Progress in Neuropsychopharmacology & Biological Psychiatry 95 (2019) 109681

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Inhibitory regulation of the prefrontal cortex following behavioral sensitization to amphetamine and/or methamphetamine psychostimulants: A review of GABAergic mechanisms

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ARTICLE INFO

Keywords:
Sensitization
Prefrontal cortex
GABA
Inhibition
Methamphetamine
Amphetamine
Psychostimulants

ABSTRACT

Behavioral sensitization to repeated psychostimulant administration has been proposed to reflect many of the neurochemical and behavioral changes that are characteristic of a range of disorders, including drug addiction and psychoses. While previous studies have examined the role of dopamine and glutamate neurotransmission in mediating sensitization, particularly within the prefrontal cortex (PFC), the role of inhibitory GABAergic processing of the PFC in the expression of sensitization is not well understood. Recent research, however, has proposed an emerging role of GABA synthesis, reuptake, ionotropic and metabotropic receptor regulation, and interneuronal changes following sensitization to methamphetamine and/or amphetamine within the PFC. The aim of this review, therefore, is to synthesize research findings on changes to the GABAergic network following sensitization induced by amphetamines (i.e., amphetamine and/or methamphetamine) in the PFC. In addition to providing an overview of global PFC changes, we also provide evidence of regional specific inhibitory influences on sensitized circuitry, focusing on the prelimbic and orbitofrontal cortices. We propose a neural circuit through which inhibitory PFC GABA changes mediate sensitized disease states, focusing on the interaction between the prelimbic and orbitofrontal cortices with subcortical brain structures and the mesolimbic system. Methodological considerations and avenues for future research are also discussed.

1. Introduction: behavioral sensitization

Behavioral sensitization refers to the unique phenomenon whereby repeat exposure to stimulus, such as a drug, results in a progressively increased behavioral and neurochemical response to that stimulus following a period of abstinence. While repeated exposure to a drug will cause a progressive reduction in the responsiveness to the effects of the drug, or 'tolerance', repeated administration of psychostimulants, such as amphetamine (AMPH) and/or methamphetamine (METH), can lead to an increased sensitivity to the behavioral (motor stimulant) and neurochemical (dopamine) effects (Robinson and Becker, 1986a). For example, while psychostimulants induce locomotor activity when administered acutely (Fray et al., 1980), a chronic intermittent administration regime will induce significantly more locomotor activity and striatal (nucleus accumbens, see Segal and Kuczenski (1997)) dopamine release when the subject is re-exposed to the same drug following a withdrawal period (Pierce and Kalivas, 1997; Ujike and Sato, 2004).

Sensitized behavior is most apparent after a period of abstinence and re-exposure to a drug. *Initiation* refers to the transient cellular and molecular changes that coincide with repeated drug exposure that cause an increase in behavior, such as increased locomotor activity. A large body of literature has shown that the initiation of sensitization is critically dependent on dopamine regulation in the mesolimbic pathway, specifically within the ventral tegmental area (Chen et al., 2009; Kalivas et al., 1993; Kalivas and Weber, 1988; Pierce and Kalivas, 1997; Pierce and Kumaresan, 2006; Vanderschuren and Kalivas, 2000a; Vezina, 2004). *Expression*, on the other hand, refers to the enduring neural changes that follow from the initiation process that maintain a persistent behavioral sensitivity to the stimuli. While the molecular mechanisms that characterize the initiation process have been well established, the expression of sensitization is more ambiguous, particularly given that the neuronal events that coincide with expression of sensitization appear to be distributed throughout the motivational circuit, including the nucleus accumbens (NAc), ventral tegmental area (VTA), the ventral pallidum, and the prefrontal cortex (PFC) (Pierce and Kalivas, 1997; Steketee, 2003).

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https://doi.org/10.1016/j.pnpbp.2019.109681
Received 13 April 2019; Received in revised form 18 June 2019; Accepted 26 June 2019
Available online 27 June 2019
0278-5846/

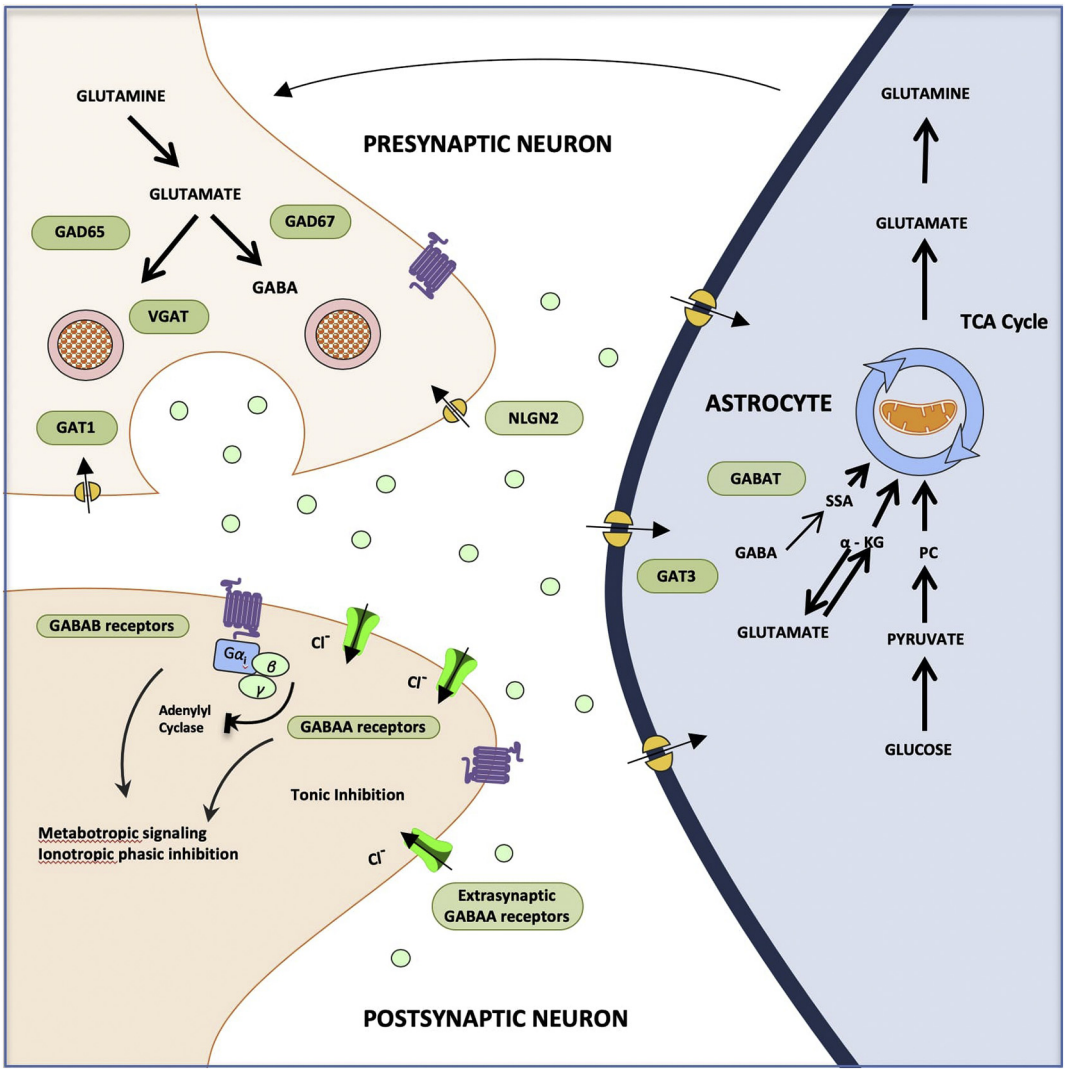

Fig. 1. A diagrammatic representation of the production, transport, reuptake, action and degradation of GABA (γ-aminobuytric acid) at an inhibitory synapse in the cortex. GABA is produced by the α-decarboxylation of glutamate by the rate-limiting enzyme, glutamate-decarboxylase (GAD). GAD is present as two isoforms, GAD_{67} and GAD_{65}, which mediate the production of the cytoplasmic and synaptic stores of GABA in the presynaptic neuron, respectively. GABA is transported to the neuronal membrane and synapse through the affinity of VGAT to bind to inhibitory vesicles. Exocytosis of GABA into the synapse activates a constellation of postsynaptic ionotropic ($GABA_A$) and metabotropic ($GABA_B$) receptors that mediate phasic inhibition and slow synaptic inhibitory neurotransmission, respectively. GABA spillover can also activate extrasynaptic $GABA_A$ receptors that are responsible for the tonic inhibition of postsynaptic neurons. GABAergic signaling is terminated through the reuptake of GABA to either the presynaptic membrane, via the GABA transporter 1 (GAT_1), or to astrocytes through the action of GABA transporter 3 (GAT_3). GABA is metabolized to glutamate and succinic-semialdehyde via the action of GABA transaminase ($GABA_T$). Drawing designed and created by adapting various slides purchased from Motifolio (http://motifolio.com/).

Behavioral sensitization has been traditionally studied in animals, and a large body of literature extending over several decades has shown robust and reliable evidence of behavioral sensitization across many stimulant drugs, environments (Badiani et al., 1995) and across a large range of animal subjects (Pierce and Kalivas, 1997; Steketee, 2003; Vanderschuren and Kalivas, 2000b). However, even early research noted evidence of sensitization in humans (Down and Eddy, 1932), and specifically, studies have shown humans sensitize to the effects of amphetamines (Sax and Strakowski, 2001; Strakowski et al., 2001; Strakowski et al., 1996). For example, subjects that are given three separate administrations of AMPH show increased motor activity and eyeblink responses following their third administration compared to the first or second exposures (Strakowski and Sax, 1998). Also, three injections of AMPH in humans induces dopamine release in the NAc after an AMPH challenge at both 2 weeks and 1 year later (Boileau et al., 2006), providing evidence that humans sensitize to the behavioral and neurochemical of amphetamines. Consequently, sensitization is traditionally interpreted in the context of addiction, with the mechanisms likened to increased negative symptoms (Comer et al., 2001) or craving associated with drug use that may lead to relapse following withdrawal (Cornish and Kalivas, 2001; Kalivas et al., 1998; Robinson and Berridge, 1993). Alternatively, studies have also used the sensitization paradigm to model various aspects of psychotic syndromes, particularly with regard to vulnerability to psychotic relapse (Weidenauer et al., 2017), with drug-induced locomotor sensitization often regarded as an animal model of stimulant-induced psychosis (Robinson and Becker, 1986b; Snyder, 1973; Ujike, 2002). Therefore, examination of the neural changes that mediate sensitization will enable further understanding of the mechanisms responsible for different aspects of addiction and psychosis.

Extensive research has shown that the prefrontal cortex (PFC) is implicated in the biology of sensitization to psychostimulants. For example, while the VTA and the NAc are critically involved in the initiation and expression of locomotor sensitization, respectively (Cador

et al., 1995; Paulson et al., 1991; Pierce and Kalivas, 1997; Steketee, 2003), excitatory projections from the PFC to the mesolimbic pathway, specifically the ventral tegmental area, are pivotal for locomotor sensitized behavior (Li et al., 1999; Li and Wolf, 1997; Morshedi et al., 2009; Pierce et al., 1998; Robinson and Kolb, 1997; Sorg et al., 2001; Wolf, 1998). Therefore, it follows that the role of glutamate and dopamine in the PFC following sensitization has been well described (for reviews see Steketee, 2003; Pierce and Kalivas, 1997). However, the role of inhibitory regulation of the PFC via GABAergic neurotransmission and interneurons has received considerably less attention. The aim of the current review, therefore, is to provide a review of the literature that has examined the role of inhibitory (i.e., GABA) mechanisms in behavioral sensitization, with the goal of providing an updated view on the neurocircuitry that subserves sensitized responding to psychostimulants, focusing on amphetamine and/or methamphetamine. For the purposes of this review, 'amphetamines' refer to both amphetamine and/or methamphetamines, rather than catecholamine/monoamine releasing psychostimulants, such as cocaine, or phenethylamines, such as 3,4-Methylenedioxymethamphetamine (i.e.,MDMA).

2. Inhibitory regulation of the prefrontal cortex

2.1. The GABAergic system

γ-aminobutyric acid (GABA) is the most ubiquitous inhibitory neurotransmitter in the central nervous system. Indeed, 25–50% of synapses contain GABA, 20–30% of neurons synthesize GABA and most neurons expresses GABA receptors (Koella, 1981; Sivilotti and Nistri, 1991). While GABA has both excitatory and inhibitory roles across various stages of brain development (Ben-Ari et al., 1994; Gao et al., 2001; Obrietan and van den Pol, 1995), GABA in the adult mammalian CNS is inhibitory, where in the PFC it regulates neuronal excitability through the inhibition of pyramidal cells and interneurons.

2.1.1. GABA synthesis, release, reuptake and metabolism

Reliable inhibitory regulation of the PFC relies on a large network of genes/proteins that control GABA synthesis, release, reuptake and metabolism. GABA is synthesized from the α-decarboxylation of glutamate by two allelic forms of the rate-limiting enzyme glutamate-decarboxylase, GAD_{67} and GAD_{65} (Roberts et al., 1950). While both GAD_{67} and GAD_{65} are present in all GABAergic cells, they diverge in terms of their relative concentration and subcellular localization (Erlander et al., 1991; Erlander and Tobin, 1991; Esclapez et al., 1993; Esclapez et al., 1994; Feldblum et al., 1993), with both playing different roles in GABA production. The activity of GAD isoforms is regulated by a pyridoxial 5′-phosphate cofactor, which either activates or silences when it is attached or released to the enzyme, respectively (Phillips, 2015). GAD_{67} is typically saturated with the cofactor, meaning that it predominantly exists in its active state. As such, GAD_{67} is localized throughout the neuronal body and regulates the cytoplasmic pool of GABA (Fig. 1) (Soghomonian and Martin, 1998), with over 90.0% of GABA production derived from GAD_{67} activity (Asada et al., 1997). GAD_{65}, on the other hand, is primarily expressed at axon terminals, where it regulates synaptic inhibitory neurotransmission through GABA vesicular filling only under sustained periods of elevated synaptic phasic activity (Choi et al., 2002; Hensch et al., 1998; Kash et al., 1997; Patel et al., 2006; Stork et al., 2000; Tian et al., 1999).

GABAergic neurotransmission is also regulated by specific mechanisms that control the release and reuptake of GABA at the synapse. GABA is packaged into vesicles and stored in the neuronal terminal until it is released by neuronal depolarization with the assistance of vesicular GABA transporter (VGAT). VGAT is found at terminals of GABAergic neurons where it facilitates the Ca^{2+} dependent vesicular transport of cytoplasmic GABA to the neuronal membrane for exocytosis into the synapse (Bellocchio et al., 1998; Chaudhry et al., 1998; Dumoulin et al., 1999; Fattorini et al., 2015; Fremeau Jr. et al., 2001). This places VGAT as pivotal for GABA-mediated inhibitory neurotransmission. The activity of synaptic GABA is terminated by Na^+ dependent GABA transporters, which are responsible for the reuptake of GABA at inhibitory synapses (Conti et al., 2004). Four distinct transporters for GABA are known: GAT_1, GAT_2, GAT_3 and BGT_1 (Borden et al., 1995a; Borden et al., 1995b). GAT_2 and BGT_1 are found exclusively outside the brain in the liver, kidney and leptomeninges, although there is some evidence for GAT_2 in some blood vessels of the brain (Zhou et al., 2012). The reuptake of GABA at inhibitory synapses in the PFC is regulated by the expression of GAT_1 and GAT_3 (Dalby, 2003). GAT_1 is predominantly localized to terminals and glia (Conti et al., 2004; Gadea and Lopez-Colome, 2001) where it regulates basal GABA levels in the extracellular space, while GAT_3 is exclusively found in glia (Conti et al., 2004). As such, GAT_3 is critically involved in the reuptake of GABA to the glutamate/glutamine cycle where it is metabolized by GABA-aminotransferase ($GABA_T$) to glutamate and succinic-semialdehyde (Fig. 1) (van der Laan et al., 1979).

2.1.2. $GABA_A$ receptors

GABA exerts its inhibitory effects by binding to GABA receptors on cortical neurons. There are two main types of GABA receptors: ionotropic $GABA_A$ receptors and metabotropic $GABA_B$ receptors. $GABA_A$ receptors are hetero-oligomeric membrane proteins composed of five receptor subunits that form a central chloride channel pore. $GABA_A$ receptors are structurally and pharmacologically complex, with each receptor composed from a pool of 19 distinct subunits, with each subunit encoded by separate genes and categorized into different family classes (α 1–6, β1–3, γ1–3, δ, ε, π, θ, ρ1–3). Receptors comprised of different subunit combinations are considered distinct receptor subtypes. Given the hetero-pentameric arrangement of $GABA_A$ receptors, together with the diversity of subunits available, it follows that a large number of permutations of $GABA_A$ receptors are possible; however, interestingly, only 20 have been clearly identified in the mammalian CNS (McKernan and Whiting, 1996). Indeed, $GABA_A$ receptor stoichiometry typically consists of 2α, 2β and 1γ, with the α1β2γ2 receptor combination the most abundant in most brain regions (McKernan and Whiting, 1996) and combinations of α1, α2, α3, α5, β2, β3 and γ2 subunits representing over 80% of benzodiazepine sensitive $GABA_A$ receptors in the adult brain (Pirker et al., 2000a). Variability across the individual subunits that compose the $GABA_A$ receptor is also salient, as more than one type of subunit is required (Schofield et al., 1987; Sieghart et al., 1999), subunits cannot be expressed in isolation and not all subunits can colocalize together to produce a functional receptor (Verdoorn et al., 1990). These findings suggest a high degree of specificity in the collection of subunits that compose $GABA_A$ receptors. Indeed, staining studies across the brain have shown considerable overlap in the expression of α1 and β2, α2 and β3, α4/6 and δ, suggesting that these combinations are generally expressed together (Jechlinger et al., 1998; Pirker et al., 2000b; Sur et al., 1999).

Depending on their arrangement, $GABA_A$ receptors represent distinct entities with specific functional and spatial-temporal profiles. While $GABA_A$ receptors were traditionally described as mediators of phasic inhibitory neurotransmission, a growing body of literature has shown that $GABA_A$ receptors can be located either synaptically or extrasynaptically (Fig. 1), with extrasynaptic $GABA_A$Rs mediating tonic inhibition secondary to ambient levels of GABA or GABAergic spillover (Brickley and Mody, 2012; Farrant and Nusser, 2005; Wei et al., 2003). Synaptic $GABA_A$ receptors that mediate phasic inhibition, and the hyperpolarization of postsynaptic neurons, typically comprise of α1, α2, α3, β2/3 and γ2 subunits. Extrasynaptic $GABA_A$ receptors, on the other hand, comprise of α4, α5, α6, together with β2/3 and δ subunits, although combinations with α1 and γ have been reported (Barnard et al., 1998; Crestani et al., 2002; Mortensen and Smart, 2006; Nusser et al., 1998).

2.1.3. $GABA_B$ receptors

$GABA_B$ receptors are metabotropic G-protein inhibitory receptors with seven transmembrane domains. $GABA_B$ receptors are found as two subtypes, $GABA_B1$ and $GABA_B2$. While $GABA_A$ receptors are located postsynaptically, $GABA_B$ receptors are found both pre and post-synaptically (Fig. 1) (Chalifoux and Carter, 2011), thereby having the capacity to alter both afferent and efferent inhibitory neurotransmission at the synapse, respectively. The activation of $GABA_B$ receptors can alter multiple cellular processes via slow synaptic transmission, either through the inhibition of neurotransmitter release (presynaptically) or through the inhibition of adenylate cyclase and downstream molecular pathways (postsynaptically). Activation of postsynaptic $GABA_B$ receptors can also increase the intracellular potassium concentration by opening potassium ion channels, which ultimately hyperpolarizes the postsynaptic neuron and produces a slow inhibitory post-synaptic current.

2.1.4. Interneurons

The majority of neurons (70–80%) in the cortex are excitatory pyramidal neurons that provide major excitatory projections between brain regions. Interneurons, on the other hand, constitute the remaining 20–30% of neuronal cortical cell types and have diverse molecular, morphological, physiological and synaptic properties (Cauli et al., 1997; DeFelipe, 1993, 2002; Kawaguchi and Kubota, 1997; Markram et al., 2004). Unlike pyramidal cells, interneurons have aspiny dendrites, receive excitatory and inhibitory synapses onto their soma, and their axons typically project laterally across columns or within the same localized area, meaning that they do not project to distant brain regions (Markram et al., 2004). In light of their axon restrictions, interneurons are also called 'local circuit neurons', and the majority of interneurons are inhibitory and use GABA as their neurotransmitter.

A major characteristic of inhibitory interneurons is their capacity to target different subdomains of neurons, which ultimately gives rise to their considerable variability in the cortex (DeFelipe, 1997; Somogyi et al., 1998). Classification of interneuron subtypes, however, is difficult due to the lack of objective features that can be used as classifying criteria (Ascoli et al., 2008). For example, dendritic morphology is the most variable feature of GABAergic interneurons and interneuron type cannot be determined by dendritic information alone. However, axonal morphology is more specific across interneuronal subtypes, and therefore axonal targeting, in conjunction with additional morphological and neurochemical phenotypes, can be used to differentiate amongst classes of inhibitory interneurons. While a range of interneuronal subtypes can be distinguished, the prevalence of each type varies as a function of species, brain region and neuronal layer.

Inhibitory interneurons can be distinguished based on their electrophysiological output and their molecular markers. Interneurons are typically characterized as representing three-broad classes of cells associated with irregular spiking (Porter et al., 1998), bursting (Kawaguchi and Kubota, 1993; Toledo-Rodriguez et al., 2004) and fast-spiking patterns (Chow et al., 1999; Toledo-Rodriguez et al., 2004). Fast-spiking interneurons have a constant high frequency firing rate with minimal interval between spikes, which is readily distinguishable from pyramidal cells and other interneuronal subtypes (Zaitsev et al., 2009). Fast-spiking cells form axons that target the perisomatic region, proximal dendrites, the initial axon segment and the cell body of pyramidal cells (Fig. 2). They are differentiated from other neuronal subtypes by the presence of the calcium binding protein parvalbumin (Freund, 2003), and parvalbumin-expressing cells have the highest density in layers 3 and 4 of the PFC. Fast-spiking cells can be further differentiated into two distinct subtypes, basket and chandelier cells (Fig. 2). Basket cells can be large, small or nested basket cells, all of which innervate the soma, the proximal dendrites and spines of pyramidal cells (Marin-Padilla, 1969; Wang et al., 2002). Chandelier cells, on the other hand, synapse onto the initial axon segment of pyramidal cells, and can therefore be referred to as axo-axonic cells (Somogyi, 1977). Parvalbumin-expressing neurons innervate either the axon or soma of pyramidal cells, placing them in a position to provide strong inhibitory control over dendritic integration, postsynaptic action potentials, and cell firing of excitatory efferents (Miles et al., 1996; Zhu et al., 2004). Indeed, parvalbumin-expressing cells regulate feed-forward inhibition and neuronal output, and given they have contact with a vast number of postsynaptic targets, these are requisite for the neuronal oscillation and synchronization of large groups of neurons (Cobb et al., 1995; Massi et al., 2012; Pouille and Scanziani, 2001; Sohal et al., 2009; Volman et al., 2011).

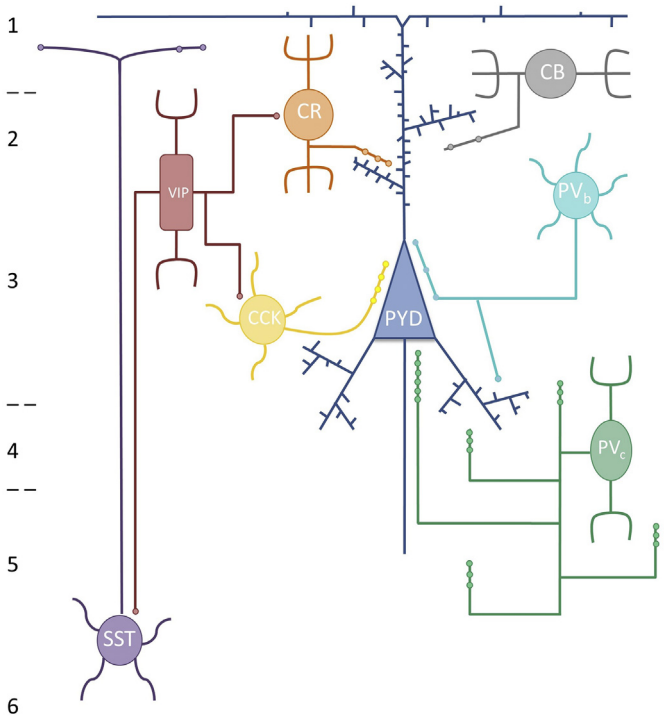

Fig. 2. Graphical representation of the various interneuronal subtypes in the prefrontal cortex (PFC) as expressed by their molecular markers. Parvalbumin (PV) is present in fast-spiking chandelier (PVc; green) and basket cells (PVc; light blue), which target the initial axon segment and perisomatic region and pyramidal cells (PYD; blue), respectively. Similarly, cholecystokinin-containing basket cells (CCK; yellow) target the initial axon segment of the pyramidal neuron. Somatostatin (SST; purple) cells are intrinsic to martinotti cells that target the pyramidal distal dendritic arbor while vasoactive intestinal peptide (VIP; red) is localized to multipolar cells that innervate other interneurons, suggesting they play a role in neuronal disinhibition. The calcium binding proteins, calbindin (CB; grey) and calretinin (CR; orange) represent bouquet interneurons that are characterized by a bursting and irregular spiking patterns, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Non fast-spiking cells, on the other hand, show an adaptive firing pattern whereby the interval between spikes increases with stimulus duration, and compared with fast-spiking cells, they have slower membrane constants and have slower synaptic inputs and outputs (Jonas et al., 2004). The majority of non fast-spiking cells innervate at dendritic sites away from the soma or initial axon segment (Fig. 2) (Megias et al., 2001), suggesting that they have a distinct functional role compared to parvalbumin-expressing fast-spiking cells. Non fast-spiking cells are more heterogeneous than fast-spiking cells and contain a distinct collection of neuropeptides. Cholecystokinin containing basket cells also target the perisomatic region of pyramidal cells (Fig. 2), although their input is different compared to parvalbumin-expressing basket cells (Somogyi et al., 2004). Martinotti cells, which are characterized by the presence of somatostatin, innervate mostly the distal dendritic arbor of pyramidal cells (Fig. 2) (Kawaguchi, 1995;

Kawaguchi and Kondo, 2002). Calbindin-containing double bouquet/neurogliaform cells have a dense axonal arbor around its own soma, suggesting that it projects predominantly to nearby dendrites (Kalinichenko et al., 2005). Overall, these findings suggest that non fast-spiking cells likely alter excitatory input to pyramidal cells, particularly given that they synapse onto pyramidal dendrites, and therefore have the capacity to modulate excitatory integration and the plasticity of glutamatergic synapses. However, vasoactive intestinal peptide-containing multipolar cells directly inhibit other interneurons (Pi et al., 2013), suggesting a prominent role of vasoactive intestinal peptide interneurons in the disinhibition of interneurons in the cortex.

3. The prefrontal cortex GABAergic system and behavioral sensitization

Findings have suggested a role of PFC GABAergic neurons in sensitization to amphetamines. Bu et al. (2013) found that GABA was reduced in the PFC following sensitization to METH, a finding they believed was secondary to increased GABA metabolism in the PFC. METH sensitization has also been shown to down-regulate the expression of GAD_{67} protein (Wearne et al., 2015) while Peleg-Raibstein et al. (2008) similarly found that GAD_{67} protein was downregulated in the inner layers of the PFC following AMPH sensitization. Interestingly, the expression of GAD_{67} mRNA appears to be unchanged in the PFC following sensitization (Wearne et al., 2016b), indicating potential post-translational modifications, increased GAD_{67} protein metabolism, or reduced afferent inhibitory drive to the PFC from distal brain regions following sensitization to METH.

There is also evidence that the mRNA expression of GABA transporters (GAT_1 and GAT_3) is upregulated in the PFC following METH sensitization (Wearne et al., 2016b). As both GAT_1 and GAT_3 are located on astrocytes (Conti et al., 2004), these changes may refer to reuptake of GABA to the glutamate/glutamine cycle where GABA is metabolized into succinate (Bak et al., 2006). Interestingly, succinic acid semialdehyde, an intermediate in the degradation of GABA, is increased following METH sensitization in the PFC (Bu et al., 2013). This adds further support that accelerated removal and metabolism may be responsible for reduced GABA in the PFC following sensitization to amphetamines. An alternative, albeit not mutually exclusive interpretation, is that increased transporter expression may change the inhibitory modulation of pyramidal cells following sensitization in the PFC, particularly given that GAT_1 and GAT_3 regulate the tonic inhibition of pyramidal neurons (Kinney, 2005). In line with a reduction in GABA regulation of PFC neurons, the re-application of AMPH shows reduced inhibitory currents in pyramidal cells of the mPFC from AMPH sensitized animals when compared to controls (Paul et al., 2016)

With regard to GABA receptor function, sensitization to AMPH is associated with unchanged $GABA_A$ receptor binding in the global PFC (Gruen et al., 1999). However, METH sensitization upregulated the expression of gephyrin protein (Wearne et al., 2015), suggesting that METH sensitization is associated with alterations to $GABA_A$ receptor clustering. Indeed, the mRNA expressions of $GABA_A$ receptor subunits (α3 and β1) are upregulated in the PFC of METH sensitized rats (Wearne et al., 2016b), suggesting increased postsynaptic phasic inhibition and the hyperpolarization of efferent projections (Hines et al., 2012). As METH sensitization is associated with reduced GABA in the PFC (Bu et al., 2013), these changes may also represent compensatory mechanisms to maintain phasic inhibition of efferent projections secondary to decreased GABA at the synapse.

In regard to metabotropic receptor function, sensitization to AMPH is not associated with altered $GABA_B$ receptor binding in the PFC (Zhang et al., 2000), although the same study showed that $GABA_B$ receptor coupling to G proteins was increased, suggesting that sensitization may be associated with increased inhibitory metabotropic receptor signaling (Zhang et al., 2000). There is also evidence that the mRNA expression of $GABA_B1$ is upregulated in the PFC following sensitization to METH (Wearne et al., 2016b). Furthermore, Arai et al. (2009) found that chronic METH administration produced cognitive deficits in recognition memory that were ameliorated by baclofen but not gaboxadol, a $GABA_A$ receptor agonist, suggesting that $GABA_B$ receptors may be specifically involved in mediating cognitive dysfunction associated with METH use and sensitization. In support for the role of $GABA_B$ receptors in the PFC, baclofen administration ameliorated METH induced PPI, a cognitive deficit typically associated with hyperdopaminergic PFC function (Mizoguchi and Yamada, 2011). Interestingly, intra-PFC administration of $GABA_B$ receptor agonists, SK597541 or baclofen, significantly reduced basal and AMPH-induced dopamine levels in the PFC (Balla et al., 2009), suggesting that $GABA_B$ compounds may inhibit dopaminergic neurons that are otherwise hyperexcitable following sensitization, with this inhibition normalizing cognitive dysfunction.

Sensitization to amphetamines has also shown down-regulation of the expression of parvalbumin and neuroligin2 in the PFC (Morshedi and Meredith, 2008; Wearne et al., 2015), suggesting that METH sensitization is associated with alterations to inhibitory synapses and interneuronal subtypes. Furthermore, given that fast-spiking parvalbumin-containing cells mediate neuronal oscillations and neural synchrony during cognitive tasks (Başar et al., 2001), particularly in the PFC (Benchenane et al., 2011), the findings suggest that alterations to the GABAergic network may present a biological substrate that could underpin executive dysfunction following chronic METH use. Some evidence also suggests that METH use is associated with loss of calbindin interneurons in the cortex. For example, Kuczenski et al. (2007) found decreased calbindin expression in the neocortex following extended exposure to METH. Additionally, users of METH with human immunodeficiency virus have loss of calbindin interneurons compared to HIV positive non-users (Langford et al., 2003), suggesting this loss may be specific to METH administration. While these findings suggest that calbindin cells are implicated in GABAergic dysfunction of the PFC following METH use, these findings should be interpreted with caution given the compounding neurodegenerative effects of HIV in combination with METH use (Liu et al., 2009; Reiner et al., 2009). Consequently, it is uncertain whether these changes reflect the effect of METH sensitization on calbindin-positive interneurons in the PFC or the effects of neurodegeneration.

Collectively, these findings suggest that multiple components of the GABAergic network are altered following sensitization to amphetamines in the PFC. These alterations appear to represent both presynaptic and postsynaptic changes and are likely secondary to the requirements of the PFC environment. While the functional significance of these remains to be determined, these findings indicate the PFC inhibitory GABAergic system plays an adaptive role following sensitization to amphetamines.

4. Regional PFC GABA changes following sensitization to amphetamines

The PFC is a heterogeneous area of multiple brain regions, where functional output appears dissociated across subregions of the PFC. For example, the orbitofrontal cortex (OFC) is associated with decision-making, social cognition, and goal-directed behaviour (Bechara et al., 2000; Rolls, 2000); the dorsolateral prefrontal cortex (DLPFC) is associated with executive functioning (Barone and Joseph, 1989; Curtis and D'Esposito, 2003; Kaller et al., 2011); and, the anterior cingulate cortex is involved in autonomic function and impulse control (Critchley et al., 2003; Marsh et al., 2013; Pardo et al., 1990; Paus and sbreve, 2001). Several studies have suggested a role of GABAergic neurotransmission across subregions of the PFC in response to sensitization to amphetamines.

4.1. The prelimbic cortex

The prelimbic cortex (PRL), a component of the mPFC of the rat, is analogous to the DLPFC in humans with respect to higher-order cognitive function (Granon and Poucet, 2000), and our own research has suggested that the GABAergic system of the PRL is affected by sensitization to amphetamines. Numerous inhibitory markers are upregulated in the PRL following sensitization to METH, including GAD_{67}, GAD_{65}, GAT_1, GAT_3, VGAT, $GABA_T$, $GABA_A\beta2$, and $GABA_B1$ (Wearne et al., 2016a). Elevated expression of GAD_{67} and GAD_{65} suggests increased production of GABA while the increased mRNA expression of GAT_1 and GAT_3 also indicates increased reuptake of GABA to the astrocytic glutamate/glutamine cycle where GABA is metabolized to glutamate (Bak et al., 2006). Interestingly, $GABA_T$, the catalytic enzymes responsible for the degradation of GABA (van der Laan et al., 1979), is increased in the PRL following sensitization to METH. As such, increased GABA metabolism may serve as a feedback mechanism to reduce the amount of GABA in the synapse to provide a constant supply of glutamate in the PRL. In support of this view, VGAT and glutamate vesicular transporter 1 (VGlut1) are diametrically regulated to maintain excitatory/inhibitory homeostasis (Turrigiano and Nelson, 2004). For example, bicuculline, an excitatory $GABA_A$ receptor antagonist, increases VGAT mRNA expression in primary cortical cultures (De Gois et al., 2005). Therefore, the finding that VGAT mRNA expression is upregulated in the PRL provides evidence of that the PRL is hyperexcitable following sensitization to METH. Additionally, the increased expression of GAD_{67}, GAD_{65} and VGAT create a union that facilitates the degradation of glutamate and the synthesis and packaging of GABA into the synapse. This could potentially serve to compensate for excess glutamate and to minimise glutamatergic neurotoxicity. It cannot be determined, however, whether GABAergic changes are due to increased re-uptake and metabolism or increased production of GABA. These changes, therefore, may attempt to maintain inhibitory homeostasis secondary to PRL pyramidal cells being hyperexcitable by METH sensitization. In line with this, we have recently demonstrated that local application of the $GABA_A$ receptor agonist gaboxadol into the PRL dose-dependently reduced the expression of METH sensitization. Gaboxadol has high affinity for $GABA_A$ receptors containing the delta subunit, suggesting that increasing GABA tone at extrasynaptic $GABA_A$ receptors works to restore regular function of the PRL subregion in METH sensitized animals (unpublished data).

There is also evidence of inhibitory neuronal changes following sensitization to amphetamines. For example, the expression of somatostatin, vasoactive intestinal peptide, and cholecystokinin are increased in the PRL following sensitization to METH (Wearne et al., 2017), indicating increased demand from somatostatin-martinotti, vasoactive intestinal peptide-multipolar, and cholecystokinin-basket cells, respectively. Increased expression for calcium binding proteins, calbindin and calretinin, is also found in the PRL following sensitization to METH (Wearne et al., 2017), which likely reflects increased bursting and irregular spiking of bouquet interneurons. There is also some evidence that the altered GABAergic changes described above are occurring within specific interneuronal cell types. For example, $GABA_A\beta2$ mRNA expression correlates with the expression of somatostatin, $GABA_T$ with the expression of neuropeptide Y, and VGAT correlates with the expression of calretinin following sensitization to METH in the PRL (Wearne et al., 2017). More specifically, the increased expression of GAD_{67} and GAT_1 positively correlate with the expression of parvalbumin, suggesting that these changes may be occurring within parvalbumin-containing neurons, including basket and chandelier cells (Wearne et al., 2017). The expressions of GAD_{67}, GAD_{65} and GAT_1 also correlated with the expression of cholecystokinin, suggesting that these changes are occurring within basket cells that target the initial axon segment of the pyramidal neuron. Together, GABAergic neurotransmission following METH sensitization in the PRL may involve specific changes within parvalbumin and cholecystokinin-containing interneurons.

4.2. The orbitofrontal cortex

In contrast to findings in the PRL, several ionotropic $GABA_A$ receptors are increased in the OFC following sensitization to METH, including $GABA_A\alpha1$, $GABA_A\alpha3$, $GABA_A\alpha5$, and $GABA_A\beta2$ (Wearne et al., 2016a). $GABA_A$ receptors containing α1, α3 and β2 subunits mediate phasic inhibition and the hyperpolerization of efferent cells (Hines et al., 2012), while $GABA_A$ receptors containing the α5 subunit are situated extrasynaptically and regulate the tonic inhibition of postsynaptic neurons (Fritschy and Mohler, 1995; Pirker et al., 2000b). Therefore, these findings suggest elevated phasic and tonic GABAergic inhibition of efferent pyramidal cells in the OFC following METH sensitization. There is also evidence that metabotropic receptor $GABA_B2$ is elevated in the OFC following sensitization to METH.

The expression of parvalbumin, calbindin, vasoactive intestinal peptide and cholecystokinin are also elevated in the OFC following sensitization to METH (Wearne et al., 2017). These findings suggested increased demand on GABA neurons that target other interneurons (multipolar cells) or the perisomatic region of pyramidal cells (basket cells). Also, increased expression of calbindin and parvalbumin may suggest increased bursting and fast-spiking firing of double bouquet, basket and chandelier cells. The finding of increased parvalbumin expression in the OFC is significant, as fast-spiking interneurons are hypothesized to mediate the neuronal oscillations requisite for cognitive function. As such, METH sensitization may lead to changes to OFC function that could have profound consequences on behavioral and cognitive phenotypes mediated by the PFC. Interestingly, the expression of $GABA_A\alpha1$ and $GABA_A\alpha5$ are differentially correlated with the expression of somatostatin in the OFC following sensitization to METH, suggesting they may both be implicated in the phasic and tonic inhibition of martinotti cells. No other correlations between $GABA_A$ receptor mRNA expression and interneuronal markers were identified in the OFC (Wearne et al., 2017). Therefore, altered GABA neurotransmission mediated by ionotropic and metabotropic receptors in the OFC may be localized to glutamatergic pyramidal cells (Wearne et al., 2016a).

5. A model of inhibitory regulation of the prefrontal cortex and associated circuitry following sensitization to amphetamines

The expression of sensitization derives from increased dopamine and glutamate transmission in the NAc (Cornish and Kalivas, 2001; Pierce and Kalivas, 1997; Steketee and Kalivas, 2011). Additionally, persistent changes to the VTA include increased glutamatergic and reduced GABAergic transmission, both of which stimulate the firing of dopamine neurons and the dopamine efflux in the NAc that modulate increased locomotor behavior (Garris et al., 1994; Johnson et al., 1992; Lacey et al., 1988; Pierce and Kalivas, 1997; Suaud-Chagny et al., 1992). Sensitization is also dependent on additional nuclei throughout the motivational circuit that work in concert to maintain increased sensitivity to amphetamines. For example, the mesolimbic pathway can be activated by glutamatergic projections from the mPFC to the VTA (Li et al., 1999) while activity of the VTA can be mediated by afferent projections from the laterodorsal tegmentum (LDT) (Nelson et al., 2007; Omelchenko and Sesack, 2005), basolateral amygdala (Lintas et al., 2012) and hippocampus (Lodge and Grace, 2008). Therefore, several important brain structures are implicated in the circuitry of sensitization (Fig. 3). Interneurons are able to modulate the mesolimbic system through inhibition of excitatory projections from the PFC, meaning that the PFC GABAergic network is in a position to mediate sensitized behavior. In addition to this, GABA projection neurons from the PFC to the NAc have been identified and may also play a role in mediating sensitized behavior (Lee et al., 2014).

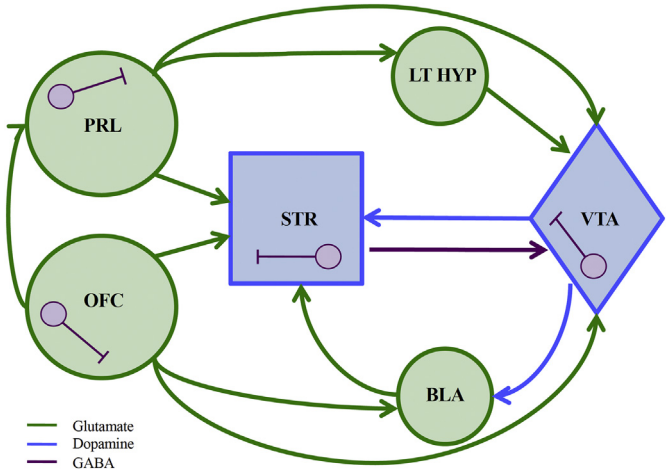

Fig. 3. A representation of the circuitry involved in behavioral sensitization under normal conditions. The striatum (STR), including the nucleus accumbens (NAc) is the output to motor circuits. The NAc is modulated by dopamine (blue) projections from the ventral tegmental area (VTA) and glutamatergic (green) projections from the prelimbic cortex (PRL), orbitofrontal cortex (OFC) and basolateral amygdala (BLA). The VTA, lateral hypothalamus (LT HYP) and BLA also receive glutamatergic afferents from the PRL and OFC. The OFC, PRL, VTA and NAc are also regulated by local inhibitory neurons (interneurons; purple). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

5.1. Inhibitory regulation of the prelimbic cortex in sensitization

Sensitization to repeated AMPH administration is associated with presynaptic changes to the GABAergic network, including increased GABA synthesis, reuptake, and metabolism in the PRL. There is also evidence of increased demand from interneuornal subtypes and many of the changes to synthesis and reuptake appear to be occurring within parvalbumin and cholecystokinin-containing interneurons. These findings suggest that increased reuptake and metabolism of GABA may serve to maintain neuronal excitation of the PRL by enabling increased glutamatergic synthesis. Indeed, several lines of evidence suggest that the PRL is excitable during the expression of sensitization. For example, lidocaine-induced blockade of the mPFC blocks locomotor sensitization to AMPH (Degoulet et al., 2009) while sensitization to AMPH is associated with increased burst firing of neurons within the same region (Aguilar-Rivera et al. (2015). Furthermore, extracellular glutamate is increased in the mPFC following AMPH and METH exposure (Del Arco et al., 1998; Stephans and Yamamoto, 1995) suggesting that glutamatergic efferents of the PRL may be involved in the expression of sensitization. Therefore, the finding that $GABA_T$ was elevated in the PRL (Wearne et al., 2016b) provides molecular evidence that a hyperglutamatergic environment may be maintained by increased GABAergic metabolism. As glutamatergic pyramidal neurons provide major excitatory afferents to the mesolimbic pathway, the increased excitation of the PRL following sensitization can be been interpreted as increased excitatory drive from the PFC to the pathways heavily implicated in sensitization. Indeed, Fanous et al. (2011) found that *c-fos* expression was increased in PRL neurons that project to the VTA following sensitization to AMPH. As glutamate and $GABA_B$ receptors in the VTA promote and inhibit psychostimulant-induced motor activity (Johnson and North, 1992; Kalivas et al., 1990), respectively, the increased sensitivity of glutamatergic efferents from the PRL may promote elevated locomotor activity elicited by METH challenge. As such, the findings described here may promote increased excitation of sensitization circuitry that maintains the sensitivity to relapse.

While the glutamatergic innervation of the PFC to the VTA has been well established, this does not diminish the possibility that elevated PRL activity could be strengthening the connection between the PFC and other important nuclei. Indeed, Ahn et al. (2013) found altered oscillatory patterns between the PFC and the hippocampus following repeated AMPH injections, raising the possibility that increased excitation of the PRL could mediate altered activation of the hippocampus at the point of the expression of sensitization to AMPH. Furthermore, using a retrograde label with dual Fos immunoreactivity, Morshedi and Meredith (2008) found that *c-fos* expression was specifically upregulated in PRL neurons that project to the lateral hypothalamus and not the NAc or basolateral amygdala following AMPH challenge. This is an interesting finding as upregulated drive from the PRL to the NAc has been demonstrated in cocaine sensitized rats (Pierce and Kalivas, 1997; Vanderschuren and Kalivas, 2000b), yet this has not specifically been determined in METH sensitization. However, as previously mentioned, the ability for VTA stimulation to attenuate PRL activation of NAc neurons becomes lost following METH sensitization (Brady, Glick and O'Donnell, 2005), indicating that PRL-NAc communication becomes strengthened following repeated METH exposure. Collectively, these findings suggest that excited neurons of the PRL may activate multiple pathways in addition to the VTA connection, rendering the ability to delineate the efferents regulated by the GABA changes described here increasingly complex (Fig. 3).

In light of the findings presented above, the PRL is associated with increased production, release and reuptake of GABA following sensitization to METH (Wearne et al., 2016b), potentially within cholecystokinin and parvalbumin-containing interneurons (Wearne et al., 2017). While these findings can be interpreted as an attempt to compensate for increased excitation of this region, it is also possible that these changes could promote elevated activity of some glutamatergic outputs while the increase in GABAergic production could be inhibiting others. It will be important for future studies to determine whether the changes describe here are specifically modulating efferents implicated in the expression of sensitization, and how these modulate sensitized behavioral output.

5.2. Inhibitory regulation of the orbitofrontal cortex in sensitization circuitry

There is a paucity of research on the role of the OFC in mediating sensitized behavior and its relationship amongst the associated circuitry of sensitization. However, overexpression of the transcription factor ΔFosB in the OFC can induce sensitization to in drug naïve animals, although this is in reference to cocaine and not METH/AMPH (Winstanley et al., 2009). Nevertheless, the OFC appears to be an important brain structure in the regulation of sensitized circuitry. Furthermore, the aforementioned studies suggest that several GABA receptor transcripts are upregulated in the OFC following sensitization to METH (Wearne et al., 2016a). However, with the exception of the relationship between $GABA_A\alpha1$, α5 and somatostatin interneuronal mRNA expression, there were few correlations between the GABAergic changes and the expression of interneuronal makers (Wearne et al., 2017). Consequently, GABA receptor changes following METH sensitization may be predominantly localized on pyramidal glutamatergic cells in the OFC. The results suggest a decrease in excitatory output of the OFC secondary to elevated inhibition of glutamatergic circuits, and may provide evidence that the GABAergic system promotes reduced excitatory drive to distal brain regions during sensitization. Indeed, dendritic branching is decreased (Crombag et al., 2005) and the OFC is underactive (Goldstein and Volkow, 2011; Goldstein et al., 2001) during abstinence following chronic exposure to amphetamines. As such, the decrease in excitatory output may provide evidence that the GABAergic system promotes reduced activation of the OFC following sensitization. However, while findings implicate the GABAergic system of the OFC in the neurobiology of METH sensitization, the specific glutamatergic pathways regulated by increased $GABA_A$ receptor inhibition are yet to be discovered.

Prior studies have shown that the OFC projects to nuclei of the

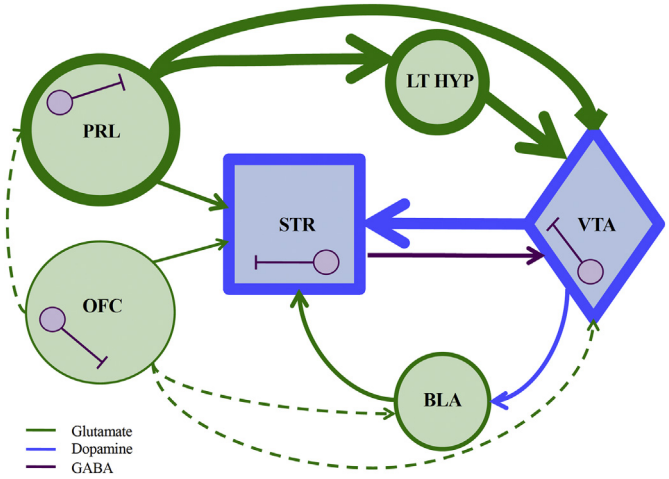

Fig. 4. A simplified representation of the circuitry subserving the expression of amphetamine-type psychostimulant-induced behavioral sensitization. Following sensitization, the hyperexcitable PRL maintains excitatory drive with projections that specifically target the LT, HYP and VTA. This elevated excitation maintains the sensitivity of the VTA-STR pathway (mesolimbic) to system and subsequent challenge. Glutamatergic projections from the OFC are underactive, which also maintain the sensitivity of the mesolimbic system to locomotor response and psychotic relapse following challenge. It is hypothesized that this sensitivity could be mediated by reduced excitation on local interneurons at efferent targets such as the VTA. Bolded lines represent overactive areas or pathways while stippled lines represent underactive regions of the circuit.

motive circuit, including the VTA (Johnson et al., 1968), striatum (Ferry et al., 2000), the subthalamic nucleus (STN) and additional regions of the PFC, including the medial PFC (Price, 2007). Consistent with the findings described above for the PRL, the OFC also has strong connections with the amygdala (Barbas, 2007) and the lateral hypothalamus (Rolls et al., 1976). Therefore, the efferents of the OFC suggest that this region is in a position to modulate sensitized circuitry and motor behavior. Indeed, studies have shown increased locomotor activity following lesions to the OFC (de Bruin et al., 1983; Kolb, 1974; Kolb, 1984), suggesting that the OFC has an inhibitory role on motor output. These findings therefore suggest that the increased inhibition of the OFC during the expression of sensitization to METH could also mediate elevated activity of the mesolimbic pathway and subsequent locomotor activity (Fig. 4). It is likely that the OFC could influence locomotor output through an intermediary brain structure rather than directly inhibiting glutamatergic afferents to the mesolimbic system, or alternatively, the OFC could mediate locomotor responses by providing reduced excitation to GABAergic interneurons in the VTA, which would have the overall effect of neuronal excitation (Fig. 4). It is also important to recognize that the OFC, like the PFC, is a brain structure consisting of numerous subregions that may differentially affect sensitization, and studies have yet to delineate the unique contribution each of this subregions play with respect to sensitized behaviour. Overall, in light of the changes described throughout, the OFC may be a feature of the sensitized circuitry that should be thoroughly explored in future studies, particularly with respect to how inhibitory changes in the OFC affect the functioning of downstream areas that directly innervate the mesolimbic pathway.

6. Methodological limitations, considerations & future directions

Several methodological considerations of the reviewed literature should be addressed. Firstly, there is a paucity of research that has examined the role of GABAergic mechanisms in sensitized circuitry, meaning many of the conclusions identified above are drawn from singular studies from isolated laboratories. As such, the ability to critique, scrutinize, and weigh the scientific evidence in this space was limited. Even though we provide a theoretical model of how these findings fit together to underlie sensitized behavior, future research is paramount to reproduce and replicate these findings to not only validate the model, but to cement the significance of GABAergic mechanisms in behavioral sensitization to amphetamines. Additionally, to date the majority of findings relating to the neurobiological mechanisms of sensitization derive from animal studies. While this provides a model that examines sensitization without the presence of additional confounding variables, such as expectation effects, the control of internal validity also compromises the ecological, and therefore translational, validity of the findings to human populations. Further studies in human subjects are necessary to not only identify the neurobiological mechanisms involved in behavioral sensitization, but to examine the psychological characteristics and outcomes that coincide with sensitization to amphetamines in a real world setting, such as expectation effects to drugs of abuse.

With respect to the sensitization paradigm itself, an important consideration is the progression of GABAergic changes throughout the sensitization paradigm. Many of the changes described in the literature are at one time point and likely represent the state of the sensitized system at the time-point of the expression of sensitization to amphetamines. The GABAergic system may be differentially regulated throughout the initiation, expression, maintenance and withdrawal periods. Indeed, the increase in various GABAergic mRNAs reported in the literature may be the result of inhibitory homeostasis of the PFC. That is, the inhibitory profile of the PFC may reflect the restoration of GABAergic deficits induced by repeated exposure to amphetamines that mediate altered excitatory and inhibitory neurotransmission. This raises the possibility that GABAergic genes and proteins are not unidirectional and may be in a constant state of change throughout the initiation and maintenance of behavioral sensitization. Further support for this argument derives from the fact that there is some cognitive recovery and resolution of pathology within the PFC following chronic METH exposure (Chang et al., 2002). It will be important for future research to examine the time course changes of GABAergic components throughout the initiation, expression, and long-term withdrawal of sensitization to amphetamines to determine whether such biological factors in the PFC attempt to mediate neuronal homeostasis.

Another important consideration is the withdrawal period employed in each study. Several previous analyses have been hampered by sensitization protocols where a challenge drug exposure is administered following two to three days of withdrawal. This presents a significant issue in delineating conclusions from molecular changes as it is uncertain whether the results are due to sensitization or the direct effects of withdrawal. As such, it has been proposed that studies should leave at least one-week withdrawal following chronic psychostimulant exposure for full manifestation of behavioral sensitization to challenge drug administration (Pierce and Kalivas, 1997). Additionally, the findings described here are, for the most part, descriptive in nature, rendering the ability to draw conclusions regarding the functional significance of these changes difficult. Furthermore, it has yet to be determined whether the differential changes in expression of GABAergic mRNAs have changed sufficiently to have biological consequences. However, it has been suggested that even modest decreases in mRNA expression of GAD_{67} in schizophrenia can have critical and functional consequences (Hashimoto et al., 2008), and genetic knock-out of the GAD_{67} gene is lethal (Buddhala et al., 2009). Furthermore, as an optimal level of GABAergic function is critical for the appropriate execution of different PFC-mediated behaviors, such as executive functioning, these findings suggest that these molecular alterations may have significant consequences on cells, regions, circuitry and behavior. In support of this, the best validation for these findings will be to carry out causal experiments that can determine whether changes in GABAergic expression in these regions of the brain are sufficient to drive behavioral or biological changes. For example, manipulation of GABA

receptors in the OFC could assist in determining whether these changes do alter sensitization and its underlying neural circuitry.

7. Concluding remarks

Sensitization results in multiple changes to GABAergic proteins, genes and interneuronal markers across global and localized subregions of the PFC. These effects appear to occur in a regionally-dependent manner and suggests that these GABAergic changes may also be occurring within particular subsets of inhibitory cells across the PFC. These findings, therefore, provide evidence that GABAergic neurotransmission plays an adaptive role once the PFC has been sensitized to the effects of amphetamines. They may also explain how altered inhibitory control of efferent networks from the PFC may maintain sensitized circuitry, sensitivity to drug-induced rewards, and a persistent vulnerability to psychotic relapse in chronic psychosis. Future investigation into the cellular changes identified in these experiments is warranted, while behavioral and cellular manipulations into the mediating effects of GABA could add further insight into whether GABAergic changes are compensatory to additional biological changes, or whether they reflect primary mediators of sensitized behavior.

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