles are present in the escape path (Eaton and Emberley, 1991; Zwaka et al., 2022).

The startle/escape neural circuit of fish is fairly well understood, mediated by a pair of cells known as Mauthner cells (M-cells), as previously reviewed (Eaton et al., 2001; Korn and Faber, 1996). Unlike in mammals where the startle response to acoustic stimuli is commonly studied, most studies involving fish tested the startle/escape response in response to vibrational stimuli or tactile stimuli applied to the head or tail. However, there are a few papers that specifically address startle in

fish in response to acoustic stimuli, which are then relevant for this review.

Using adult goldfish, Zottoli (1977) implanted electrodes near M-cells, identified by an extracellular negative field potential of 1 mV or greater when stimulated antidromically from the spinal cord. In response to 200 Hz acoustic stimuli, Zottoli (1977) observed that spikes in the right M-cell preceded EMG responses in the left side of the body, while spikes in the left M-cell preceded EMG responses in the right side of the body. Thus, M-cells project contralaterally to motor neurons (Zottoli, 1977). Greenwood et al. (2010) studied one pufferfish species with ASR and one species without. The authors observed that the species that did not demonstrate ASR also lacked M-cells, whereas the species that did startle had M-cells. Onset latencies of the M-cell responses were, on average, 4.9 ms, and muscle contractions occurred about 1.1–2.1 ms after the M-cell spikes, which is fast enough to mediate the ASR (Zottoli, 1977).

The threshold at which ASR occurs in fish is regulated by inhibition and excitation at the level of the M-cell (Weiss et al., 2008). To ensure that the ASR only occurs above a certain sound level, sound-evoked M-cell inhibition is stronger than sound-evoked excitation at lower sound levels, but excitation is stronger than inhibition at louder sound levels (Weiss et al., 2008). When the authors neutralized electrical inhibition, subthreshold sounds then led to spikes from the M-cell (Weiss et al., 2008).

Through various electrophysiological experiments, a study concluded that ASR is more likely mediated by inputs to M-cells from the posterior VIIIth nerve rather than inputs from the anterior VIIth nerve (Zottoli and Faber, 1979). M-cells have lateral dendrites and ventral dendrites, and a study by Medan et al. (2018) found that the lateral dendrite is responsible for processing acoustic input from the VIIIth nerve and lateral line (LL) input. Meanwhile, the ventral dendrite receives visual input and tactile input. Mirjany et al. (2011) found that the LL is necessary for directionality when fish are startled in an open field. The ASR was non-directional when the LL was eliminated with cobalt or gentamicin treatment, specifically the anterior LL nerve. Transection of the posterior LL nerve did not affect directionality (Mirjany et al., 2011).

In summary, ASR in fish is mediated by a similarly short sensorimotor pathway as in mammals. The primary acoustic startle circuit appears to involve the posterior VIIIth nerve and M-cells. Major differences between fish and mammalian startle are the directionality of the motor response in fish and the fact that it is an all-or-none response.

3.4. Neural basis of ASR in insects/bugs

The acoustic startle response is not extensively studied in insects, and the characteristics of the ASR itself varies considerably between insect species. An older review by Hoy et al. (1989) reviewed ASR in moths, green lacewings, field crickets, praying mantises, tettigonids, and locusts. In terms of the neural mechanisms, there were no specific brain regions or neurons identified for most species (Hoy et al., 1989). However, in crickets, there was an interneuron designated as “int-1″ that is responsive to ultrasound and can elicit an avoidance response when field crickets are in flight (Hoy et al., 1989).

Bushcrickets respond to loud, high frequency acoustic stimuli with a threshold of 76 dB ranging from 25 to 60 kHz, a latency of 31-ms, and no directionality (Libersat and Hoy, 1991). This response is characterized by extension of the front and middle legs, wings folding backwards, sometimes causing the bushcricket to fall from the air, and straightening of the antennae. The ASR is proposed to be mediated by the T-neuron (Libersat and Hoy, 1991). The T-neuron has a response latency of 12-ms, which is fast enough to mediate the ASR in bushcrickets. This neuron also has characteristics in common with PnC giant neurons and M-cells, including low spontaneous activity, large axon diameter, and habituation in response to repetitive stimuli (Libersat and Hoy, 1991). The T-neuron is most sensitive to sounds ranging from 13 to 60 kHz and weakly responsive to low frequency acoustic stimuli (Libersat and Hoy, 1991).

Moths that evolved in environments with bats exhibit ASR in response to ultrasound (Fullard et al., 2004). This response is characterized by cessation of flight, decreased flight time, and erratic flying (Fullard et al., 2004; Roeder, 1962). The neural basis for this ASR may include the A2 cell, an auditory receptor neuron. A2 cells have thresholds around 80 dB SPL for 25 kHz stimuli (Fullard et al., 2007), which is similar to the threshold of PnC giant neurons and M-cells. Additionally, Fullard et al. (2007) studied moths that evolved with and without bats in their environment. Moths that evolved without bats did not exhibit ASR and this was associated with A2 cell regression (Fullard et al., 2007).

Drosophila larvae startle in response to 500 Hz sounds, which is around the frequency of wasp sounds (Zhang et al., 2013). This response is characterized by mouthhook retraction, freezing, excessive turning, and moving backwards (Sun et al., 2018; Zhang et al., 2013). Chordotonal neurons are part of the circuit that mediates this ASR. Interference with chordotonal neuron synaptic transmission abolished the ASR in response to 500 Hz pure tones ranging from 60 to 80 dB SPL (Zhang et al., 2013).

3.5. Neural basis of ASR in humans

Behavioural ASR in humans is similar to ASR in other mammals (Braff et al., 2001), so the primary ASR neural circuit that has been elucidated mostly in rodents could essentially be applied to the human neural circuit. Indeed, a few studies using human subjects confirm that the neural mechanisms underlying acoustic startle in humans are similar to that of other mammals. Two studies by Brown et al. (1991a), (1991b) concluded that the origin of the human ASR is in the caudal brainstem, specifically the bulbopontine brainstem, based on the pattern of muscle recruitment in people with and without hyperekplexia. Using measurements of regional cerebral blood flow, Pissiota et al. (2002) confirmed that startling stimuli elicited neural activity in an area corresponding to the PnC, specifically the posterior medial pons area.

Nakamura et al. (2015) recorded brainstem auditory evoked potentials (BAEPs) from patients with Tay–Sachs disease. These patients exhibited an augmented startle reflex, which was still present even when peaks III and V of the BAEPs disappeared (Nakamura et al., 2015). Peak III corresponds to the superior olivary nucleus and peak V corresponds to the inferior colliculus, indicating that, like in other mammals, these structures are not part of the primary ASR circuit in humans (Nakamura et al., 2015).

4. Discussion/Conclusion

Overall, the acoustic startle response is a highly conserved protective response that can be observed in many species. Studies from invertebrates and fish have been useful and complementary to studies in mammals, mostly rodents, in understanding the ASR neural circuitry. In mammals, the neural pathway includes CRNs, the PnC, and spinal cord motor neurons. In fish, the pathway includes the VIIIth nerve, M-cells, and spinal cord motor neurons. In invertebrates, the acoustic startle neural pathway is not well-understood but tentatively appears to be mediated by neurons that share similar properties to PnC giant neurons and M-cells.

Many studies in fish and invertebrates, such as *Aplysia* or *C. elegans*, used tactile or other stimuli to elicit the startle response (Maguire et al., 2011; Monesson-Olson et al., 2014; Pirri and Alkema, 2012) and were therefore excluded from this review which focuses on the acoustic startle response (ASR) specifically. However, it is important to note that studies that elicit the startle response through other sensory modalities are nevertheless valuable for further exploring the startle pathways and modulatory pathways (Bosch et al., 2001; Currie and Carlsen, 1987; Fourtner and Drewes, 1977; Hirata et al., 2005; Kindt et al., 2007). Additionally, the PnC does not just mediate the ASR. The PnC is also involved in startle responses that are elicited through other sensory

modalities such as tactile and vestibular stimuli (Li and Yeomans, 1999; Schmid et al., 2003; Yeomans et al., 2002), and perhaps even visual stimuli (Peter et al., 2008). This sensory integration in the PnC, potentially by PnC giant neurons, parallels how M-cells in fish can process acoustic, visual, and tactile input (Medan et al., 2018).

Comparing the fish startle pathway with the mammalian startle pathway, it is compelling to speculate to what extent the M-cells of fish are homologous with the PnC giant neurons in mammals. PnC giant neurons are very low in numbers with around 100 cells per side and they are among the largest neurons in the brain (Koch et al., 1992; Lingenhöhl and Friauf, 1992). They are not spontaneously active (Lingenhöhl and Friauf, 1992) and when they fire, a startle response is elicited (Davis et al., 1982). Fish have one M-cell on each side of the brain and, like the PnC giant neurons, M-cells are large and have a high firing threshold (Faber et al., 1989). Both types of neurons receive and integrate input from various sensory modalities (García-Hernández and Rubio, 2022; Medan et al., 2018; Schmid et al., 2003; Yeomans and Frankland, 1995) and project to motor neurons, albeit M-cells project contralaterally (Zottoli, 1977).

One of the remaining important questions is regarding tonic control of neuronal activity in startle-mediating neurons by inhibitory and/or excitatory projections, influencing the startle threshold and baseline startle magnitudes. There is evidence for a tight inhibitory control of M-cells in fish (Weiss et al., 2008), which seems to determine the startle threshold. This is poorly understood in mammals and has not been studied systematically for PnC giant neurons. However, the fact that PnC giant neurons can be inhibited by GABA, glycine, and metabotropic glutamate receptors implies that there might be a similar inhibitory control in mammals. Studies in rodents implicate that excitatory cholinergic influence may also be essential to maintain startle reactivity (Azzopardi et al., 2018; Fulcher et al., 2020; MacLaren et al., 2014). Future studies will require a combination of neuron-specific electrophysiological recordings, inhibition and/or excitation manipulations, and behavioural studies to further explore the role of tonic inhibition and excitation in determining the ASR threshold, as well as startle response magnitudes. Alterations in these measures are linked to disorders that are characterized by increased startle (e.g., autism spectrum disorders) or decreased startle (e.g., psychopathy). Therefore, more in-depth research into the specific neurotransmitters and receptors involved in mediating the ASR and determining threshold would be of clinical interest.

In summary, the primary ASR neural circuit consists of few synapses and fast neurotransmission to allow for a rapid behavioural response to loud, sudden sounds. The ASR appears to be mediated by a low number of large and potentially homologous neurons that are geared for speed. These neurons, located in the brainstem, integrate sensory information from different modalities, have a high firing threshold, and directly activate motor neurons. Their activity seems to be modulated by a number of neurotransmitters that either increase or decrease the startle response in a tonic fashion.

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