Mechanisms of Dopamine D2 Receptors in Regulating Sensory Gating

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Abstract

Schizophrenia is a common psychiatric disorder of unknown etiology. Extensive literature indicates that symptoms such as cognitive impairment and thought disorder manifested by schizophrenia patients are closely associated with deficits in sensory gating function. Sensory gating refers to the process of filtering irrelevant sensory information from external sensory inputs in a stimulus-rich environment, thereby executing attention-related cognitive processes to respond to salient stimuli. The classic paradigm for investigating sensory gating is prepulse inhibition of the startle reflex. Studies have demonstrated that dopamine D2 receptors can participate in modulating the process of prepulse inhibition; however, the underlying mechanism by which dopamine D2 receptors regulate prepulse inhibition remains unclear. Elucidating the key brain regions, neural circuits, and molecular mechanisms through which dopamine D2 receptors regulate sensory gating, namely prepulse inhibition, will facilitate in-depth research on sensory gating function in schizophrenia.

Full Text

Mechanisms Underlying the Role of Dopamine D2 Receptors in Regulating Sensory Gating

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Abstract

Schizophrenia is a common psychiatric disorder with unclear etiology. Extensive literature indicates that symptoms such as cognitive disturbances and thought abnormalities in schizophrenia patients are closely related to deficits in sensory gating function. Sensory gating refers to the process of filtering irrelevant sensory information from the environment and executing attention-related cognitive processes to respond to salient stimuli. The classic paradigm for studying sensory gating is prepulse inhibition (PPI) of the startle reflex. Research has found that dopamine D2 receptors can participate in regulating the PPI process, but the mechanisms by which dopamine D2 receptors regulate PPI remain unclear. Investigating the key brain regions, neural circuits, and molecular mechanisms through which dopamine D2 receptors regulate sensory gating (i.e., PPI) will facilitate in-depth research on sensory gating function in schizophrenia.

Keywords: dopamine, sensory gating, dopamine D2 receptor, prepulse inhibition, schizophrenia

Schizophrenia is a common psychiatric disorder with unclear etiology, with a lifetime prevalence of 0.3–0.66% [**?**], causing serious harm to patients' physical and mental health. Symptoms of schizophrenia can be divided into three aspects: positive symptoms, negative symptoms, and cognitive deficits. Positive symptoms are primarily manifested as delusions (irrational, unrealistic, and impossible false beliefs that patients firmly hold) and hallucinations (perceiving external stimuli without external sensory input, such as hearing non-existent voices or seeing non-existent objects), which are particularly evident in acute schizophrenia patients. Negative symptoms include emotional blunting (lack of emotional expression), emptiness (lack of motivation), and social withdrawal. Cognitive symptoms refer to impairments in learning, memory, attention, and executive function [**?**, **?**].

Extensive literature indicates that the cognitive disturbances and thought abnormalities exhibited by schizophrenia patients are closely related to deficits in sensory gating function [**?**]. Sensory gating refers to filtering irrelevant sensory information from salient sensory information in an environment filled with sensory stimuli, and then executing attention-related cognitive processes to respond to prominent stimuli [**?**, **?**]. If sensory gating function is impaired, normal cognitive activities cannot be effectively completed due to interference from large amounts of irrelevant information. Multiple studies have shown that schizophrenia patients exhibit deficits in sensory gating function, manifesting as cognitive disturbances, attention deficits, and thought disorders [**?**]. The classic paradigm for studying sensory gating function is prepulse inhibition (PPI) of the startle reflex [**?**]. The startle reflex refers to the whole-body muscle flexion and extension reflex in humans or animals under sudden strong stimulation (such as sound or light), behaviorally manifested as a startle response [**?**]. PPI refers to the presentation of a weaker stimulus (prepulse) 30–500 ms before a stronger stimulus (pulse), which inhibits the startle response to the stronger stimulus [**?**].

PPI deficits reflect patients' inability to filter irrelevant information. Braff et al. first reported PPI deficits in schizophrenia patients [**?**], and further clinical studies found that PPI deficits in schizophrenia patients are closely related to various important positive and negative symptoms. For example, PPI abnormalities are associated with thought disorder and distractibility in schizophrenia patients, and antipsychotic drugs can improve PPI deficits while alleviating schizophrenia symptoms [**?**]. Based on the PPI phenomenon, Graham proposed the processing protection theory [**?**], suggesting that prepulse stimuli not only trigger central processing of the stimulus but also initiate a gating process that reduces processing of subsequent strong interfering stimuli, thereby protecting early perceptual encoding of the prepulse signal. Therefore, PPI actually reflects the sensory gating process through the activity of the motor system and serves as an experimental model for measuring sensorimotor gating function.

Due to its high cross-species validity, the PPI deficit model in rodents is widely used to screen antipsychotic drugs. Studies have shown that dopamine receptor agonists can disrupt normal PPI. For example, both the direct dopamine receptor agonist apomorphine (which acts directly on dopamine receptors) and the indirect dopamine receptor agonist amphetamine (which indirectly activates dopamine receptors by increasing synaptic dopamine) can cause PPI deficits [**?**, **?**, **?**]. Research indicates that amphetamine increases dopamine content in the synaptic cleft by blocking dopamine transporter function [**?**, **?**], while apomorphine acts directly on dopamine receptors similar to dopamine [**?**]. Subsequently, many studies have confirmed that dopamine receptor agonists can disrupt PPI, while dopamine receptor antagonists such as haloperidol and clozapine can reverse PPI deficits, thereby establishing the important role of dopamine receptors in regulating PPI deficits [**?**, **?**].

Dopamine receptors mainly include two categories: D1-like receptors, including dopamine D1 and D5 receptors; and D2-like receptors, including dopamine D2, D3, and D4 receptors. Extensive studies have shown that PPI deficits induced by dopamine receptor agonists are mainly mediated by dopamine D1 and D2 receptors, but the roles of dopamine receptors differ across rodent PPI models. Dopamine D2 receptors primarily regulate PPI function in rats, while dopamine D1 receptors more prominently regulate PPI function in mice [**?**, **?**, **?**]. For example, researchers found that amphetamine-induced disruption of PPI in rats is mediated by dopamine D2 receptors rather than D1 receptors, and the presence of D1 receptors is not necessary for amphetamine to exert its disruptive effects on PPI in rats [**?**]. Moreover, studies have shown that dopamine D2 receptor agonists quinpirole and 7-OH-DPAT can disrupt PPI in rats, while dopamine D2 receptor antagonists can restore quinpirole-induced PPI deficits [**?**].

However, compared to rats, the role of dopamine D2 receptors in regulating PPI in mice is less pronounced. Experiments with intraperitoneal injection of dopamine receptor agonists in mice have shown that dopamine D1 receptors rather than dopamine D2 receptors play a major role in regulating PPI in mice. For example, after intraperitoneal injection of the non-selective dopamine re-

ceptor agonist apomorphine, PPI in dopamine D1 receptor knockout mice was unaffected, while PPI in dopamine D2 receptor knockout mice and wild-type mice was disrupted [**?**]. Additionally, although some studies found that the dopamine D2 receptor antagonist eticlopride could restore PPI deficits induced by dopamine D1 receptor agonists, these studies also found that the dopamine D2 receptor agonist quinpirole had no effect on PPI in mice [**?**]. However, Ralph and colleagues later found that dopamine D2 receptor agonists could disrupt PPI in certain mouse strains (C3H/HeJ, SPRET/EiJ, and CAST/EiJ) [**?**]. The different performance of dopamine D2 receptors in regulating PPI in rats and mice suggests species differences in dopamine D2 receptor function, which may be due to differences in the distribution density of presynaptic and postsynaptic dopamine D2 receptors in rats and mice [**?**].

As a phenotype of schizophrenia, PPI deficits reflect cognitive impairments in schizophrenia to some extent, and exploring the regulatory mechanisms of PPI can promote research on cognitive deficits in schizophrenia. Dopamine D2 receptors are the main target for treating schizophrenia. PPI deficits exhibited by schizophrenia patients can be simulated by injecting dopamine D2 receptor agonists in rodents, and both typical and atypical antipsychotic drugs can improve PPI deficits by inhibiting dopamine D2 receptor function in rodents. Therefore, this review primarily focuses on the PPI model to explore the mechanisms by which dopamine D2 receptors regulate sensory gating in animals, and to better understand the specific mechanisms of cognitive symptoms in schizophrenia through a clearer understanding of this model, thereby better serving the treatment of schizophrenia.

2. Neural Circuits of Prepulse Inhibition

Neural circuits are the basis of brain function, and clarifying the composition and working principles of neural circuits that mediate and modulate PPI is crucial for further research on PPI mechanisms. For PPI, there are two main circuits involved in its regulation: the primary circuit that mediates PPI and the circuit composed of higher centers that modulate PPI.

2.1 Primary Circuit of Prepulse Inhibition

The primary neural circuit that mediates PPI is located in the brainstem and is mainly involved in the occurrence of PPI. Studies have found that PPI can still be observed after surgical removal of the forebrain in rats, indicating that the primary circuit mediating PPI is located in the brainstem [**?**, **?**], mainly including the inferior colliculus (IC), superior colliculus (SC), pedunculopontine tegmental nucleus (PPTg), and pontine reticular nuclei (PnC). Therefore, PPI is considered an automated process [**?**]. Research shows that these nuclei constitute the primary neural circuit of PPI [**?**], and the primary neural circuit includes both the excitatory circuit for the startle response and the inhibitory circuit that mediates PPI. Specifically, the excitatory circuit for the startle response involves auditory stimuli transmitted via auditory receptors to the

cochlear nucleus, which sends fibers projecting to the pontine reticular nucleus, which in turn sends fibers to motor neurons in the brain and spinal cord to elicit the startle response. The inhibitory circuit that mediates PPI involves auditory prepulse stimuli transmitted through the ascending auditory pathway to the inferior colliculus in the midbrain. The deep layers of the superior colliculus receive projections from the inferior colliculus and transmit signals upward to the pedunculopontine tegmental nucleus. Upon receiving the auditory prepulse signal, the pedunculopontine tegmental nucleus activates cholinergic neurons within it and projects downward to the pontine reticular nucleus located in the middle to upper pons, acting on M-type cholinergic receptors in the pontine reticular nucleus to achieve inhibition of the startle stimulus by the auditory prepulse [**?**] (Figure 1 [Figure 1: see original paper]). The pontine reticular nucleus can receive projections from auditory sensory neurons and the pedunculopontine tegmental nucleus, and can also send fibers to motor neurons in the brain or spinal cord [**?**, **?**, **?**].

2.2 Higher Centers Regulating Prepulse Inhibition

The complete PPI process can occur in the brainstem without forebrain involvement, but PPI receives top-down modulation from forebrain regions [**?**, **?**]. In animal experiments, manipulating the forebrain through specific brain lesions, localized injection of specific receptor agonists, antagonists, or neurotoxins, and electrical stimulation can be used to explore the neural circuit mechanisms by which the forebrain regulates PPI. Studies have found that forebrain regions involved in PPI regulation mainly include the nucleus accumbens (NAc) [**?**, **?**, **?**], ventral tegmental area (VTA) [**?**], hippocampus (HPC) [**?**], amygdala [**?**], and prefrontal cortex (PFC) [**?**].

Swerdlow et al. proposed the CSPP circuit (Figure 2 [Figure 2: see original paper]) [**?**, **?**], i.e., the limbic cortex-striatum-pallidum-pontine tegmentum circuit [**?**, **?**]. In addition to receiving dopaminergic projections from the ventral tegmental area, the nucleus accumbens also receives glutamatergic projections from limbic cortices (mainly including the prefrontal cortex, hippocampus, and amygdala) and sends GABAergic projections to the ventral pallidum and pedunculopontine tegmental nucleus [**?**]. That is, the prefrontal cortex, amygdala, and hippocampus regulate PPI through the nucleus accumbens, while the nucleus accumbens regulates PPI through the ventral pallidum and pedunculopontine tegmental nucleus downstream [**?**].

Many studies have confirmed that multiple regions in the forebrain and brainstem are involved in PPI regulation, and these regions mainly exert their effects on PPI through the dopaminergic neurotransmitter system. Dopaminergic neurons are mainly located in the ventral tegmental area and substantia nigra pars compacta, projecting to other brain regions and forming four main pathways: (1) the nigrostriatal pathway, with fibers originating from the substantia nigra pars compacta and terminating in the striatum; (2) the mesolimbic pathway, with fibers originating from the ventral tegmental area and terminating in the

limbic system; (3) the mesocortical pathway, with fibers originating from the ventral tegmental area and terminating in the prefrontal cortex; and (4) the tuberoinfundibular pathway, with fibers originating from the arcuate nucleus and terminating in the portal circulation of the median eminence. Combined with the CSPP circuit, this review mainly discusses the role of four brain regions—the prefrontal cortex, hippocampus, amygdala, and striatum—in regulating PPI. The prefrontal cortex, hippocampus, amygdala, and ventral striatum mainly receive dopaminergic projections from the ventral tegmental area, while the dorsal striatum mainly receives dopaminergic projections from the substantia nigra pars compacta. Many studies have shown that dopamine D2 receptors play an important role in the regulation of PPI by the forebrain. Based on the distribution of dopamine receptors in different brain regions, this review mainly explores the mechanisms by which dopamine D2 receptors regulate PPI in the prefrontal cortex, hippocampus, amygdala, and striatum.

3.1 Prefrontal Cortex

As an important brain region for regulating cognitive function, the prefrontal cortex is involved in the regulation of various higher cognitive functions including attention, motivation, learning, and memory. Numerous studies have demonstrated that the prefrontal cortex receives dopaminergic projections from the ventral tegmental area (VTA) and regulates subcortical brain regions through glutamatergic outputs, thereby participating in PPI regulation. Both inhibition and excessive activation of dopaminergic synaptic transmission in the prefrontal cortex may disrupt PPI in animals. For example, local injection of 6-hydroxydopamine (6-OHDA) in the prefrontal cortex can reduce dopamine levels by approximately 90%, leading to PPI disruption [**?**]. However, some studies have reached inconsistent conclusions. Lesioning the prefrontal cortex with the excitotoxin ibotenic acid did not affect PPI but enhanced the disruptive effects of apomorphine on PPI. Local injection of the dopamine D1/D2 receptor blocker cis-flupenthixol in the medial prefrontal cortex also failed to disrupt PPI in Wistar rats [**?**], possibly because the lesions did not reach the extent required to disrupt PPI.

Although studies have confirmed that PPI in rodents can be regulated by activating or inhibiting dopamine receptors in the prefrontal cortex, the mechanisms by which dopamine D2 receptors regulate PPI remain unclear. Studies have found that injection of the dopamine D2 receptor antagonist sulpiride in the medial prefrontal cortex of rats can disrupt PPI, and only high doses of sulpiride can reduce PPI across all prepulse intensities [**?**]. However, local injection of the dopamine D2 receptor antagonist haloperidol in the prefrontal cortex can reverse PPI deficits induced by the dopamine receptor agonist apomorphine [**?**], indicating that dopamine D2 receptor antagonists can also reverse PPI deficits. In summary, both antagonism and agonism of dopamine D2 receptors in the prefrontal cortex can disrupt PPI, suggesting that moderate activation of dopamine D2 receptors helps maintain normal PPI. The application of the typical antipsy-

chotic haloperidol in the prefrontal cortex can normalize PPI, indicating that the prefrontal cortex may be a key brain region where dopamine D2 receptor antagonists reverse PPI deficits in schizophrenia.

Early studies found that activation or inhibition of dopamine receptors in the prefrontal cortex can regulate PPI, while more recent research has investigated the mechanisms of dopamine receptor involvement in PPI regulation at the neural circuit level. Results show that dopaminergic neuron axons from the ventral tegmental area form synaptic contacts with glutamatergic neurons in the prefrontal cortex, regulating the excitability of glutamatergic neurons by activating dopamine receptors, thereby modulating subcortical brain region function [**?**]. Glutamatergic neurons in the prefrontal cortex project to the nucleus accumbens and ventral tegmental area, and studies have shown that dopamine D2 receptors are mainly located on pyramidal neurons in the prefrontal cortex [**?**]. Therefore, dopamine may inhibit excitatory projections in the prefrontal cortex by acting on dopamine D2 receptors on glutamatergic neurons, thereby enhancing dopaminergic input to the nucleus accumbens [**?**, **?**], leading to PPI deficits in rats.

In summary, current studies show that local injection of dopamine D2 receptor antagonists in the rat prefrontal cortex can disrupt PPI, supporting the view that dopamine deficiency in the prefrontal cortex leads to sensory gating deficits, and that prefrontal cortex regulation of PPI may be achieved through modulation of the nucleus accumbens. However, the effects of reduced dopamine function in the prefrontal cortex on PPI require further investigation.

Interestingly, local injection of dopamine receptor agonists in the prefrontal cortex can also cause PPI deficits. For example, local injection of apomorphine in the prefrontal cortex leads to PPI deficits [**?**], suggesting that excessive dopaminergic synaptic transmission in the prefrontal cortex also disrupts PPI. Studies have found inconsistent effects of amphetamine and apomorphine on PPI in rats, with amphetamine failing to disrupt PPI while apomorphine can [**?**]. This discrepancy may be due to different mechanisms of action of these two dopamine receptor agonists. The direct dopamine receptor agonist apomorphine can act on postsynaptic dopamine D2 receptors, while the indirect agonist amphetamine increases presynaptic dopamine release. The stimulation level of direct agonists on receptors may be higher than that of indirect agonists, while the postsynaptic effects of amphetamine-promoted dopamine release may be consistent with normal conditions [**?**]. In the aforementioned studies, the use of non-selective dopamine D2 receptor agonists produces interactions among multiple dopamine receptors, making the investigation of dopamine' s role in regulating PPI difficult and complex. With improved specificity of dopamine receptor agonists, it has become possible to study the role of individual receptors in regulating PPI.

3.2 Hippocampus

As a key brain region regulating selective attention, the hippocampus is also involved in PPI regulation, but its modulation of PPI may occur more through indirect pathways [**?**]. Studies on hippocampal neural circuits have found that the hippocampus receives dopaminergic projections from the ventral tegmental area. Multiple studies have shown that rats with hippocampal lesions do not exhibit PPI deficits but become more sensitive to PPI disruption induced by dopamine receptor agonists. For example, after lesioning the ventral hippocampus with the excitotoxin ibotenic acid, rats showed increased sensitivity to apomorphine-induced PPI deficits [**?**]. Consistent with this result, neonatal rats with excitotoxic hippocampal lesions showed decreased PPI function after puberty and increased sensitivity to apomorphine-induced PPI deficits [**?**], indicating that ventral hippocampal damage enhances the effects of dopamine receptor activation on PPI disruption. In the dorsal hippocampus, studies have found that dorsal hippocampal lesions in SD rats enhance PPI without altering sensitivity to apomorphine-induced PPI deficits [**?**].

In summary, PPI is regulated by dopaminergic synaptic transmission in the hippocampus, but the role of dopamine D2 receptors in this process remains to be discussed. For example, studies have found that local injection of the dopamine D2 receptor agonist quinpirole and amphetamine into the CA1 region of the dorsal hippocampus of Wistar rats can clearly cause PPI deficits, but the disruptive effect of amphetamine on PPI can only be reversed by the dopamine D1 receptor antagonist SCH23390, not by the dopamine D2 receptor antagonist sulpiride [**?**]. Additionally, studies have found that animals with ventral hippocampal damage are more susceptible to PPI disruption by the dopamine D2 receptor agonist quinpirole [**?**]. Furthermore, juvenile rats that experienced maternal separation from postnatal day 1 to 21 showed poorer PPI function after puberty [**?**], with decreased dopamine D2 receptor expression in the nucleus accumbens and hippocampus [**?**]. In summary, dopamine D2 receptors in the hippocampus play an important role in regulating PPI behavior. With the development of chemogenetics and optogenetics technologies and the development of specific dopamine D2 receptor agonists or antagonists, it will be more helpful to understand the mechanisms by which dopamine D2 receptors in the hippocampus regulate PPI.

3.3 Amygdala

The amygdala has received considerable attention in etiological research on schizophrenia, and dopamine in the amygdala is also involved in PPI regulation [**?**]. Most studies on amygdala regulation of PPI have focused on the basolateral amygdala. Studies have found that local injection of dopamine into the basolateral amygdala leads to PPI deficits [**?**], suggesting that dopamine receptors in the basolateral amygdala may be involved in PPI regulation. Further studies have found that injection of the non-competitive GABA_A receptor antagonist picrotoxin and the NMDA receptor antagonist MK-801 into the baso-

lateral amygdala disrupts PPI, but this disruptive effect can be reversed by the dopamine D2 receptor antagonist haloperidol [**?**], suggesting that the disruptive effects of picrotoxin and MK-801 on PPI in the basolateral amygdala may be mediated by dopamine D2 receptors. Studies on dopamine receptors have found that both dopamine D1 and D2 receptors are involved in the basolateral amygdala' s regulation of PPI. Stevenson and Gratton' s study demonstrated that injection of the dopamine D2 receptor antagonist raclopride into the basolateral amygdala reduced PPI in rats, with higher doses of raclopride producing more pronounced disruptive effects [**?**]. Later, researchers found that injection of the direct dopamine receptor agonist apomorphine, the indirect dopamine receptor agonist amphetamine, and the dopamine D2 receptor agonist quinpirole into the basolateral amygdala all led to reduced PPI [**?**]. The inconsistent results between Stevenson and Gratton' s study and Salum' s study may be due to quinpirole' s higher affinity for dopamine D4 receptors compared to raclopride, but this possibility requires verification. Research on amygdala regulation of PPI has mainly focused on the basolateral amygdala, while the role of dopamine D2 receptors in other amygdala subregions, such as the central and medial amygdala, in PPI regulation needs to be explored using new technologies.

3.4 Striatum

The striatum is divided into the ventral striatum and dorsal striatum. The ventral striatum is primarily the nucleus accumbens (NAc), which mainly receives dopaminergic projections from the ventral tegmental area, while the dorsal striatum mainly receives dopaminergic projections from the substantia nigra pars compacta. Studies have demonstrated that both the ventral and dorsal striatum play important roles in regulating PPI in rodents. In studies of normal mice, mice with poorer PPI function, especially female mice, showed higher dopamine content and dopamine D2 receptor expression in the striatum compared to animals with normal PPI [**?**]. In transgenic animal studies, high levels of dopamine in the striatum (caudate nucleus and nucleus accumbens) of dopamine transporter knockout mice led to significant PPI deficits [**?**], and intraperitoneal injection of the dopamine D2 receptor antagonist raclopride could reverse PPI deficits induced by increased striatal dopamine content [**?**].

The ventral striatum' s involvement in PPI regulation is mainly mediated by the nucleus accumbens. The nucleus accumbens not only receives dopaminergic projections from the ventral tegmental area but also receives glutamatergic projections from the hippocampus, prefrontal cortex, and amygdala. The interaction of these projections can regulate the excitability of nucleus accumbens neurons, thereby exerting regulatory effects on PPI [**?**]. Therefore, the nucleus accumbens appears to be a key subcortical integration "hub"connecting forebrain and limbic structures that control cognition and behavior, with the dopamine projection from the ventral tegmental area to the nucleus accumbens considered a key pathway for regulating PPI [**?**, **?**]. Some studies on the nucleus accumbens have found that activation of dopamine D1/D2 receptors in the nucleus accum-

bens induces PPI deficits. For example, direct injection of dopamine into the nucleus accumbens leads to reduced PPI [?], and injection of the dopamine receptor agonist apomorphine into the nucleus accumbens also causes PPI deficits, but prior injection of 6-OHDA into the nucleus accumbens can alleviate PPI deficits [?], suggesting that normal dopamine content in the nucleus accumbens may be crucial for maintaining normal PPI levels.

Most research results indicate that dopamine regulation of PPI in the nucleus accumbens mainly occurs through dopamine D2 receptors [?]. Researchers injected the dopamine D2 receptor agonist quinpirole into the nucleus accumbens and found that PPI in rats decreased, while systemic injection of the dopamine D2 receptor antagonist haloperidol could reverse PPI impairment caused by quinpirole, indicating that activation of dopamine D2 receptors in the rat nucleus accumbens can disrupt PPI [?]. Studies on the role of dopamine D1 receptors in the nucleus accumbens in regulating PPI have found that injection of the dopamine D1 receptor antagonist SCH23390 into the rat nucleus accumbens does not affect PPI [?]. In mouse PPI models, the role of dopamine D2 receptor excitability in regulating PPI remains controversial. Mohr et al. found that injection of quinpirole into the nucleus accumbens of C3H mice actually increased PPI, while injection of the dopamine D1 receptor agonist DAR-0100 (dihydrexidine) did not affect PPI [?].

Some studies have confirmed that the nucleus accumbens receives projections from the prefrontal cortex, hippocampus, and amygdala, and may regulate PPI through direct or indirect pathways. The next-level center for nucleus accumbens regulation of PPI may be located in the ventral pallidum (VP) [?], and this regulatory mechanism may be mediated by the GABAergic projection circuit from the nucleus accumbens to the ventral pallidum [?, ?]. For example, studies have found that local injection of the GABA_A receptor agonist muscimol into the ventral pallidum can reverse PPI deficits caused by dopamine injection into the nucleus accumbens [?]. Consistent with this result, studies have found that local injection of the NMDA receptor agonist quinolinic acid into the nucleus accumbens can induce PPI deficits in rats, while local injection of muscimol into the ventral pallidum can reverse PPI deficits [?]. However, Kretschmer and Koch believe that the nucleus accumbens regulates PPI through monosynaptic direct projections to the pedunculopontine tegmental nucleus [?]. It is speculated that this direct effect may be mediated by GABA release within the pedunculopontine tegmental nucleus, as functional inhibition of excitability in the pedunculopontine tegmental nucleus with muscimol can cause PPI deficits in rats.

In the pathway from the substantia nigra pars compacta to the dorsal striatum, Rodrigues S et al. found that functional inhibition of dorsal striatum excitability with muscimol did not affect PPI [?], a result consistent with Kodsi and Swerdlow' s findings [?], indicating that inhibiting dorsal striatum function does not affect PPI. However, the same study found that injection of the dopamine D2 receptor antagonist sulpiride into the dorsal striatum did not affect animal PPI

[?].

4. Molecular Mechanisms of Dopamine D2 Receptor Regulation of PPI

Dopamine receptors have multiple signal transduction pathways. Activation of dopamine D1 receptors mainly activates adenylate cyclase through Gα proteins to produce cAMP (cyclic adenosine monophosphate), which can exert specific effects by activating PKA (protein kinase A). In contrast, activation of dopamine D2 receptors mainly couples dopamine with Gi/o proteins, inhibiting cAMP production and subsequently inhibiting PKA activity [?]. In addition, activation of dopamine D2 receptors can also reduce the phosphorylation levels of Akt (protein kinase B) and its downstream GSK3 (glycogen synthase kinase 3) through atypical signaling pathways. The regulatory effects of dopamine D2 receptors on behavior cannot be separated from the involvement of specific signal transduction pathways. In transgenic mice lacking dopamine transporters in the striatum, sustained high levels of dopamine in the synaptic cleft lead to reduced Akt phosphorylation levels, which indirectly leads to reduced GSK3 phosphorylation levels and increased activity [?, ?].

4.1 AKT/GSK3 Pathway in PPI Regulation

Akt, also known as protein kinase B (PKB), is a protein kinase that can cause serine/threonine phosphorylation. Akt phosphorylation mainly occurs at two sites: threonine 308 and serine 473. The upstream signaling pathway that regulates Akt is mainly the phosphatidylinositol signaling pathway. Phosphorylated PIP3 can cause Akt to accumulate at the cell membrane, and PKD1 (phosphatidylinositol-dependent kinase 1) can act on Akt to cause phosphorylation at threonine 308, while phosphorylation at the other site (serine 473) is caused by the PDK2/rictor-mTOR complex [?]. GSK3 has two isoforms, GSK3α and GSK3β, which are two related serine/threonine protein kinases initially discovered in relation to insulin regulation of glycogen synthesis. GSK3α and GSK3β have intrinsic activity when not phosphorylated, but become inactivated once serine 21 (GSK3α) or serine 9 (GSK3β) is phosphorylated. Akt can inactivate GSK3α and GSK3β by phosphorylating them [?]. Existing studies have confirmed that activation of dopamine D2 receptors can regulate PPI through downstream signaling pathways. Moreover, activation of dopamine D2 receptors induces the formation of a signaling complex of β-arrestin2, Akt, and glycogen synthase kinase 3 (GSK-3). Researchers injected amphetamine into mice and found that PPI in Akt1 knockout mice was significantly lower than in wild-type mice [?], indicating that Akt1 plays a role in the process of dopamine affecting PPI.

Some studies have also demonstrated that GSK3 is involved in PPI regulation. Chronic exposure to antipsychotic drugs (clozapine and risperidone, etc.) increased GSK3 expression in rat brain regions, while drugs such as amphetamine

can disrupt PPI and inhibit GSK3 activity [**?**]. Subsequently, researchers injected the GSK3 inhibitor SB216763 into the medial prefrontal cortex of mice and found that PPI was disrupted, supporting the role of GSK3 in regulating PPI [**?**]. However, some studies reported that PPI was impaired in DISC1 (Disrupted-in-Schizophrenia-1) mice, and the GSK3β inhibitor TDZD-8 could restore PPI in DISC1 mice [**?**]. Additionally, some studies reported that the GSK3 inhibitor SB216763 could reduce PPI disruption caused by the serotonin type 1 receptor agonist RU24969 and the NMDA receptor antagonist ketamine [**?**, **?**]. In summary, GSK3 plays a role in regulating PPI, but there is some controversy regarding whether increased GSK3 activity disrupts PPI or reverses disrupted PPI. Moreover, the above studies only addressed the role of GSK3 in mouse PPI, while the role of GSK3 in rat PPI remains unknown.

4.2 G Protein/cAMP/PKA Pathway

The role of the dopamine D2 receptor Gi/o/cAMP/PKA pathway in PPI has been investigated to some extent [**?**]. Culm and colleagues injected pertussis toxin into the NAc of SD rats to inhibit Gi/o protein function and found that the disruptive effect of the dopamine D2 receptor agonist quinpirole on PPI was reduced, and pertussis toxin did not affect PPI in normal animals [**?**]. Therefore, researchers believe that the PPI disruption effect caused by dopamine D2 receptor activation is mediated through the Gi/o pathway in the nucleus accumbens, indicating that adenylate cyclase and PKA play important roles [**?**]. Subsequently, Culm found that local injection of the PKA agonist Sp-cAMPS into the nucleus accumbens could reverse PPI deficits caused by systemic administration of the dopamine D2 receptor agonist quinpirole [**?**].

Based on these findings, both the PKA and PKB signaling transduction pathways may play certain roles in the signal transduction pathways of dopamine D2 receptor regulation of PPI.

5. Summary and Outlook

As a classic model for measuring sensory gating, PPI is a cross-species phenomenon that is easy to quantify and has been widely applied in research on schizophrenia and other diseases. Although the primary center mediating PPI is located in the brainstem, it is regulated by forebrain structures such as limbic cortex and striatum, and involves different neurotransmitters including dopamine, glutamate, and GABA. Forebrain regulation of PPI mainly includes brain regions such as the prefrontal cortex, hippocampus, amygdala, and striatum, which form the CSPP circuit [**?**]. Dopamine is an important neurotransmitter in the CSPP circuit' s regulation of PPI, but how dopamine D2 receptors exert their regulatory effects on PPI in the CSPP neural circuit remains to be studied, and the molecular mechanisms by which dopamine D2 receptors regulate PPI remain inconclusive. Although experiments have demonstrated that both the G protein/cAMP/PKA pathway and the AKT/GSK3 pathway play important roles, the specific regulatory mechanisms remain unknown.

Based on the above, many questions remain regarding the mechanisms by which dopamine D2 receptors regulate PPI. First, although the brain regions where dopamine D2 receptors regulate PPI have been extensively studied and the CSPP circuit has been proposed, questions remain about the role of dopamine in the circuit regulating PPI. With the development of viral tracing, chemogenetics, and optogenetics technologies, the neural circuits between brain regions regulating PPI can be more thoroughly analyzed. Moreover, due to genetic or structural differences between different animal strains, experimental results obtained in rats cannot be directly applied to humans. Therefore, further research needs to employ functional magnetic resonance imaging and electroencephalography techniques to better explore the mechanisms of sensory gating models in humans or non-human primates and apply these findings to the treatment of schizophrenia patients. Second, although the signaling pathways by which dopamine D2 receptors regulate PPI have been studied, controversies remain. Therefore, future studies can use tool drugs, transgenic technology, or viral injection to block either the G protein/cAMP/PKA pathway or the AKT/GSK3 pathway to observe PPI performance in animals, thereby exploring the roles of these two pathways in dopamine D2 receptor regulation of PPI. Finally, dopamine D2 receptors are influenced by strain differences when regulating PPI in rats and mice, and studies have shown that this influence is due to differences in the distribution density of dopamine D2 receptors in brain regions of rats and mice. Therefore, more transgenic technology needs to be applied to explore how different distribution densities of postsynaptic dopamine D2 receptors affect PPI.

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