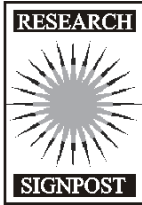



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The nucleus accumbens regulation of sensorimotor gating in animal models and neuropsychiatric disorders

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Abstract

A weak lead stimulus, or “prepulse”, inhibits the startling effects of a subsequent intense abrupt stimulus. The ability of this weak sensory event to inhibit (“gate”) a motor response provides an operational measure of sensorimotor gating, called “prepulse inhibition” (PPI). PPI has been widely used in translational models to understand the biology of brain-based inhibitory mechanisms, and their deficiency in neuropsychiatric disorders. Limbic cortex, striatum, pallidum and pontine tegmentum regulate PPI; this

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circuitry has been studied in rats to reveal the neurochemical and neuroanatomical substrates regulating PPI at a high level of resolution. The nucleus accumbens (NAC) is a key subcortical component of this circuitry. In this chapter, we summarize findings that suggest differences in the regulation of PPI by NAC core and shell subregions, and that implicate NAC neurotransmission of dopamine, excitatory amino acids and neuropeptides, NAC intracellular signal transduction pathways and the expression of specific NAC genes in the regulation of PPI. The NAC regulates PPI as part of an integrated circuit that includes afferents from the medial prefrontal cortex (MPFC), basolateral amygdala (BLA) and hippocampus (HPC), and NAC efferents to the ventral pallidum (VP), the dorsomedial thalamus (MD) and pedunculopontine tegmental nucleus (PPTg). By understanding this gating "system" from the level of circuit connectivity down to genetic control, it may be possible to identify both the cause of PPI deficits in neuropsychiatric disorders, and therapeutic targets in these disorders.

1. Introduction

Sensorimotor gating of the startle reflex can be assessed across species, using a paradigm in which a weak lead stimulus, or “prepulse”, inhibits the startling effects of a subsequent intense abrupt stimulus (Figure 1). The ability of this weak sensory event to inhibit (“gate”) a motor response provides an operational measure of sensorimotor gating, called “prepulse inhibition” (PPI). PPI has been widely used in translational models to understand the biology of brain-based inhibitory mechanisms, and their deficiency in neuropsychiatric disorders. PPI is reduced in patients with specific neuropsychiatric disorders and in rats after manipulations of limbic cortex, striatum, pallidum or pontine tegmentum (“CSPP” circuitry). Limbic CSPP circuitry has been studied in rats to reveal the neurochemical and neuroanatomical substrates regulating PPI at a high level of resolution; in turn, this PPI “blueprint” is being translated onto human disorders, to help localize the neural basis for gating deficits and their clinical manifestations in humans.

In the last two decades, substantial progress has been made towards identifying the brain circuitry that regulates PPI of the startle reflex. The NAC is a key subcortical integrative “hub” in this circuitry, connecting forebrain and limbic structures that control cognition and behavior, as well as sensorimotor gating. As such, it is well positioned both to be a locus contributing to gating deficits in several disorders, and also to be a target for therapeutics aimed at restoring normal gating in patients. In this chapter, we will summarize the current knowledge about the role of the NAC and its associated circuit connections in the regulation of PPI.

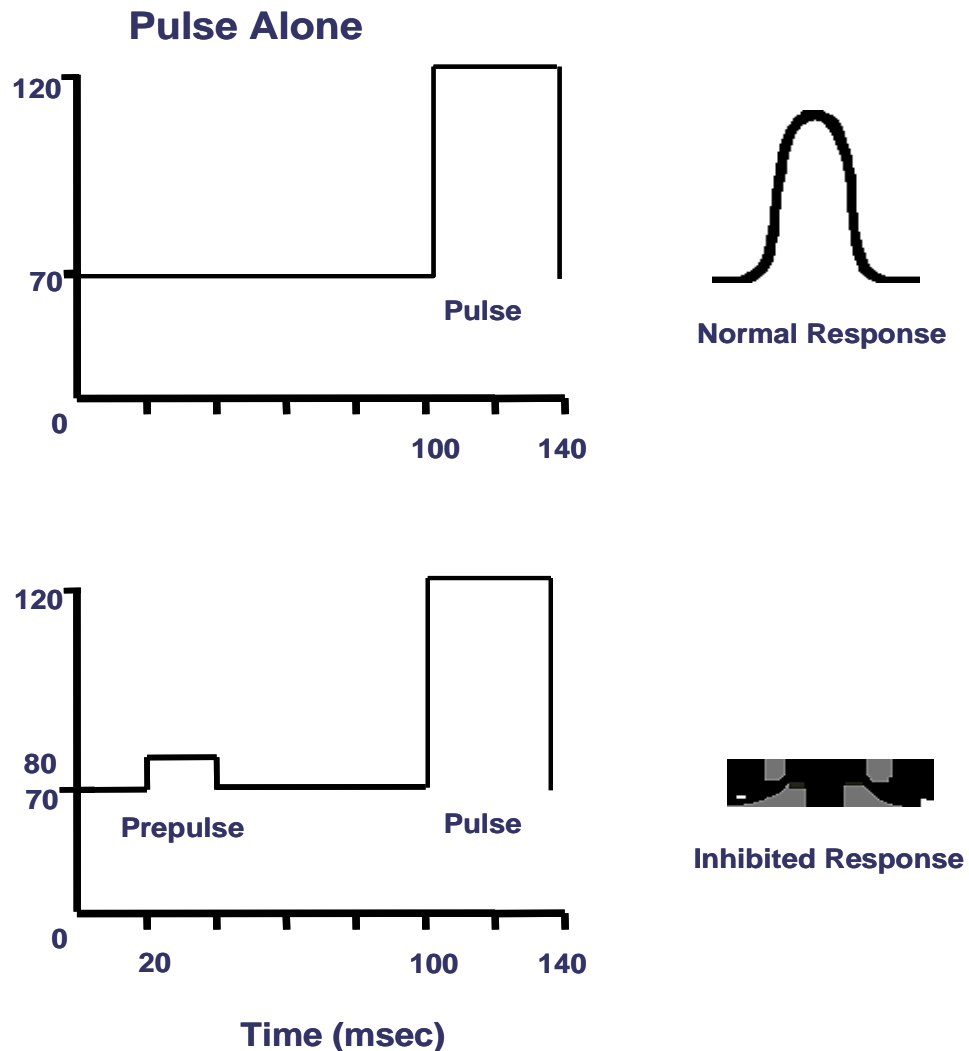


Figure 1. Stimulus configurations in PPI paradigms: Startle is elicited by a “pulse” noise burst (top), and is inhibited when the pulse is preceded 60-120 ms earlier by a weak prepulse (bottom).

2. Prepulse inhibition (PPI)

The startle reflex is a constellation of responses to a sudden, intense stimulus that is usually classified as a defensive response. In humans, the blink reflex component of startle is measured using electromyography of the orbicularis oculi. In rats, a stabilimeter is used to measure the whole-body flinch elicited by stimuli that are similar to those used in humans. In 1982, Davis et al. reported a primary mammalian acoustic startle circuit (*1*), now thought to consist of 3 synapses linking the auditory nerve with the spinal motor neuron. This simple startle reflex demonstrates several conceptually important forms of plasticity, including PPI, which is the normal suppression of the startle reflex when the intense startling stimulus is preceded by a weak

prestimulus (2-4), PPI occurs whether the prepulse and startling stimuli are in the same or different sensory modalities. It is not a form of conditioning, since it occurs on the first exposure to the prepulse and pulse stimuli. While the inhibitory effect of the prepulse on startle is exerted in the pons (5), descending forebrain influences regulate the inhibitory “tone” within the pons, and determine the degree to which the prepulse inhibits the subsequent motor response. PPI thus appears to reflect the activation of ubiquitous “hardwired” centrally mediated behavioral gating processes that are regulated by forebrain circuitry.

In a conceptual model (6), a weak stimulus activates neural processes that blunt responsivity to sensory events during a brief temporal window. The gating “window” is empirically determined to be approximately 30-500 ms in duration, in both rats and humans (2, 5). This period of reduced responsivity might serve to momentarily protect information contained in the weak stimulus, so that it can be processed without interference from subsequent stimuli.

PPI is studied under controlled conditions in the laboratory. Under natural circumstances, sensorimotor gating is conceptualized as being continuously active in waking humans, contributing adaptive value by enhancing the ability to segregate a continuous stream of sensory and cognitive information, and to selectively allocate attentional resources to salient stimuli. Specific characteristics of an individual’s gating processes are viewed to be plastic, shaped by genetic and developmental forces, but are also sensitive to changes in environment, stressors, or the neurochemical milieu of the nervous system (6). A substantial, pathological breakdown in the gating “window” would impair the orderly, hierarchical processing of sensory events and result in flooding of sensory information with a fragmenting impact on cognition (7).

3. PPI and neuropsychiatric disorders

Interest in PPI as a measure of sensorimotor gating grew from the observation that human disorders with known dysfunction in brain substrates that regulate PPI are accompanied by evidence of impaired cognitive or sensorimotor inhibition. At least 10 investigative groups have reported PPI deficits in schizophrenia patients (8, cf. 9), making this finding among the most replicated quantitative markers of brain-based disturbances in this disorder. Our laboratory and others have also reported deficient PPI in patients with Huntington's Disease (10, 11), Tourette Syndrome (12, 13) or obsessive compulsive disorder (14-16). These disorders are all characterized by a loss of gating in sensory, motor or cognitive domains, and by abnormalities in forebrain circuitry that modulates PPI. Other disorders, such as Paroxysmal Nocturnal Enuresis, are characterized by PPI deficits that may reflect abnormalities within pontine elements of startle gating circuitry.

4. Animal models of PPI

Because PPI can be measured across species, it is important to note that many inferences related to the neural regulation of PPI that have emerged from animal studies have been supported by studies of PPI in humans (cf. 9). Animal studies have demonstrated changes in PPI after a variety of manipulations of environmental conditions, neural elements and genes. Experimental manipulations in these studies have included single or multiple, concurrent interventions, such as brain tissue lesions (generalized or cell-specific), intracerebral infusions of transmitter- or receptor-specific pharmacologic agents, electrical stimulation or kindling, and systemically administered neurotoxins. These experimental manipulations are often combined with anatomical and neurochemical analyses, ranging from careful lesion reconstruction to fiber-tracing techniques, microdialysis and measures of early gene activation. Genetic approaches, including strain comparisons, selective "pharmacogenetic" inbreeding, and genetic knockouts, have also added to our understanding of the brain circuitry regulating PPI (13). Many of these experimentally-induced PPI deficits in laboratory animals have been utilized in models for understanding the pathophysiology of impaired sensorimotor gating in schizophrenia patients and for predicting antipsychotic activity in novel compounds (17).

5. The NAC and the neuronal circuitry of PPI

As reviewed by Fendt et al. (18), the mammalian acoustic startle circuit includes serial connections linking the auditory nerve, the cochlear root neurons, the nucleus reticularis pontis caudalis (PnC), and the spinal motor neuron. Midbrain systems are most critical for the fast relay of these PPI stimuli. Acoustic prepulses for PPI are relayed through the inferior colliculus. The superior colliculus (SC) appears to play an important early role in the mediation of acoustic PPI. Prepulse-induced collicular activation is quickly relayed through the PPTg. The transient activation of midbrain nuclei by PPI stimuli is converted into long-lasting inhibition of the giant neurons of the PnC (18).

While these pontine elements *mediate* PPI by transducing the effects of the prepulse directly into the primary startle circuit, studies in humans and laboratory animals have revealed that PPI is *regulated* by much "higher" neural elements. It is important to emphasize that these structures are not required for the real-time phasic prepulse-induced suppression of startle activity; in fact, PPI remains intact after transcollicular knife cuts (19). Furthermore, PPI can be elicited within 10 ms of prepulse onset, and it is not possible for neuronal activation triggered by the prepulse to be transduced to the furthest rostral extent of the forebrain, be processed, and then return to the pons in time to modify a startle pulse presented 10 milliseconds later. Rather,

pontine PPI circuitry is regulated in a tonic “thermostat-like” fashion by sequential and parallel neural connections between limbic cortex (including temporal cortex and medial prefrontal cortex), hippocampus (HPC), the ventral striatum (including the NAC), the ventral pallidum (VP), and the pontine tegmentum (cf. 20, 21). This limbic cortico-striato-pallido-pontine circuitry converges with the primary startle circuit at the level of the PnC (Figure 2).

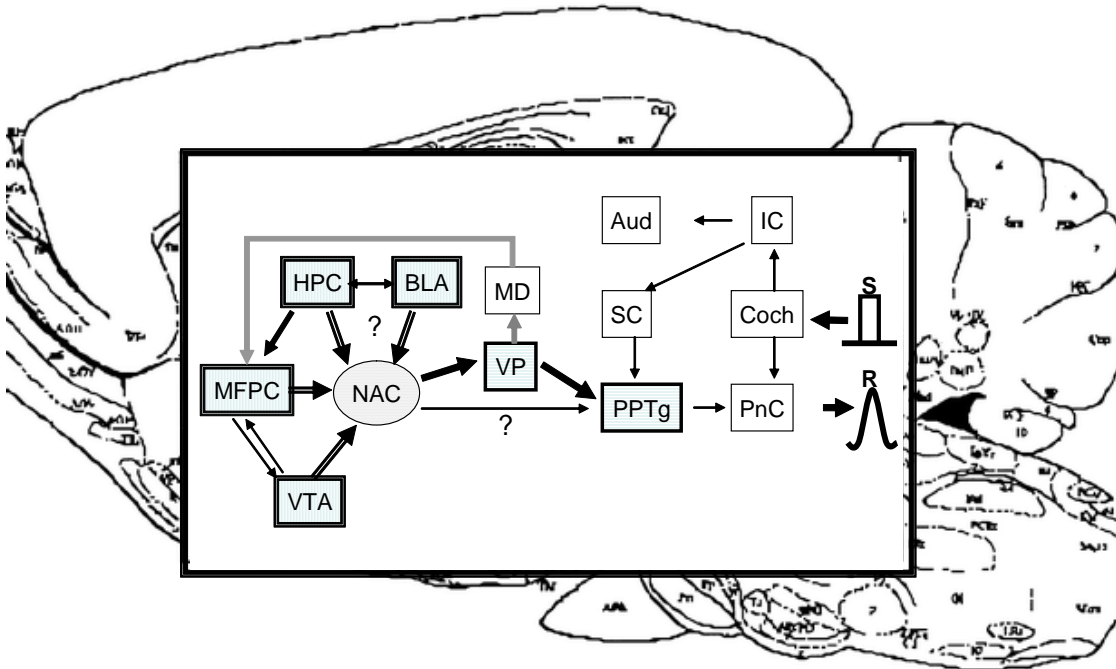


Figure 2. Schematic model of neural substrates regulating acoustic startle and PPI in the rat, modified from previous evolving diagrams (20, 21, 139, 140). Many connections within this circuitry are omitted, for simplicity of representation, but are discussed within the text. For example, while this figure emphasizes a role for the ventral striato-pallidal circuitry in the regulation of PPI, a discussion of the role of the dorsal striato-pallidal circuitry, and other basal ganglia components can be found referenced sources. Some findings discussed herein raise doubts about the role of specific connections in the regulation of PPI, as indicated by "?". In this figure, an acoustic stimulus *S* elicits a startle response *R* via a simple pontine circuit. Prepulse effects on *R* may be mediated via the PPTg, which is regulated by descending serial and parallel projections from the forebrain. Neurotransmitter identities of excitatory and inhibitory connections can be found within materials referenced in the text. This model is highly schematized, clearly incomplete, and based on work by many groups (see text). *Aud* auditory cortex, *BLA* basolateral amygdala, *Coch* cochlea, *IC* inferior colliculus, *MPFC* medial prefrontal cortex, *MS* medial septal nucleus, *NAC* nucleus accumbens, *HPC* hippocampus, *MD* mediodorsal thalamus, *PnC* nucleus reticularis pontis caudalis, *PPTg* pedunculopontine nucleus, *SC* superior colliculus, *VP* ventral pallidum, *VTA* ventral tegmental area.

6. The regulation of PPI by the nucleus accumbens

6.1. NAC lesions and PPI

One often-employed strategy for exploring the contribution of a brain region to the regulation of a behavior is to measure changes in the behavior after the region has been damaged or inactivated. While this approach clearly has some interpretative limitations, studies employing ablative or cytotoxic lesions of the NAC in rats have been interpreted to suggest a role of this structure in the regulation of PPI (22, 23). Such a role for the NAC was first suggested by findings that ablative lesions of the NAC blocked the startle-inhibiting effects of pulsatile tail pressure in rats (24). Subsequent studies confirmed and extended this evidence, demonstrating the loss of PPI after electrolytic or cytotoxic lesions on acoustic startle PPI in rats (22, 23, 25). These effects of ablative lesions were evident when damage was restricted to either the NAC core or shell subregions (23). In contrast, differential effects of NAC core vs. shell inactivation on PPI were reported by Pothuizen et al. (26), who detected reduced PPI after temporary inactivation of the NAC core, but not shell, by the GABA_A receptor agonist muscimol. Whether this outcome reflects subregional differences in sensitivity to GABAergic inactivation, vs. differences in the regulation of PPI per se, is difficult to assess.

6.2. NAC DA and PPI

PPI is disrupted in rats by systemic administration of a variety of DA agonists: indirect agonists (e.g. amphetamine (AMPH)) as well as direct D₁/D₂ (e.g. apomorphine (APO)), D₂/D₃ (e.g. quinpirole) and D₃-preferential (e.g. pramipexole) agonists. This was first demonstrated using low doses of APO in rats after depletion of NAC DA (27), and subsequently extended to higher doses of both in intact rats (28). Since that time, PPI disruptive effects have been demonstrated using a long list of DA agonists, in rats, mice and humans (9, 29, 30).

Work by several groups suggests that at least some of the effects of DA agonists on PPI may be mediated by increased DA activity in the NAC. First, as noted above, low doses of APO that do not decrease PPI in control rats potentially disrupt PPI in rats that are surgically altered to have "supersensitive" DA receptors in the NAC (27). Second, the extracellular level of DA in NAC increases in rats after treatment with the indirect DA agonist amphetamine, and the magnitude and time course of this effect correspond very closely with the loss of PPI in these rats (31). Complementary data shows that the deficits of PPI induced by amphetamine or isolation is reversed by depletion of DA in the NAC (32, 33). Third, PPI is disrupted in rats by infusion of the D₂ agonist quinpirole or DA into the NAC or anteromedial striatum (34-37). The effects of intra-NAC quinpirole or DA infusion on PPI are reversed by systemic

treatment with D₂ antagonists (36, 38). Finally, there is a significant inverse relationship between NAC DA content and PPI in intact rats (39); consistent with this, rats (and humans) with low levels of basal PPI (and hence potentially elevated endogenous levels of NAC DA) are most sensitive to the PPI-enhancing effects of DA antagonists (40). Thus, the NAC appears to be one important substrate for the DA agonist-induced loss of PPI in rats, and conceivably, NAC DA levels may contribute to individual differences in PPI among intact, untreated rats.

Although dopamine D2 receptors in the rat NAC play an important role in the regulation of PPI in rats, they may interact in a synergistic manner with D1 receptors (41, 42). Interestingly, while D1 receptors may not independently regulate PPI in rats, it appears that they do play a more prominent role in regulating PPI in mice (43, 44). More recent evidence in rodents and humans also suggests that PPI can be disrupted by agonists preferential for the D3 receptor (45, 46), and that D3 antagonists may be capable of restoring PPI in isolation-reared rats (47). These findings are intriguing, as the expression of D3 receptors in the brain is highly localized, and expression levels in the NAC are amongst the highest in the brain in humans and rodents (48). The relative degree to which these different DA receptor subtypes contribute to the normal regulation of sensorimotor gating, or its disruption in pathological states, may be an important issue in the development of novel therapeutic agents.

6.3. NAC excitatory amino acids and PPI

While there is some evidence that NAC glutamatergic activity can modify PPI in the rat (37, 49), more is known about the PPI-regulatory effects of NAC alpha-amino-3-hydroxy-5-methyl-4-isoxazol propionic acid (AMPA). Infusion of AMPA into either the core or shell subregions of the NAC reduces PPI (50). Within the NAC core, the PPI-disruptive effects of AMPA are DA-dependent: they are blocked by either 6-OHDA lesions or systemic haloperidol injections. In contrast, the PPI-disruptive effects of intra-shell AMPA infusion are not reversed by DA blockade (50). These results suggest that, within the NAC core, activation of non-NMDA receptors causes a reduction in PPI via a facilitatory effect on presynaptic DA release. Such a mechanism is consistent with findings that blockade of non-NMDA receptors in the NAC core with CNQX prevents the PPI-disruptive effects of intra-core infusion of the DA releaser amphetamine. This effect is also restricted to the NAC core subregion: intra-shell infusion of amphetamine reduces PPI, but this effect is not opposed by co-infusion of CNQX (50). Thus, in contrast to the NAC core, within the NAC shell, DA and non-NMDA glutamate transmission appear to independently regulate PPI.

Kretschmer and Koch (37) demonstrated that PPI is disrupted by intra-NAC infusion of the glycine-site NMDA antagonist, 7-chlorokynurenic acid (7-CLKYN). Interestingly, neither these effects of 7-CLKYN, nor the PPI-

disruptive effects of systemic administration of the NMDA antagonist, dizocilpine, were opposed by lesions of the VP; in contrast, these same lesions blocked the PPI-disruptive effects of NA DA receptor stimulation. These authors interpreted their findings to suggest a divergence of NAC efferent projections, with those mediating the NAC DAergic regulation of PPI projecting to the VP, and those responsible for a NAC glutamatergic regulation of PPI bypassing the VP, and projecting directly to the PPTg.

6.4. NAC neuropeptides and PPI

The mesolimbic DA system is rich with neuropeptides, and the roles of several of these peptides in regulating PPI have been investigated. Behavioral changes after manipulations of some of these peptides – like cholecystokinin (CCK), neurotensin (NT), somatostatin (SS) and oxytocin (OX) - suggest that they may be permissive or interactive with the primary behavioral effects of mesolimbic DA or glutamate substrates (51). A profile consistent with these influences has begun to emerge in relation to the impact of mesolimbic neuropeptides on PPI. Thus, intra-NAC infusion of CCK appears to have little direct impact on PPI, but augments the PPI-disruptive effects of apomorphine (52). Cysteamine, which depletes SS, was shown to oppose the PPI-disruptive effects of systemic amphetamine administration (53). Similarly, PPI is not typically sensitive to systemic treatment with the peptide OX, but OX opposes the PPI-disruptive effects of dizocilpine (54).

Perhaps the most compelling evidence for the role of a mesolimbic peptide in the regulation of PPI relates to NT. Intra-NAC infusion of NT also has no direct impact on PPI, but complex interactions have been reported between NT and PPI-disruptive drugs, in which low doses of intra-NAC NT oppose the PPI-disruptive effects of amphetamine, while higher doses of NT either have no effect on, or actually potentiate the amphetamine effects (55-57). NT infusion into the ventral tegmental area has no significant effect on PPI, even at doses that significantly increase locomotor activity (57). Additionally, systemic treatment with the NT agonist PD 149163 appears to reverse the PPI-disruptive effects of both amphetamine and dizocilpine (39). Others have reported an important role of NT in the ability of antipsychotic drugs to normalize the PPI-disruptive effects induced by pharmacological, environmental, and genetic disruption of NT neurotransmission (cf. 58,59). They also demonstrated that viral vector overexpression of NT1 receptor in NAC completely blocked D-amphetamine- and dizocilpine-induced PPI deficits, while only partially antagonizing the effects of these drugs on locomotor activity (61).

Interestingly, rat strain – or at least strain-dependent properties of PPI – may be an important determinant of mesolimbic DA and neuropeptide effects on PPI. For example, rat strains with low basal PPI levels appear to be more sensitive to the PPI-enhancing effects of both atypical antipsychotics (40) and

NT (62). Whether this sensitivity reflects genetic differences in PPI-regulatory circuitry, or simply the impact of greater arithmetic range on the key dependent measure, is not well established. For example, the importance of variable “range” are suggested by evidence that one can most easily detect PPI-enhancing effects of antipsychotics under stimulus conditions that yield low basal PPI levels, even in relatively “high gating” Sprague Dawley rats (63). On the other hand, the contribution of genetic differences is suggested by evidence from selective crosses of “low gating” and “high gating” rat strains, that can yield novel strains in which basal PPI and PPI drug sensitivity can be dissociated (64).

6.5. NAC intracellular signal transduction and PPI

Evidence indicates that the DAergic regulation of PPI is mediated by D2 receptor activation in forebrain regions, particularly the NAC, and the subsequent reduction in GABAergic release “downstream” in the VP and perhaps other NAC projection targets (see above). Until recently, this model has left a mechanistic “black box” between the point of D2 receptor activation, and that of reduced VP GABA release. However, recent studies have identified elements of NAC D2-linked G-protein signal transduction pathways that may mediate the impact of DA agonists on PPI (Figure. 3, adapted from Kelly *et al.* (65). This pathway provides a means for the activation by cAMP of a number of important proteins, and is kept in balance by the synthesis of cAMP by adenylyl cyclase (AC), and the hydrolysis of cAMP by phosphodiesterase (PDE).

Culm *et al.* (66) demonstrated that D2 stimulation disrupts PPI by activating the inhibitory G α i/o proteins in the NAC, thereby reducing cAMP signaling by inhibiting AC activity. This mechanism is sensitive to adaptation, and the PPI-disruptive effects of D2 activity wane after prolonged D2 stimulation due to sensitization of cAMP signaling (66). This process does not involve changes in AC activity, since D1-mediated activation of cAMP remains unaltered. Rather, blunted sensitivity to D2 effects on PPI are accompanied by increased PKA activity, and CREB phosphorylation. NAC PKA activation appears to blunt the ability of D2 activation to disrupt sensorimotor gating, since the PPI-disruptive effects of the D2 agonist, quinpirole, are blocked by activation of NAC PKA via intra-NAC infusion of the cAMP analog, Sp-cAMPS. CREB phosphorylation in the NAC appears to play a role in several important behavioral responses to stimuli ranging from anxiogenic (67) to rewarding (68). Antipsychotics increase striatal PKA activity and induce CREB phosphorylation (69, 70), and under specific conditions (e.g. low basal inhibitory drive (29, 40)) can enhance PPI.

More direct evidence implicates G-protein signal transduction pathways in the regulation of PPI, and suggests that genetic alterations in these pathways can modify PPI levels. Mice expressing a constitutively active G α s subunit have *increased* striatal/NAC and *reduced* hippocampal/cortical cAMP levels,

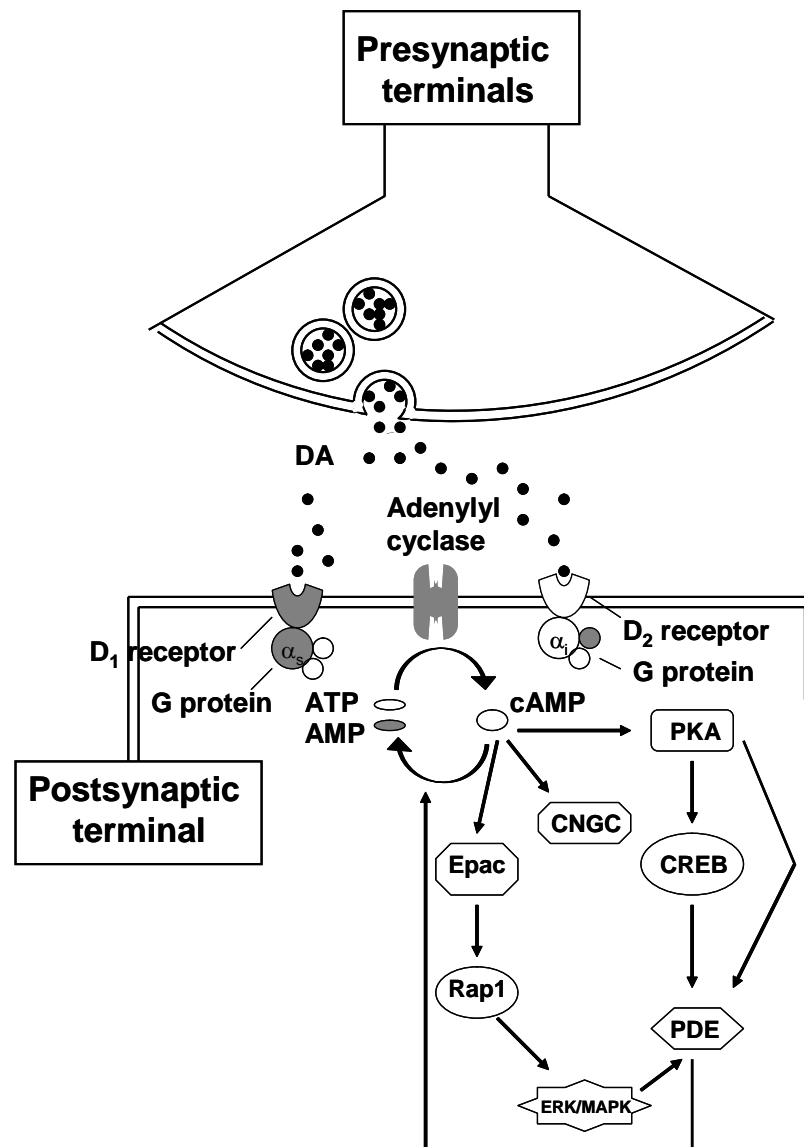


Figure 3. G-protein signal transduction cascade. D2 activation inhibits adenylyl cyclase (AC) activity. The resulting reduction in cAMP activity is associated with PPI deficits, that can be opposed by PKA activation, CREB phosphorylation or phosphodiesterase (PDE) inhibition (see text for references).

and exhibit PPI deficits compared to wild type (WT) littermates (65). Similar patterns of cAMP changes are elicited by AMPH, which also disrupts PPI in WT mice. PPI deficits in *Gas*-overactive mice are thought to reflect reduced cortical cAMP activity, since both PPI and cAMP reductions are opposed by haloperidol, the PDE-4 inhibitor rolipram, and genetically-engineered PKA activation. Converging evidence comes from recent studies in PDE-4B KO mice, which demonstrated marked PPI deficits - yet together with increased startle amplitudes - in this mouse type (71). Furthermore, PPI in WT mice is

impaired by intracerebroventricular administration of Rp-cAMPS, a competitive inhibitor of cAMP protein kinase A types I and II, and is increased by rolipram, which also blocks the PPI-disruptive effects of AMPH (65). Lastly, reduced PPI in postpartum rats is associated with reduced NAC (but not dorsal striatum) cAMP content (72). Thus, in both rat and mouse models, reduced forebrain cAMP activity is associated with PPI deficits, and these deficits are opposed by PKA activation and/or CREB phosphorylation.

Further evidence for the involvement of striatal cAMP (and potentially cGMP) signaling in PPI comes from novel behavioral, anatomical and pharmacological studies on PDE10a. PDE10a is a recently discovered PDE subtype that hydrolyzes both cAMP and cGMP (73). Interestingly, is strongly expressed in the striatum (74) and high levels of PDE10a protein and mRNA have been discovered in GABAergic medium spiny neurons of the NAC, caudate nucleus and olfactory tubercle. Medium spiny neurons are the predominant cell type of this brain region representing a convergence site for glutamatergic input from cortical and thalamic regions, and dopaminergic input from the midbrain (75). Importantly, evidence demonstrates that the preferential PDE10a inhibitor papaverine reverses PPI deficits induced by NMDA receptor antagonists and DA agonists in mice and rats (76, 77). These data further suggest that cAMP (and possibly cGMP) signaling downstream of DA receptor activation, or blockade by NMDA antagonists, in restricted brain regions that include the NAC, potentially regulate PPI in rodents.

While there is less direct evidence for the clinical relevance of these mechanisms, reduced cortical and basal ganglia cAMP concentration, and reduced cAMP PDE activity are reported in Tourette Syndrome (TS) (78, 79), a heritable disorder characterized by PPI deficits (12, 13).

6.6. NAC genes and PPI

There is compelling evidence that vulnerability for developing schizophrenia can be inherited (80). While this vulnerability is conveyed via genes, it must ultimately be mediated via changes in brain circuitry. Significant effort is being put towards identifying these vulnerability genes through the use of endophenotypes (81-83), and models are also being used to study the neural circuit basis of specific abnormal physiological processes in schizophrenia (84). PPI is one useful endophenotype that is deficient in schizophrenia patients and their unaffected first degree relatives (8, 9, 85, 86).

Animal studies have begun to focus on the genetics of brain substrates that regulate PPI (87-89). For example, there are heritable differences in the dopaminergic regulation of PPI in both mice (44, 90) and rats (91). Albino Sprague Dawley rats (SD) are significantly more sensitive to the PPI-disruptive effects of DA agonists (e.g. APO and AMPH), compared to hooded Long Evans rats (LE) (91-93). These differences are: 1) innate (91, 93); 2)

neurochemically specific (92); 3) follow relatively simple inheritance patterns (91); 4) cannot be explained by differences in maternal behavior (93); 5) appear to be linked to the inheritance of coat pigmentation (89, 91) and 6) to differences in NAC DA-linked signal transduction, at the levels of G-protein function (89) and perhaps CREB phosphorylation (94).

Not surprisingly, heritable differences in sensitivity to the PPI-disruptive effects of DA agonists appear to be related not only to differences in DA-linked signal transduction pathways, but also to differential gene expression patterns in the NAC. For example, we recently reported that one hundred and four genes exhibited significantly different NAC expression levels in SD and LE rats (50 genes at the $p < 0.001$ level and 104 genes at the $p < 0.01$ level) (95). Pathway analysis revealed that many of these genes contribute to DA receptor signaling, synaptic long-term potentiation or inositol phosphate metabolism. Many genes exhibiting substantial expression differences are thought to play important roles in disorders of impaired gating, including schizophrenia (e.g. Comt: $p < 4.81 \times 10^{-17}$).

7. NAC inputs and PPI

While the discussion thusfar has focused on the NAC and its role in regulating PPI, the impact of this “limbic-motor interface” on behavior, including PPI, reflects the fact that it processes inputs from several limbic and cortical regions, and integrates and translates these signals to lower motor circuitry. Significant changes in PPI follow experimental manipulations of at least three "limbic cortical" subregions that provide afferent inputs to the NAC in the rat: the hippocampus (HPC), the medial prefrontal cortex (MPFC) and the basolateral amygdala (BLA). The specific manipulations of the HPC, MPFC and BLA that result in a loss of PPI are consistent with existing models for the involvement of these brain regions in the pathophysiology of schizophrenia and other brain disorders. A substantial literature describes evidence for the PPI-regulatory effects of each of these structures, that will be reviewed briefly here. The reader is referred to several important reports of the role of these structures in the regulation of PPI (96-111). For many years, the working hypotheses surrounding each of these regions had been that their PPI-regulatory effects were mediated by projections to the NAC, and/or changes in NAC DA transmission. More recently, findings appear to emphasize interactions among these three limbic cortical regions in the regulation of PPI, either independent of, or in addition to, any role of the NAC (112-114).

The HPC has a complex infrastructure; in some cases, anatomical specificity in the neurochemical regulation of PPI within various hippocampal regions has been difficult to demonstrate, while in other cases, some inter-regional differences exist. In general, activation of the ventral hippocampus in adult rats (via infusion of neuro-excitatory chemicals like NMDA, picrotoxin

or carbachol, or electrical stimulation) leads to a reduction or loss of PPI (100-102). Lesions of the ventral hippocampus in adult rats have little direct impact on PPI, but after a delay of one month can render PPI “supersensitive” to the disruptive effects of direct (103) and indirect (104) DA agonists. By contrast, ventral hippocampal lesions in neonatal rats leads to reduced basal levels of PPI, in addition to an enhanced PPI-APO sensitivity in adulthood (105). These changes in PPI after neonatal ventral hippocampal lesions (NVHLs) support the construct validity of this model, which is based on the hypothesis that schizophrenia is a disorder of early developmental hippocampal dysfunction.

In some, but not all (50) cases, the PPI-disruptive effects of hippocampal manipulations are opposed by antipsychotics, and most commonly, by atypical antipsychotics such as clozapine (101). This link suggests the possible involvement of forebrain DA activity in hippocampally-mediated PPI changes. However, the mechanism for such an HPC-NAC interaction is not yet understood. In fact, the PPI-disruptive effects of intra-HPC NMDA infusion are not opposed by lesions of the major HPC-NAC projection through the fornix (112). Rather, lesions of the MPFC oppose the effects of ventral hippocampal stimulation on PPI. Our preliminary findings using a disconnection design suggest that the circuitry responsible for reduced PPI after HPC activation does not engage the NAC (115). Conceivably, the NAC may contribute to some of the delayed manifestations of ventral HPC damage – such as an enhanced sensitivity to PPI-disruptive effects of DA agonists – but may not participate in the regulation of PPI by acute ventral HPC activation.

Like the HPC, ablative lesions of the MPFC have little or no impact on basal levels of PPI in rats. Cytotoxic lesions of the MPFC have alternatively been reported to modestly but significantly reduce PPI (by 10-15%) (106) or to increase PPI at a trend level (103) and to a level of statistical significance (116). Lesion locations and size differed in these three studies, as did the pre-test history of the rats (food deprivation for partial reinforcement extinction testing in (106), but not in (103) or (116)). PPI is generally reduced by manipulations that decrease MPFC DA “tone”, such as depletion of MPFC DA by infusion of 6-hydroxydopamine (6OHDA)(117), or intra-MPFC infusion of D₁ or D₂ antagonists (107). It has been proposed that reduced MPFC DA transmission disrupts PPI via disinhibition of descending glutamatergic fibers, that results in subcortical increases in DA transmission in the NAC. Such a model is consistent with the finding that the PPI-disruptive effects of MPFC 6-OHDA lesions are blocked by systemic injection of haloperidol (117).

While there is general agreement across studies that prefrontal cortex DA contributes to the regulation of PPI in rats, there is less agreement about the specifics of this brain-behavior relationship. Thus, studies report a role of different receptor subtypes (D₁ vs. D₂) and MPFC subregions (MPFC vs. orbitofrontal cortex) in this capacity, and even differences in whether PPI is

disrupted by DA agonists or antagonists in the MPFC (108). Methodological differences across studies make it difficult to reconcile these various findings. While we have consistently detected PPI-disruptive effects of both systemic and intra-MPFC D1 blockade (113, 118, 119), we also demonstrated that: 1) the PPI-disruptive effects of intra-MPFC D1 blockade are not sensitive to systemic D2 antagonists, at doses that completely prevent the PPI-disruptive effects of the DA releaser, AMPH (118); 2) the PPI-disruptive effects of systemic D1 antagonism are insensitive to systemic D2 blockade, NAC DA depletion, or cytotoxic lesions of the MPFC (119). These findings call into question both the role of subcortical DA neurotransmission in the loss of PPI after MPFC D1 blockade, and the unique role of the MPFC in the regulation of PPI-disruptive effects of systemic D1 blockade.

As with lesions of the ventral HPC, cytotoxic lesions of the MPFC may also have an indirect impact on PPI, because they have been reported to result in a delayed increase in sensitivity to the PPI-disruptive effects of the DA agonist APO (103, 109). Such a "secondary" effect might reflect an increased DA receptor sensitivity in the aftermath of the loss of a descending tonic facilitatory influence on subcortical DA activity (120). This mechanism would be "arithmetically" opposite to that proposed to account for the PPI-disruptive effects of MPFC 6-OHDA lesions, but might be analogous to that observed after cytotoxic lesions of the ventral HPC, which result in a loss of tyrosine hydroxylase immunoreactivity in subcortical structures, as well as the MPFC and entorhinal cortex (121).

A third structure that regulates PPI and provides a substantial projection to the NAC is the BLA. Interestingly, PPI is disrupted by manipulations that at least superficially would be expected to suppress BLA output (e.g. ablative or cytotoxic lesions (110, 111) or NMDA antagonism (18) or increased BLA output (e.g. electrical kindling (122), or intra-BLA infusion of picrotoxin (18). The PPI-disruptive effects of intra-BLA infusion of either picrotoxin or dizocilpine are reversed by the high potency D₂ antagonist haloperidol (123), and those of BLA lesions are opposed by the atypical antipsychotic, quetiapine (99). Interestingly, as with the MPFC, there is some evidence that the BLA is a locus for a DAergic regulation of PPI, with D1 blockage increasing PPI, and D2 blockade decreasing PPI, in Long Evans rats (97). We have seen only marginal effects of intra-BLA DA infusion (34) or AMPH infusion (unpublished observation) on PPI in SD rats, conceivably because these manipulations activated opposing effects of both D1 and D2 receptor subtypes.

8. NAC outputs and PPI

The NAC is a long distance from the spinal motor neuron, and this distance must be traversed in order for the NAC to regulate any changes in a spinal motor reflex or its sensitivity to prestimuli. Ultimately, this regulation

must reflect changes within the pontine elements that mediate PPI. In the simplest sense, it would appear that NAC efferents access this pontine circuitry via two routes: either 1) directly, via descending projections to the PPTg (either monosynaptically or through an intermediate synapse within the ventral pallidum (VP)); or 2) indirectly, via NAC → VP → mediodorsal thalamic connections that “feed forward” into the MPFC and other limbic cortical regions. Because the focus of this chapter is the NAC, only a brief description of these efferent projections will be included, and the reader is referred to several important reports that focus on the involvement of the VP, MD and PPTg in the regulation of PPI (18, 22, 37, 124-126).

A number of studies have demonstrated that the PPI-disruptive effects of NAC manipulations (e.g. drug infusions or lesions) are prevented when the VP activity is suppressed, either by infusion of GABA agonists or by cytotoxic lesions (22, 37, 127). Additionally, the PPI-disruptive effects of NAC DA stimulation are reproduced by blockade of VP GABA receptors (25, 127). Systemic administration of DA agonists in rats disrupts PPI and causes a suppression of VP GABA efflux (128); we are now carefully assessing the convergence of these two drug effects, in terms of time course and dose sensitivity (129).

A simple model to account for these findings is that the effects of NAC DA activation are translated to lower PPI circuitry via a reduction in VP GABA efflux, and a disinhibition of VP projections to the PPTg. Two findings, however, are difficult to reconcile with this model. First, as noted above, VP lesions “spare” the PPI-disruptive effects of dizocilpine and intra-NAC 7-chlorokynurenic acid (37), which has been interpreted to suggest that the NAC-VP GABA projection is not essential to the PPI-disruptive effects of NAC glutamatergic substrates, or to the mechanisms responsible for the PPI-disruptive effects of systemically administered NMDA antagonists. Second, in mice, PPI is evoked by electrical stimulation of the VP (124). While the tonic effects of VP activation by GABA antagonists (e.g. reduced PPI after VP picrotoxin infusion) can be viewed as orthogonal to the phasic effects of VP electrical stimulation (suppression of startle), it would be difficult to account for both of these findings by a unified mechanism.

Decreased VP GABA activity may be translated to the primary startle circuit via VP efferents to the PPTg (130). We reported that electrolytic or quinolinic acid lesions of the PPTg markedly reduce or eliminate PPI in rats (125, 131), as does muscimol infusion into the PPTg (125, 132). Reports suggest that there are cytoarchitectural abnormalities in the PPTg in some schizophrenia patients (133), and developmental dysfunction in this region is thought to occur in patients with nocturnal enuresis, who also exhibit reduced PPI (134). Interestingly, both enuretic symptoms and deficient PPI can be opposed by 1-desamino-8-D-arginine vasopressin (dDAVP) (135); conceivably,

this physiology might be modeled in Brattleboro rats, who (like enuretics) exhibit abnormally low levels of basal PPI (136).

Many questions remain unstudied regarding the role of VP efferents in the regulation of PPI. Because the PPTg is but one of many targets of VP efferent fibers, it is reasonable to ask whether there is a role for other VP efferent projections in the regulation of PPI. For example, the VP provides GABAergic inputs to the mediodorsal thalamus (MD), the subthalamic nucleus (STN) (137), and a reciprocal projection to the NAC (138). In our experience, lesions of the STN in rats have no significant impact on PPI, or on the ability of APO to disrupt PPI, even though these lesions do significantly reduce other DA-mediated behaviors, such as amphetamine-stimulated locomotor activity (125). A role for the VP-MD projection in the regulation of PPI is consistent with our observations that PPI is significantly reduced by either lesions of the MD, or intra-MD muscimol infusion; these effects are substantially smaller than those observed after comparable manipulations of the PPTg (125).

9. Summary

The NAC plays an important role in the regulation of sensorimotor gating, as measured by prepulse inhibition of acoustic startle. The potent regulation of PPI by the NAC is evident after lesions of the structure, or after manipulations of NAC DA, EAA and neuropeptide function. This regulation differs substantially between the NAC core and shell subregions, at least in terms of the impact of DA - excitatory amino acids interactions on PPI. The NAC DAergic regulation of PPI appears to be mediated in the rat via D2-linked signal transduction pathways, and differences within these pathways - and within the expression of specific NAC genes - are linked to heritable differences in PPI sensitivity to DA agonists. While the NAC has well-characterized efferent and afferent connections within limbic-motor circuitries, it is not yet known whether the regulation of PPI by higher limbic-cortical structures is mediated via the NAC, or via alternative "parallel" pathways. In contrast, more substantial evidence links the NAC regulation of PPI to accumbens influences on the pontine tegmentum, exerted either directly or indirectly via GABAergic projections to the ventral pallidum. The degree to which pathology in these intrinsic NAC substrates and/or extrinsic interconnected circuitries contributes to sensorimotor gating deficits in brain disorders is an important area of ongoing research, as is the potential utility of targeting these substrates with novel psychotherapeutic agents.

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