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REVIEW

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Brain stem circuits mediating prepulse inhibition of the startle reflex

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Abstract *Rationale:* Prepulse inhibition (PPI) of the startle reflex occurs when brief, non-startling tactile, acoustic or visual stimuli are presented 20–500 ms before the startling stimulus. *Objective:* To review information about PPI-mediating brain stem circuits and transmitters, and their functions. *Results:* Midbrain systems are most critical for the fast relay of these PPI stimuli. Acoustic prepulses for PPI are relayed through the inferior colliculus (IC). The superior colliculus (SC) is important for acoustic PPI, and may be important for the mediation of tactile and visual prepulses. This collicular activation for PPI is quickly relayed through the pedunculopontine tegmental nucleus (PPTg), with lesser contributions to PPI from the laterodorsal tegmental nucleus (LDTg) and substantia nigra, pars reticulata (SNR). The transient activation of midbrain nuclei by PPI stimuli is converted into long-lasting inhibition of the giant neurons of the caudal pontine reticular nucleus (PnC). We propose that muscarinic and $GABA_B$ inhibitory receptors (both metabotropic receptors) on PnC giant neurons combine to produce the long-lasting inhibition of startle. Activation of mesopontine cholinergic neurons leads to cortical arousal, turning and exploratory approach responses. *Conclusion:* PPI is mediated by a circuit involving the IC, SC, PPTg, LDTg, SNR and PnC. By reducing startle, PPI allows the execution of approach responses and perceptual processing following salient stimuli.

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Introduction

The first descriptions of inhibitory reflex modification were provided in 1863 by Sechenov (quoted in Hoffman and Ison 1980). He found that a cutaneous flexor reflex in the frog was inhibited by presenting midbrain stimulation before the eliciting tactile stimulus. In humans, Sechenov found that tactile pre-stimulation ("tickling") inhibited a withdrawal response to an acid bath. Inhibitory reflex modulation in the auditory system was first demonstrated by Peak (1939). She presented two acoustic stimuli with an interstimulus interval of 177 ms and reported an inhibition of the perceived intensity of the second stimulus by 25%.

Hoffman and Fleshler (1963) reported that the startle response in rats can be suppressed by pulsed background noises. They observed that a constant background noise of 85 dB sound pressure level doubled the startle amplitude, whereas a pulsed background noise (500 ms off, 500 ms on) suppressed the startle amplitude by about 80%. Hoffman and Searle (1965) showed that the startle response is attenuated by a preceding noise pulse, which is not able to elicit a startle response itself, when presented 20–500 ms before the startle stimulus onset. They proposed that this attenuation phenomenon reflects an important general mechanism which is "more or less continually active, even though overt startle reactions may seldom occur". The hypothesis that this kind of suppression reflects a more general mechanism and is not a phenomenon within the auditory system (e.g., adaptation in the cochlea) was supported by evidence that the startle response is also inhibited by tactile or visual prepulses (Buckland et al. 1969; Pickney 1976). The term "pre-

pulse inhibition" (PPI) was proposed by Ison and Hammond (1971).

In the following decades, the investigation of PPI has become increasingly important (summarized in Hoffman and Ison 1980; Swerdlow et al. 1992 and this issue; Koch and Schnitzler 1997; Swerdlow and Geyer 1998; Dawson et al. 1999; Koch 1999). First, PPI provides a valuable method to investigate the principles of reflex modulation (e.g., Hoffman and Ison 1980). Second, PPI provides a low-level mechanism of sensorimotor gating (see below). Third, several psychiatric disorders, such as schizophrenia, are associated with deficits in sensorimotor gating, in particular PPI (Geyer and Braff 1987; Swerdlow et al., this issue).

Most studies examined how PPI is modulated by sensory stimuli and by the neurotransmitters dopamine, serotonin and glutamate (Swerdlow et al. 2000, and this issue). Our approach is focused on the short-latency brain stem mechanisms of PPI mediation. The aim of the present review is to summarize the information about PPI circuits and transmitters.

Characteristics of prepulse inhibition

The strongest inhibition of startle (up to 80–90%) is observed with a prepulse duration of 10–20 ms (Reijmers and Peeters 1995) using prepulse startle interstimulus intervals (ISI) between 40 and 150 ms (Hoffman and Searle 1965; Li et al. 1998a, 1998b). PPI is enhanced with increasing intensities of the prepulse up to the startle threshold (Hoffman and Searle 1968; Hoffman and Wible 1970; Hoffman 1984; Li et al. 1998a), whereas the length and the rise/decay times of the prepulse are less critical (Ison 1978; Reijmers and Peeters 1995). Similar inhibition can be observed by changing the background noise, for example, by interruption of a continuous background noise (Stitt et al. 1973) or by changing the frequency of the background noise (Stitt et al. 1974) before the startling stimulus.

Prepulses that precede the startling stimulus at ISIs less than 8–15 ms (it depends from on the prepulse intensity) can facilitate startle and reduce the latency of the startle response (Ison et al. 1973b; Reijmers and Peeters 1995). These effects are believed to be mediated by other neural system than those mediating PPI (Stitt et al. 1976). Summation between acoustic, tactile and vestibular stimuli occurs with a similarly rapid time course (0–15 ms) in primary startle reflex circuits of the hindbrain (Li and Yeomans 1999; Yeomans et al. 1999).

PPI occurs on the first trial (Hoffman and Wible 1970; but see Ison et al. 1973a; Graham 1975; Koch 1999, see Fig. 9) and so does not reflect learning. Furthermore, PPI does not depend on the number or rate of prestimuli (Wu et al. 1984). PPI is often described as showing no habituation (e.g., Wu et al. 1984), but habituation of PPI is observed if prepulses with an intensity close to detection threshold are used (Gewirtz and Davis 1995). In contrast, Reijmers and Peeters (1995, see Fig. 3) showed increased PPI after repeated testing.

Furthermore, the time between the prepulse and the startle response is too short (less than 200 ms) to evoke voluntary behavioral inhibition. Auditory PPI in humans is larger when the prepulse is delivered monaurally than binaurally (Marsh et al. 1976; Hoffman and Stitt 1980; Stitt et al. 1980; Hoffman et al. 1981; Ison and Pinckney 1990).

Taken together, the amount of PPI is strongly dependent on the prepulse intensity and the interval between prepulse and startle stimulus, weakly dependent on prepulse duration and modality, and mainly independent of the properties of the startle-eliciting stimulus (Stitt et al. 1976). An important feature of PPI is the prolonged effect on startle of the prepulse despite its short duration.

Neural basis of prepulse inhibition

In the following sections, we will review work on the neural basis of PPI mediation. PPI is observed after decerebration by transection at the anterior end of the superior colliculus (Davis and Gendelman 1977; Fox 1979; Li and Frost 2000) and after lesions of the cerebellum (unpublished observation of Leitner et al., cited in Leitner et al. 1981). Therefore, PPI must be mediated by nuclei somewhere in the brainstem, between the midbrain and the medulla. Several midbrain nuclei have been found to be needed for full expression of PPI, so we will review the importance of each, beginning with sensory inputs and proceeding to descending influences on startle circuits.

Inferior colliculus

Large lesions of the inferior colliculus (IC) increase the baseline startle amplitude and totally disrupt PPI by acoustic but not by visual prepulses (Leitner and Cohen 1985). Therefore, Saitoh and colleagues (1987) suggested that "the IC is eventually activated by the [acoustic] prepulse and generates an inhibitory phenomenon". Small, unilateral lesions of the IC decrease acoustic PPI (Li et al. 1998a). Furthermore, electrical stimulation of the IC before a 2-ms duration acoustic startle stimulus mimics an acoustic prepulse, with an optimal inhibition occurring at an ISI of 20–30 ms, followed by prolonged inhibition (Li et al. 1998b; Li and Yeomans 2000). This optimal ISI is, in turn, 20–30 ms shorter than that for acoustic prepulses. IC neurons have response latencies between 7 and 40 ms (Li and Kelly 1992a), consistent with the idea that IC mediates PPI.

The IC also plays a role in binaural inhibition which is involved in mediation of acoustic PPI. In humans, inhibition of the eyeblink reflex by an acoustic prepulse is greater when the acoustic stimulus is delivered monaurally than when delivered binaurally (Marsh et al. 1976; Hoffman and Stitt 1980; Stitt et al. 1980; Hoffman et al. 1981; Ison and Pinckney 1990). Therefore, the monaural-binaural effect on the eyeblink reflex may be mediat-

ed via the neural pathways that convey excitatory inputs to the auditory brainstem from one ear and inhibitory inputs from the other ear (Hoffman and Stitt 1980) and that the outputs of these pathways depend on a comparison between inputs from the two ears (Hoffman and Stitt 1980; Ison and Pinckney 1990).

The majority of acoustic neurons in the IC of rats are excited by contralateral ear stimulation and inhibited by ipsilateral stimulation, thus are so-called EI neurons (Flammino and Clopton 1975; Kelly et al. 1991; Li and Kelly 1992b). Binaural EI responses appear to be determined by inhibitory axonal projections from both the contralateral dorsal nucleus of the lateral lemniscus and the ipsilateral superior olivary complex (Li and Kelly 1992b; Kelly and Li 1997). It is yet not clear whether these inhibitory inputs to the IC play a role in producing binaural inhibition observed in PPI. Nevertheless, the azimuthal direction of the prepulse sound does not influence inhibition of the pinna startle reflex in decerebrate rats, indicating that binaural disparities produced by a free-field sound in the frontal azimuthal plane are not capable of modulating PPI (Li and Frost 2000). This result is consistent with the observation in humans that binaural disparities sufficient to change inhibition of eyeblink are much larger than those used for sound localization (Hoffman and Stitt 1980; Ison and Pinckney 1990). To explain the omnidirectionality of PPI, the neural pathways that link the IC with the primary startle pathway must be studied further.

In summary, the IC is a critical part of the auditory pathway mediating acoustic PPI. The central nucleus of the IC receives auditory input, which is relayed to the external nucleus of the IC before going to the middle layers of the superior colliculus. In this way, the IC may relay information between the auditory system and the PPI-mediating circuit (see also Leitner et al. 1981; Leitner and Cohen 1985).

Superior colliculus

Since PPI can be produced using acoustic, tactile or visual sensory inputs, some structures processing multi-modal may be involved in mediating PPI. The superior colliculus (SC) receives direct inputs from auditory, somatosensory and visual structures (Meredith et al. 1992), including the external nucleus of the IC, the medial lemniscus and the retina. The SC has several descending projections to the hindbrain mediating turning responses toward or away from stimuli (Dean et al. 1989). The SC also projects to the pedunculopontine tegmental nucleus (PPTg) (Redgrave et al. 1987; Semba and Fibiger 1992; Steiniger et al. 1992), an important nucleus of the PPI mediating circuit (see below). Furthermore, the SC receives massive GABA-ergic input from the substantia nigra pars reticulata (SNR) (Chevalier et al. 1981) which is also involved in PPI mediation and/or modulation (see below).

Fiber-sparing lesions of the SC attenuate PPI by approximately 45% (Fendt et al. 1994). Furthermore, pharmacological stimulation of the SC by a blockade of GABA receptors within the SC enhanced PPI (Fendt 1999). Electrical stimulation of the SC before startle stimuli had similar effects to IC stimulation, i.e., an attenuation of the startle response by approximately 80%, with the most effective inhibition occurring at ISIs between 20 and 30 ms (Li and Yeomans 2000). We have no evidence on whether visual and tactile prepulses are also processed by the SC. Furthermore, it is unknown whether SC input from forebrain areas is critical for PPI. Since the SC may not mediate all of PPI, other structures in the midbrain or forebrain may be involved in PPI mediation.

Stimulation of some regions of the deep mesencephalic nuclei inhibits the startle response (Saitoh et al. 1987). Since the SC is close to the deep mesencephalic nuclei, and particularly descending fibers from the SC pass through the deep mesencephalic nuclei, PPI produced by stimulation of the deep mesencephalic nuclei may result from activation of fibers-of-passage from SC.

Taken together, the SC has the physiological and hodological properties to act as an integrative structure relaying prepulses of different sensory modalities to the PPTg.

Pedunculopontine and laterodorsal tegmental nucleus

Both the PPTg and the laterodorsal tegmental nucleus (LDTg) are parts of the midbrain reticular formation, which has a variety of functions in behavioral modulation (summarized in Inglis and Winn 1995; Yeomans 1995a; Scarnati and Florio 1997). First hints that the PPTg may be involved in the mediation and/or modulation of PPI came from a study of Saitoh and colleagues (1987) showing that electrical stimulation of the lateral tegmental area (including the cuneiform nucleus, the inferior colliculus and the parabrachial nucleus, but also the PPTg and the LTDg) decreased the acoustic startle response. A few years later, Ebert and Ostwald (1991) demonstrated that acoustically evoked potentials in the PPTg occur in conjunction with the acoustic startle response. This short-lasting activation of PPTg neurons by acoustic stimuli has a latency of 13 ms. Garcia-Rill and colleagues concluded that the auditory evoked potential recorded from the surface or the cortex, called P13, results from activation of PPTg and LDTg cholinergic neurons, and that sensory gating of two acoustic stimuli depends on the PPTg (Reese et al. 1995; Garcia-Rill et al. 1996). Both P13 and PPI can be blocked by systemic injections of the muscarinic receptor antagonist scopolamine, or by direct injections of drugs into the PPTg that inhibit PPTg neurons (Miyazato et al. 1999a, 1999b, 2000).

Lesion studies supported the hypothesis that the PPTg and the LDTg are involved in PPI mediation. Lesions of the lateral tegmental area (including the PPTg and LDTg) attenuated PPI by approximately 50% (Leitner et al. 1981). Lesions restricted to the LDTg decreased

PPI by about 40% without affecting baseline startle amplitude (Jones and Shannon 1998). Lesions of the PPTg attenuated PPI but baseline startle amplitude was increased (Swerdlow and Geyer 1993; Kodsi and Swerdlow 1997). In these studies, only less than half of the PPTg was destroyed. Pharmacological blockade of the PPTg by microinjections of $GABA_A$ receptor agonists had similar effects as PPTg lesions (Kodsi and Swerdlow 1997). Furthermore, electrical stimulation of the PPTg before a startle stimulus inhibited the startle reflex in a similar way to prepulses; the most effective PPTg stimulation was at ISIs between 12 and 20 ms (Li and Yeomans 2000). Therefore, the PPTg is important and sufficient for the mediation of PPI, and appears to be located a few ms closer to PPI output systems than the IC or SC.

Anatomical experiments demonstrated a descending cholinergic projection from the PPTg and the LDTg to the primary startle pathway (Semba et al. 1990; Koch et al. 1993). Specific lesions of the cholinergic neurons within the PPTg blocked PPI by approximately 65% without effects on baseline startle (Koch et al. 1993). Therefore, the hypothesis was proposed that this cholinergic projection of the PPTg to the startle pathway is responsible for the mediation of PPI (Koch et al. 1993). The LDTg is made up of an even higher concentration of cholinergic neurons (70% cholinergic), and lesions of LDTg reduced PPI by about 40%, without affecting baseline startle (Jones and Shannon 1998). Therefore, both mesopontine cholinergic cell groups are important for PPI.

None of these treatments alone totally blocked PPI, however. Since the midbrain nuclei (SC, IC, PPTg) involved in PPI mediation have short-latency auditory inputs (under 20 ms) and PPI is long-lasting, the output to the primary startle pathway must be a slow inhibitory system. Several studies showed that the PPI-modulating forebrain circuitry projects via the PPTg to the primary acoustic startle pathway (summarized in Swerdlow et al. 1992 and this issue; Koch and Schnitzler 1997; Swerdlow and Geyer 1998; Koch 1999).

Ascending mesopontine cholinergic neurons: arousal and reward

PPTg and LDTg cholinergic neurons have mainly ascending projections, especially to the thalamus. These neurons have excitatory connections with virtually all thalamic nuclei, thereby facilitating inputs to each of these nuclei, and leading to strong cortical activation (Steriade et al. 1990). This cortical arousal function of mesopontine cholinergic neurons occurs at the onset of REM sleep, and when novel or important stimuli occur.

In addition, many of these LDTg and PPTg cholinergic neurons provide the strongest excitatory brainstem inputs to dopamine neurons of the ventral tegmental area and substantia nigra, pars compacta (Yeomans 1995a; Blaha et al. 1996). This cholinergic excitation of dopamine neurons occurs especially when rewarding stimuli (food, water, lateral hypothalamic stimulation) are presented (Pan et al. 2000; Rada et al. 2000). Blockade of cholinergic receptors near dopamine neurons blocks these rewarding effects, and the locomotor and rewarding effects of nicotine (Corrigall et al. 1994; Yeomans and Baptista 1997). The startle-inhibiting role of PPTg and LDTg neurons, therefore, may be a secondary effect of their important role in alerting cortex and initiating approach behaviors important for survival.

Similarly, rewarding stimuli have been found to inhibit startle. In humans, pleasant pictures (e.g., appetizing foods, attractive nudes) reduce startle sensitivity (Lang et al. 1990). In rats, neutral stimuli (e.g., lights) that have been repeatedly paired with food or with rewarding lateral hypothalamic stimulation reduce startle sensitivity (Schmid et al. 1995; Steidl et al. 2001). Furthermore, electrical stimulation of the ventral pallidum in rats, which can be rewarding, reduces acoustic startle (Li et al. 1999). Whether the PPTg and LDTg are important for these startle-inhibiting effects of rewarding stimuli is not yet determined.

Caudal pontine reticular nucleus

The caudal pontine reticular nucleus (PnC) is a critical part of the primary acoustic startle pathway (for reviews, see Davis et al. 1982; Lee et al. 1996; Yeomans and Frankland 1996; Koch and Schnitzler 1997; Koch 1999). PnC neurons also receive direct anatomical connections from second-order vestibular neurons in the vestibular nucleus, and second-order trigeminal neurons in the trigeminal nucleus (Frankland, P.W., Raboisson, P., Dallel, R., Li, L., Yeomans, J.S. and Kawaja, M.D., unpublished experiments). PnC neurons can be activated by acoustic, vestibular, and tactile stimuli (Peterson and Felpel 1971; Siegel et al. 1983; Wu et al. 1988), suggesting that in addition to acoustic startle, the PnC could mediate both vestibular and tactile startle. Therefore, the PnC may be a site for inter-modal summation of startling stimuli (Li and Yeomans 1999; Scott et al. 1999). Nevertheless, the vestibular nucleus also has direct projections to the spinal cord via the vestibulospinal tracts (Wilson 1972; Shamboul 1980; Huisman et al. 1984; Bankoul and Neuhuber 1992). A recent electrical stimulation study has indicated that there is a faster route for mediating vestibular startle without a synaptic relay in the PnC (Li et al. 2000). The heaviest projections of the lateral vestibulospinal tract from the vestibular nucleus are to layers 7 and 8 of the ventral spinal cord (Shamboul 1980). Reticulospinal projections of the PnC are to these same layers of the spinal cord. This suggests that intermodal summation of startling stimuli is also based on integration of reticulospinal and vestibulospinal signals in layers 7 and 8 of the spinal cord. It is of interest to know whether this spinal site is involved in the integration of prepulse and startling signals.

Several studies show that PnC giant neurons are inhibited strongly by acoustic prepulses (Wu et al. 1988; Lingenhöhl and Friauf 1994; Willot et al. 1994; Carlson and Willot 1998). The strength and timing of inhibition of PnC neurons suggests that PPI can occur within the PnC. There are, however, no recordings of prepulse inhibition effects in other nuclei of the primary acoustic startle circuit. Because most of these are auditory relay nuclei, it is hard to argue that multisensory inputs to the startle circuit impinge on the startle reflex before the PnC or the ventrolateral tegmental nucleus (VLTg). The VLTg is located in the ventrolateral pons and receives multimodal input from the auditory, tactile and vestibular system. The strong projections of the VLTg to facial nuclei support an important role of the VLTg for the head startle response (Yeomans and Frankland 1996).

Several studies investigated the effects of transmitters in the PnC on PPI. Acetylcholine receptor agonists (carbachol, acetyl-β-methylcholine) reduced the tone-evoked activity of the PnC giant neurons (Koch et al. 1993). Microinjections of the muscarinic receptor antagonist scopolamine into the PnC of awake rats decreased PPI, whereas injections of the muscarinic/nicotinic receptor agonist carbachol slightly enhanced PPI (Fendt and Koch 1999). Further work demonstrated that the PPTg and the LDTg are the source of the cholinergic input into the PnC (Semba et al. 1990; Koch et al. 1993). Systemic injections of the muscarinic receptor antagonist scopolamine inhibited PPI most strongly at ISIs of 100 and 300 ms, unlike apomorphine that inhibited PPI at all ISI, suggesting that muscarinic receptors are especially important for PPI at long ISIs (Jones and Shannon 2000a, 2000b).

GABA transmission within the PnC is also involved in PPI mediation. PPI is attenuated after injections of the $GABA_B$ receptor antagonist phaclofen but not after injections of the $GABA_A$ receptor antagonist picrotoxin into the PnC (Koch et al. 2000). It is presently unknown which projections to the PnC use GABA as a transmitter, but a possible source of GABAergic projections to the PnC is the SNR (see below). Lesions of the SNR significantly reduced PPI (Koch et al. 2000).

Although glycine receptors are widely distributed within the PnC (Koch and Friauf 1995), glycine seems to play no role in PPI. Injections of the glycine receptor agonist β-alanine, as well as injections of the glycine receptor antagonist strychnine did not affect PPI (Koch and Friauf 1995).

No studies have found a complete blockade of PPI after injections of transmitter antagonists into the PnC. The muscarinic receptor antagonist scopolamine led to a PPI reduction by approximately 50% of baseline PPI (Fendt and Koch 1999). The $GABA_B$ receptor antagonist phaclofen attenuated PPI by approximately 35% (Koch et al. 2000). As yet, there are no studies with combined injections.

Substantia nigra

The SNR plays an important role in the inhibitory control of motor behavior (Chevalier and Deniau 1990). Koch and co-workers (2000) found a PPI reduction of approximately 60% after lesions of the SNR. Since SNR-lesioned rats showed no further PPI reduction after amphetamine or dizocilpine (both drugs act in the PPI modulating circuit) (Swerdlow et al. 1990; Bakshi and Geyer 1998), the authors concluded that the SNR, like the PPTg, is a part of the PPI mediating pathway but also a target structure of the PPI modulatory input. Furthermore, SNR lesions blocked the facilitation of the startle response seen after systemic injections of dopamine D_1 receptor agonists (Meloni and Davis 1997).

SNR neurons use GABA as a transmitter and project to the PnC (Yasui et al. 1992). Furthermore, GABA within the PnC is involved in PPI mediation. Therefore, Koch and colleagues (2000) proposed that a GABAergic projection from the SNR to the PnC is a part of the PPI mediating pathway.

Proposed PPI circuits

Hoffmann and Ison (1980) proposed that PPI is mediated by a slow inhibitory pathway that runs parallel to the fast excitatory pathway of the acoustic startle system. Swerdlow and colleagues (1992) summarized the neural basis of PPI modulation and suggested a PPI mediating "loop" near the primary startle circuitry.

Carlson and Willot (1996) proposed a neural model of PPI in which acoustic prepulses were mediated by "the IC and other auditory nuclei", and these signals were relayed to the PnC where the PPI pathway and the "subcollicular startle pathway" converge.

Fendt, Koch and colleagues (Fendt et al. 1994; Koch and Schnitzler 1997; Fendt 1999; Koch 1999) proposed that acoustic prepulses are processed via the ascending auditory pathway including the IC (Fig. 1). The IC activates the SC, which also receives input from other sensory modalities (auditory, tactile and visual). The anatomical connection between the SC and the PPTg activates a cholinergic projection to the PnC to mediate PPI. This hypothetical pathway was supported by stimulation studies by Li and colleagues (Li et al. 1998b; Li and Yeomans 2000) showing that a brief stimulation of the IC, SC or PPTg elicits a prolonged inhibition of the startle response. They conclude that PPI must be mediated by long-lasting inhibitory systems responding to short-lasting outputs from these midbrain nuclei.

How does the transient excitation of PPTg, LDTg and SNR by stimuli that produce PPI get converted into long-lasting inhibition of the startle reflex? Evidence that both muscarinic and $GABA_B$ receptors are important for PPI near PnC suggests that long-lasting metabotropic inhibition of PnC neurons is the key mechanism. Of the five muscarinic receptors, M_2 and M_4 subtypes inhibit adenylyl cyclase, and are the only muscarinic receptors that have been found to inhibit neuronal activity in several sites (Gomeza et al. 2001). Over 70% of brain stem muscarinic receptors are of the M_2 type (Levey et al. 1993). Both M_2 and $GABA_B$ receptors react to ligand/re-

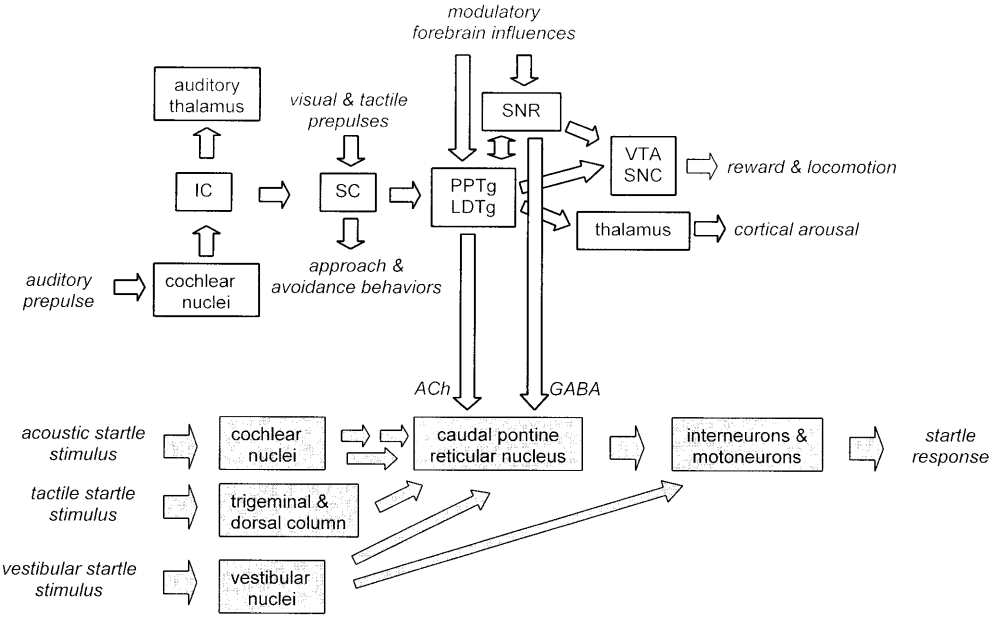

Fig. 1 A hypothetical circuit mediating PPI of the startle response

ceptor combination within 30–100 ms (Bear et al. 2001). This is fast enough to account for the time course of PPI, but is quicker than the effects of most G-protein-mediated responses. More work will be needed to characterize the genetically defined receptors mediating PPI more precisely.

Biological significance of prepulse inhibition

What functional advantage results from PPI of startle? A common interpretation is that PPI is simply a distraction that disrupts attention to the startling stimulus (Filion et al. 1998; Schell et al. 2000). This interpretation does not suggest, however, what the functional importance of the startling stimulus or the prepulse stimulus might be.

Several studies indicate that the prepulse must be clearly detectable, and so the prepulse is less effective if habituated (Gewirtz and Davis 1995; but see also Schell et al. 2000), or disrupted by pharmacological treatments (Varty et al. 1997), or not attended to by humans (Filion et al. 1993; Schell et al. 2000). PPI is not affected during sleep, however (Silverstein et al. 1980; Wu et al. 1990), but attenuated after awakening from non-REM sleep (Horner et al. 1997).

Graham (1979) pointed out that the inhibiting effect of a prepulse is contemporaneous with the period during which a stimulus is recognized. During this period of "pre-attentive processing", stimulus recognition is vulnerable to disruption, especially by the widespread changes during a startle response. Therefore, Graham argued that PPI of startle is needed to protect stimulus processing at this critical time interval. In this way, Graham proposed that perception of prepulse stimuli themselves may be very important in some way, and that startle might have less survival value in some situations than in others. Graham, however, had no idea what the function of startle might be: "It is difficult to see in what way the wide-spread flexor contractions [in startle] offer protection" (Graham 1979).

PPI occurs across mammalian species studied at a variety of postnatal ages, thus it must have a lasting survival value. According to Graham's protection-of-processing theory for explaining PPI (Graham 1975), the onset of low-intensity changes in sensory stimulation produces a "transient detection reaction" that automatically triggers a gating mechanism attenuating extraneous reactions temporarily until the perceptual processing of the lead stimulus is completed. The extraneous reactions, such as the startle reflex, would have a disruptive effect on the perceptual processing. This theory is supported by evidence that perception of the prepulse is closely associated with its ability to inhibit startle (Perlstein et al. 1989, 1993; Filion and Ciranni 1994; Norris and Blumenthal 1995, 1996; Mussat-Whitlow and Blumenthal 1997).

As an extension of Graham's "protection of processing" behavioral theory (Graham 1975), the model presented here specifies the anatomical systems involved in PPI (especially SC and PPTg/LDTg), and further specifies how their activation during PPI leads to improved perceptual processing and active exploration of novel stimuli, such as prepulses:

1. SC activation improves perceptual processing by inducing orienting toward, and foveation of, the novel stimulus, via the tectoreticulospinal pathway (Dean et al. 1989).
2. PPTg/LDTg activation improves perceptual processing by diffuse cholinergic facilitation of thalamo-cortical systems, via direct PPT/LDT projections to thalamus (Steriade et al. 1990).
3. PPTg/LDTg activation further induces active exploration (approaching, sniffing, etc.) of novel and reward-

ing stimuli via direct PPTg/LDTg activation of mesolimbic dopamine neurons (Yeomans 1995b).

During the initiation of these important perceptual/motor approach responses, startle responses (closing the eyes, bilaterally symmetric contracting of muscles throughout the body) would prevent visual input, turning responses and exploration. Although startle responses are still needed to defend against catastrophic blows that strongly activate tactile, auditory and vestibular systems, PPI systems reduce the sensitivity of the startle systems in the few hundred milliseconds where approach responses are most beneficial to processing.

These anatomical systems are hierarchically organized (see Fig. 1), so that, first, the simpler startle reflex is organized in the hindbrain to maximize speed; second, the more complex responses of orienting, approach and avoidance are organized in the midbrain, and third, the fuller processing of stimuli occurs at forebrain levels (Koch and Schnitzler 1997).

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