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A fundamental role for hippocampal parvalbumin in the dopamine hyperfunction associated with schizophrenia

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ABSTRACT

Postmortem studies in schizophrenia patients have demonstrated robust alterations in GABAergic markers throughout the neuraxis. It has been suggested that these alterations are restricted to subpopulations of interneurons, such as those containing the calcium binding protein parvalbumin. Indeed, a reduction in parvalbumin expression is a consistent observation in human postmortem studies, as well as, in a wide and diverse variety of animal models. However, it still remains to be determined whether this decrease in parvalbumin expression contributes to, or is a consequence of the disease. Here we utilize lentiviral delivered shRNA and demonstrate that a selective reduction in parvalbumin mRNA expression induces hyperactivity within the ventral hippocampus. In addition, we observe downstream increases in dopamine neuron population activity without changes in average firing rate or percent burst firing. These changes in dopamine neuron activity were associated with an enhanced locomotor response to amphetamine administration. These data therefore demonstrate that a reduction in ventral hippocampal parvalbumin expression is sufficient, in and of itself, to induce an augmented dopamine system function and behavioral hyper-responsivity to amphetamine, implicating a potential key role for parvalbumin in the pathophysiology of schizophrenia.

1. Introduction

Schizophrenia is a neuropsychiatric disease affecting up to 1% of the population (Bhugra, 2005; Saha et al., 2005). It is known to be multifactorial with both genetic and environmental factors contributing to the disease (Agid et al., 1999; Sawa and Snyder, 2002; Purcell et al., 2009). This heterogeneity has led to a number of distinct hypotheses of schizophrenia, however as yet, the specific neuropathology underlying this disease has not been conclusively determined. Nonetheless, clinical data from post mortem studies have provided some consistent observations, including an altered expression of GABAergic markers throughout both cortical and hippocampal regions (Lewis et al., 2005; Konradi et al., 2011). Specifically, decreases in glutamic acid decarboxylase (GAD)-1 mRNA and GAD-67 protein are observed throughout the cortex of schizophrenia patients (Hashimoto et al., 2003). It should be noted that these alterations in GABAergic markers are not global; rather, they are more prevalent among distinct subclasses of interneurons, including those that express the calcium binding protein parvalbumin (PV) (Lewis et al., 2005). Indeed, a decreased expression of PV is a consistent observation not only in postmortem human schizophrenia patients (Lewis et al., 2005; Konradi et al., 2011), but also in a diverse number of rodent models of the disease (Cunningham et al., 2006; Abdul-Monim et al., 2007; Behrens et al., 2007; Harte et al., 2007; Francois et al., 2009; Lodge et al., 2009). However, whether this decrease in PV expression is the cause, or a consequence, of the illness is not currently known.

Decreases in PV expression are observed in both the prefrontal cortex (Lewis et al., 2012) and the hippocampus (Konradi et al., 2011), two brain regions that are consistently implicated in schizophrenia. Deficits in prefrontal cortical function likely contribute to cognitive impairments and working memory deficits (Weinberger et al., 1986; Goldman-Rakic, 1995), whereas aberrant hippocampal function is associated with positive symptom severity (Schobel et al., 2009). We have recently demonstrated, in the methylazoxymethanol acetate (MAM) rodent model of schizophrenia (for review, see Lodge and Grace, 2009), that the dopamine hyperfunction and associated behavioral hyper-responsivity to psychomotor stimulants are driven by aberrant activity within the ventral hippocampus (vHipp) (Lodge and Grace, 2007; Perez and Lodge, 2013; Perez et al., 2013). Given that PV interneurons are perisomatic targeting (Kawaguchi and Hama, 1987; Benes and Berretta, 2001; Gonzalez-Burgos and Lewis, 2012), we posit that a loss of PV interneuron function would result in an increased pyramidal cell firing (in the vHipp) that is sufficient to induce a schizophrenia-like phenotype. Here we utilize lentiviral delivered short hairpin RNA (shRNA) to

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examine the consequence of vHipp PV knockdown, as it pertains to the dopamine dysfunction in schizophrenia.

2. Materials and methods

All experiments were performed in accordance with the guidelines outlined in the USPHS Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of the University of Texas Health Science Center.

2.1. Lentivirus administration

All survival surgical procedures were performed under general anesthesia in a semi-sterile environment. Adult male Sprague–Dawley rats obtained from Harlan Laboratories were anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and placed in a stereotaxic apparatus. Anesthesia was maintained by supplemental administration of sodium pentobarbital as required to maintain suppression of limb compression withdrawal reflex. A core body temperature of 37 °C was sustained by a thermostatically controlled heating pad. The skin was reflected and bore holes drilled bilaterally overlying the vHipp (A/P +5.3, M/L +5.2, D/V −7.0 mm from bregma). Rats were administered (0.75 μl/side) commercially available (Thermo Scientific) high-titer lentivirus particles containing GIPZ vectors expressing shRNA targeting either parvalbumin (mature antisense: TAGCAGACAAGTCTCTGGC) or a non-silencing control. Rats were sutured and housed under ABSL 2 conditions for 72 h before being transferring to standard housing conditions. Rats were housed for a period of 6 weeks prior to behavioral and electrophysiological examinations to ensure stable transgene expression.

2.2. Amphetamine-induced locomotion

Rats were acclimatized to the behavioral facility for at least 1 h prior to being placed in an open field arena (Med Associates) where spontaneous locomotor activity in the X–Y plane was determined for 45 min by beam breaks and recorded with Open Field Activity Software (Med Associates). Following the baseline period, all rats were injected with D-amphetamine sulfate (0.5 mg/kg, i.p.) and locomotor activity recorded for 45 min. A subsequent dose (2.0 mg/kg, i.p.) was then administered and an additional 45 min of locomotor activity was recorded.

2.3. Extracellular recordings

Rats were anesthetized with chloral hydrate (400 mg/kg, i.p.), as this anesthetic does not significantly depress dopamine neuron activity (Hyland et al., 2002), and placed in a stereotaxic apparatus. Anesthesia was maintained by supplemental administration of chloral hydrate as required to maintain suppression of limb compression withdrawal reflex. A core body temperature of 37 °C was sustained by a thermostatically controlled heating pad. Extracellular glass microelectrodes (impedance 6–14 MΩ) were lowered into the right ventral hippocampus (A/P +5.3, M/L +5.0, D/V −5.0 to −8 mm from bregma) using a hydraulic micropositioner (KOPF — Model 640). Putative pyramidal neurons were defined as those with firing frequencies less than 2 Hz as reported previously (van der Meer and Redish, 2011; Shah and Lodge, 2013).

Electrodes were also inserted into the right ventral tegmental area (VTA; A/P −5.3, M/L +0.6 mm from bregma and −6.5 to −9.0 mm ventral of brain surface) and the activity of the population of dopamine neurons was determined by counting the number of spontaneously active dopamine neurons encountered while making multiple vertical passes (typically 6), separated by 200 μm, in a predetermined pattern to sample equivalent regions of the VTA. Spontaneously active dopamine neurons were identified with open filter settings (low pass: 30 Hz, high pass: 30 kHz) using previously established electrophysiological criteria (Grace and Bunney, 1983) and once isolated, activity was recorded for 2 — 3 min.

2.4. Quantitative PCR

Rats were decapitated following electrophysiological recordings and the brain was separated into two hemispheres. The vHipp was dissected from one hemisphere and homogenized. RNA was precipitated, separated by filtration and the concentration determined by absorbance at 260 nm. Single stranded RNA was converted to cDNA using a High Capacity cDNA Reverse Transcription Kit (Ambion). Real time PCR was performed with FAM-labeled TaqMan primers targeting either parvalbumin (Rn00574541_m1), GAD1 (Rn00690300_m1) or GAPDH (Rn01775763_g1). Detection of FAM labeled DNA was performed by a CFX384 Real-Time PCR Detection System (Bio-Rad). ΔCt was calculated as the number of PCR cycles required for mRNA detection (compared to the control mRNA, GAPDH), while fold-changes were expressed using the $2^{-\Delta\Delta Ct}$ method.

2.5. Parvalbumin immunohistochemistry

The hemisphere not used for PCR was post-fixed for at least 24 h, and cryoprotected (25% w/v sucrose in PBS) until saturated. Hemispheres were coronally sectioned (50 μm) using a cryostat (Leica). Ventral hippocampal slices were used to detect the expression of PV. Sections were washed three times (10 min) in PBS then blocked (2% normal goat serum & 0.3% Triton X-100) for 30 min at room temperature. Primary antibodies [anti-PV 1:1000 (Abcam; ab11427)] were applied (in PBS containing 1% normal goat serum and 0.3% Triton X-100) overnight at 4 °C followed by incubation with Alexa Fluor® 594 goat anti-rabbit IgG (H + L) for 1 h at room temperature. Slices were then mounted and cover slipped with ProLong gold antifade reagent. Computer assisted estimates of PV positive interneurons were performed using Neurolucida in combination with a Zeiss epifluorescent microscope.

2.6. Analysis

Locomotor data were analyzed by three separate 2-way ANOVAs (treatment and time as factors), one for each of the relevant time periods (spontaneous, 0.5 mg/kg, 2.0 mg/kg), followed by a Holm–Sidak post-hoc test, where appropriate. Electrophysiological analysis of single unit neuron activity was performed using commercial computer software (LabChart Pro — ADInstruments), and compared with student's t-test unless data failed test for normality and/or equal variance where a Mann–Whitney Rank Sum Test was utilized. PCR data was analyzed using commercial computer software (CFX Manager — BioRad). Cell counts were performed using Neurolucida and significance determined by a student's t-test. All data are represented as the mean ± standard error of the mean (SEM) unless otherwise stated. All statistical analyses were calculated using SigmaPlot (SYSTAT Software Inc.).

2.7. Materials

High titer lentiviral particles were obtained from Thermo Scientific. Pentobarbital sodium, chloral hydrate, and D-amphetamine sulfate were all purchased from Sigma. FAM-labeled TaqMan probes, the secondary Alexa Fluor® 594 goat anti-rabbit IgG (H + L) antibody as well as the ProLong gold antifade mountant were obtained from Life Technologies. The anti-parvalbumin antibody was purchased from Abcam. All other chemicals and reagents were of either analytical or laboratory grade and purchased from various suppliers.

3. Results

3.1. Confirmation of PV knockdown

To recapitulate the postmortem finding of reduced hippocampal PV expression, we performed region specific knockdown of PV by microinjection of commercially available high-titer lentiviral particles expressing microRNA-adapted small hairpin ribonucleic acid (shRNA) targeting PV mRNA in the vHipp. Lentiviral particles expressing a non-silencing shRNA were used as a control. The knockdown of PV expression was determined postmortem by quantitative polymerase chain reaction (qPCR) and immunohistochemistry (Fig. 1). Specifically, qPCR demonstrated a decrease in mRNA expression (fold-change; control shRNA: 1.0 ± 0.7 c.f. PV shRNA: 0.2 ± 0.3) without overt changes in GAD mRNA expression (fold-change; control shRNA: 1.0 ± 0.6 c.f. PV shRNA: 1.6 ± 1.1); however, statistical analysis was precluded as PV mRNA expression was below the limit of detection in the majority (75%) of PV shRNA samples analyzed. To examine whether this decrease in PV expression resulted in a decrease in PV immunoreactivity, we performed quantitative cell counts throughout the vHipp (Fig. 1). Rats administered PV shRNA displayed a significant reduction in PV positive interneurons throughout the vHipp (control shRNA: 9.11 ± 0.39 c.f. PV shRNA: 6.74 ± 0.48 cells/mm^2; t-test, $t = 3.865$, $p < 0.05$, $n = 6$/group; Fig. 1).

3.2. Hippocampal activity

PV neurons are fast-firing and perisomatic targeting which means that they are well situated to regulate pyramidal neuron activity (Kawaguchi and Hama, 1987; Benes and Berretta, 2001; Gonzalez-Burgos and Lewis, 2012). Thus, a decrease in PV interneuron function is likely sufficient to augment pyramidal activity within the vHipp. Indeed, we now demonstrate that a decrease in vHipp PV is sufficient to increase pyramidal cell output as determined by in vivo extracellular electrophysiology in chloral hydrate anesthetized rats. Specifically, putative pyramidal neurons in PV shRNA treated rats fired on average at a rate almost twice that observed in control rats (control shRNA: 0.73 ± 0.09 c.f. PV shRNA: 1.22 ± 0.12 Hz; Mann–Whitney Rank Sum Test, $U = 169.5$, $p < 0.05$, $n = 22$–31 neurons; Fig. 2A).

3.3. Dopamine system function

We have previously demonstrated that aberrant vHipp activity results in an augmented dopamine system function (Lodge and Grace, 2007). The vHipp has been demonstrated to selectively regulate the proportion of spontaneously active dopamine neurons in the ventral tegmental area (VTA). This is thought to reflect the gain of the dopamine system (Lodge and Grace, 2007). For this reason, we examined whether vHipp PV knockdown was sufficient to alter dopamine neuron activity. Indeed, we now demonstrate that vHipp PV knockdown significantly increases dopamine neuron population activity (control shRNA: 1.02 ± 0.06 c.f. PV shRNA: 1.59 ± 0.18 cells/track; Mann–Whitney Rank Sum Test, $U = 4.50$, $p < 0.05$, $n = 7$–8 rats; Fig. 2B) without altering average firing rate (control shRNA: 4.03 ± 0.36 c.f. PV shRNA: 3.75 ± 0.28 Hz; Mann–Whitney Rank Sum Test, $U = 1597$, $p > 0.05$, $n = 49$–69 neurons; Fig. 2C) or average percent burst firing (control shRNA: 43.2 ± 3.8 c.f. PV shRNA: 35.1 ± 3.4%; Mann–Whitney Rank Sum Test, $U = 1375$, $p > 0.05$, $n = 49$–69 neurons; Fig. 2D).

3.4. Behavioral response to amphetamine

Schizophrenia patients consistently demonstrate exaggerated responses to psychomotor stimulants (Janowsky et al., 1973). A similar paradigm can be used to examine behavioral deficits in putative animal models of schizophrenia (Lodge and Grace, 2007; Perez and Lodge, 2013; Perez et al., 2013). Here we demonstrate that vHipp PV

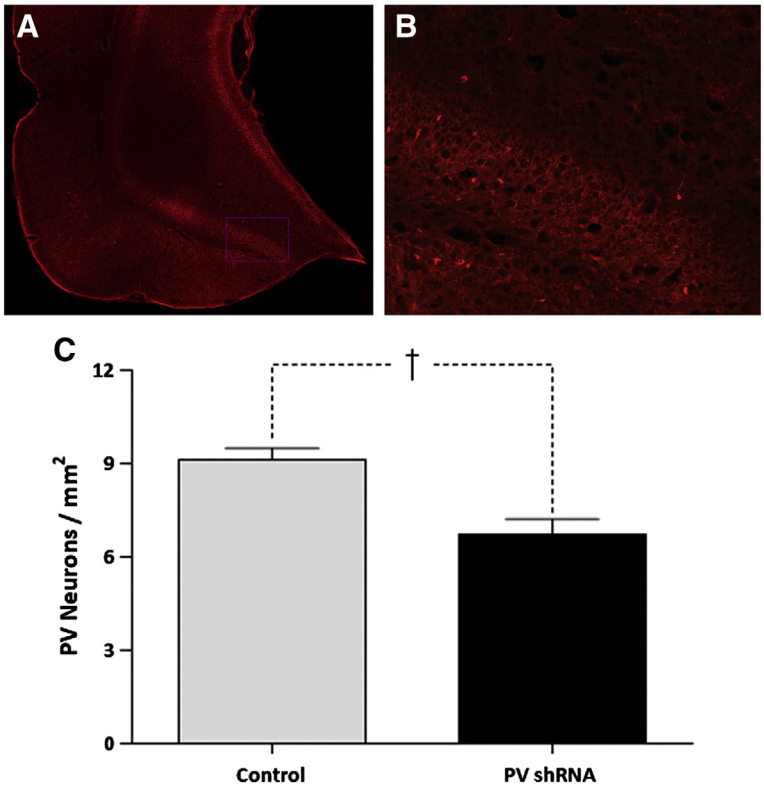

Fig. 1. Lentiviral administration of parvalbumin (PV) shRNA decreases the number of PV positive interneurons in the ventral hippocampus. Images in A & B represent PV positive neurons (red) as determined by immunohistochemistry. The graph in C depicts the quantification of computer assisted cell counts throughout the ventral extent of the hippocampus. † represents $p < 0.05$, Student's t-test.

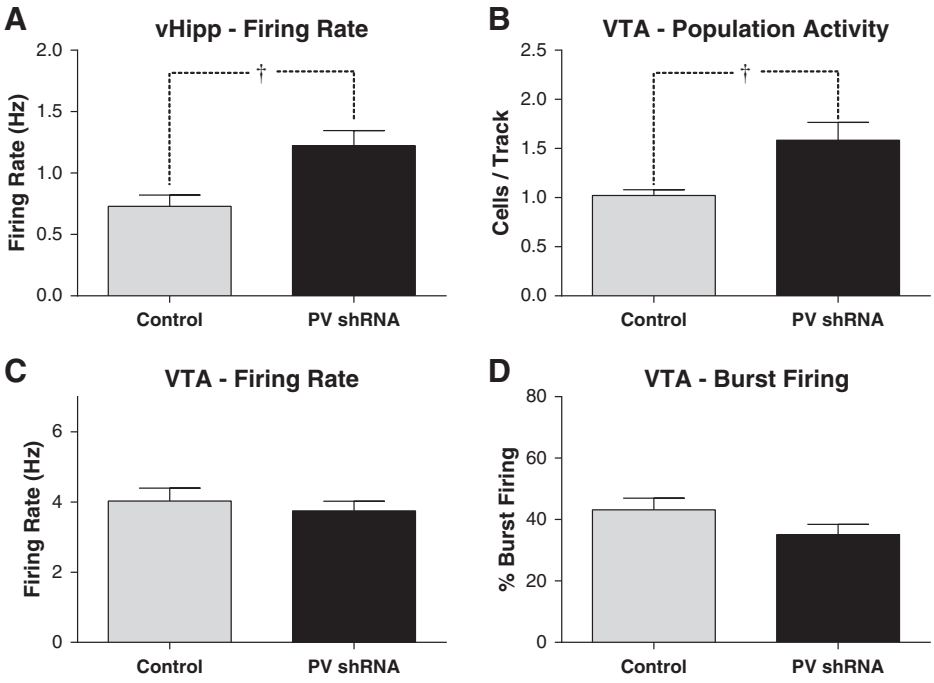

Fig. 2. Lentiviral administration of parvalbumin (PV) shRNA increases hippocampal and dopamine neuron activity. Putative pyramidal neurons throughout the hippocampus were recorded (A) and demonstrated significantly greater activity in PV shRNA treated rats. Downstream increases in dopamine neuron population activity (B) were also observed without significant changes in average firing rate (C) or burst firing (D). † represents $p < 0.05$, Mann–Whitney Rank Sum Test.

knockdown produces an enhanced locomotor response to amphetamine administration. Specifically, PV shRNA treated rats display a significantly enhanced locomotor response to low dose (0.5 mg/kg, i.p.) amphetamine administration when compared to non-silencing shRNA controls (2-way ANOVA of 0.5 mg/kg dose; $F(\text{treatment}) = 9.851$; Holm–Sidak $t = 3.139$, $p < 0.05$; Fig. 3), and also in response to the higher dose (2-way ANOVA of 2.0 mg/kg dose; $F(\text{treatment}) = 4.225$; Holm–Sidak $t = 2.056$, $p < 0.05$; Fig. 3) without changes in baseline activity (2-way ANOVA of baseline; $F(\text{treatment}) = 2.468$; $p > 0.05$; Fig. 3), consistent with previous observations in rodent models (Lodge and Grace, 2007; Perez and Lodge, 2013; Perez et al., 2013).

4. Discussion

Previous studies in postmortem schizophrenia patients, as well as, rodent models have demonstrated a reduction in PV expression throughout the cortex (Lodge et al., 2009; Lewis et al., 2012) and the hippocampus (Lodge et al., 2009; Konradi et al., 2011); however, whether this contributes to, or is a consequence of, the disease is not currently known. We now demonstrate that a reduction in vHipp PV expression is sufficient, in and of itself, to increase vHipp activity and induce downstream changes in dopamine neuron activity and a behavior that is analogous to the positive symptoms of schizophrenia.

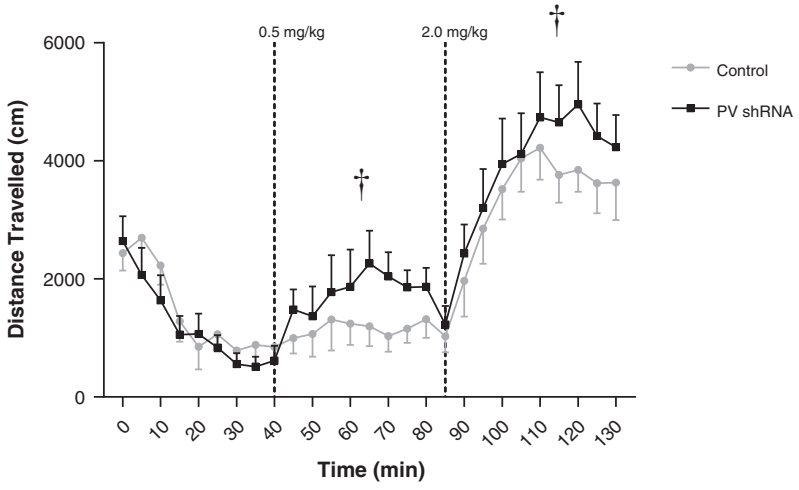

Fig. 3. Lentiviral administration of parvalbumin (PV) shRNA augments the locomotor response to amphetamine. Baseline locomotor activity was not significantly affected by vHipp PV knockdown (black squares) relative to control (non-silencing shRNA: gray circles). In contrast, the locomotor response to both low (0.5 mg/kg) and high (2.0 mg/kg) doses of amphetamine were significantly enhanced demonstrating that a decrease in vHipp PV expression is sufficient to induce behavioral alterations consistent with those observed in schizophrenia. † represents $p < 0.05$, 2-way ANOVA.

There is a considerable literature implicating aberrant dopamine signaling in the pathophysiology of schizophrenia (Abi-Dargham, 2004; Grace, 2004; Howes and Kapur, 2009; Lodge and Grace, 2011; Howes et al., 2012). This can be directly examined in rodent models by recording the electrophysiological activity of midbrain dopamine neurons (Lodge and Grace, 2007; Perez and Lodge, 2012, 2013). Such studies have suggested that the increase in dopamine system function is associated with the changes in the number of spontaneously active neurons in the absence of changes in firing rate or bursting pattern (Lodge and Grace, 2007; Perez and Lodge, 2012, 2013). Under control conditions, it is thought that about 50% of the midbrain dopamine neurons are quiescent due to a tonic GABAergic drive from the ventral pallidum (VP) (Grace et al., 2007). This provides an opportunity whereby the gain of the dopamine signal can be enhanced or attenuated by modulation of afferent inputs. In the case of schizophrenia, we posit that the ability to appropriately regulate the gain of the system is lost, as most of the dopamine neurons are spontaneously active (Lodge and Grace, 2007, 2011). As a result, it is likely that all stimuli are now being assigned the same salience, and may contribute to the paranoia consistently observed in patients. While a number of regions can regulate pallidal activity, the hippocampus has been consistently implicated in schizophrenia. The ventral regions of the hippocampus regulate the number of spontaneously active dopamine neurons via a multi-synaptic pathway that involves the nucleus accumbens (NAc) (Lodge and Grace, 2007, 2011). Thus, activation of the vHipp will increase GABAergic transmission from the NAc that, in turn, suppresses VP tone to the VTA. The net result is a disinhibition of the VTA and a selective increase in the number of dopamine neurons firing spontaneously (Lodge and Grace, 2007, 2011).

While hippocampal hyperactivity has been observed in both rodent models (Lodge and Grace, 2007; Perez and Lodge, 2013; Shah and Lodge, 2013), as well as human schizophrenia patients (Malaspina et al., 1999; Medoff et al., 2001; Heckers, 2004; Schobel et al., 2009; Kraguljac et al., 2013), the cause of this aberrant activity has not been conclusively demonstrated. One hypothesis is that a deficit in interneuron function may result in increases in pyramidal cell firing; however, this has not been verified experimentally. Here we demonstrate that selectively decreasing PV mRNA expression in the vHipp of 'normal' Sprague–Dawley rats, is sufficient to recapitulate the hippocampal hyperactivity observed in rodent models, as well as patients (Malaspina et al., 1999; Medoff et al., 2001; Heckers, 2004; Lodge and Grace, 2007; Schobel et al., 2009; Kraguljac et al., 2013; Perez and Lodge, 2013; Shah and Lodge, 2013). The exact mechanism by which a decrease in PV leads to hippocampal hyperactivity has not been conclusively demonstrated. PV is a calcium binding protein with a slow onset that does not significantly affect the amplitude of fast Ca^{2+} transients, but alters the decay of $[Ca^{2+}]_i$ (Schwaller et al., 2002). In the hippocampus, a loss of PV expression does not alter either single inhibitory postsynaptic responses or paired-pulse modulation of IPSCs (Vreugdenhil et al., 2003). Rather, an enhanced facilitation of GABA release is observed after repetitive high frequency stimulation in PV−/− mice (Vreugdenhil et al., 2003). Thus, the hyperactivity observed following PV shRNA in the current study is not likely attributable to changes in the functionality of the interneuron but may be attributable to neuronal loss. Indeed, the buffering capacity of PV has been suggested to protect from Ca^{2+}-mediated excitotoxic insult (Figueredo-Cardenas et al., 1998; Van Den Bosch et al., 2002).

In addition to increases in vHipp activity, PV shRNA induced downstream changes in VTA dopamine neuron activity. Consistent with the pharmacological studies detailed above, rats with selective vHipp PV knockdown display increases in the number of spontaneously active VTA dopamine neurons, without overt changes in firing rate or bursting pattern. This neurophysiological phenotype is consistent with that observed in rodent models of schizophrenia, such as the MAM-treated rat (Lodge and Grace, 2007; Perez and Lodge, 2012, 2013; Perez et al., 2013). Interestingly, while the increase in dopamine neuron activity is qualitatively similar to that of the MAM-treated rat, it appears to be of a smaller magnitude. This is likely due to differences between the acute PV knockdown performed in the current study and the more sustained neurodevelopmental loss observed in the MAM rat (Chen et al., 2014). Indeed, an increase in dopamine neuron population activity, similar to that observed following vHipp PV shRNA, is present following the degradation of vHipp perineuronal nets in adulthood (Shah and Lodge, 2013).

Symptoms such as hallucinations, delusions and paranoia obviously cannot be assessed in rodents; however, there are behavioral alterations that can be modeled in both patients and rats. One reliable and reproducible observation is an enhanced response to psychomotor stimulants. Thus, the administration of small doses of amphetamine will precipitate psychosis in schizophrenia patients (Janowsky et al., 1973). Similarly, rodent models display an exaggerated response to psychomotor stimulants, which is quantified by examining the magnitude of the locomotor response (Moore et al., 2006; Lodge and Grace, 2007; Perez and Lodge, 2013; Perez et al., 2013). As a behavioral correlate of the augmented dopamine neuron activity, we examined the locomotor response to amphetamine in rats treated with vHipp PV shRNA and demonstrate that a reduction in vHipp PV expression produces an enhanced response consistent with that observed in rodent models of the disease.

Taken together, we demonstrate a potential key role for PV in the pathophysiology of schizophrenia that contributes to aberrant hippocampal neuronal activity, as well as, downstream changes in dopamine system function that contribute to positive symptoms. It should be noted that deficits in PV expression in patients and rodent models are not limited to the hippocampus, but are also observed throughout the prefrontal cortex (Lewis et al., 2005). Given that we did not investigate the effects of PV knockdown in regions other than the vHipp, we cannot conclude that the symptoms are exclusively hippocampal. Indeed, deficits in PV interneuron function in the mPFC are likely associated with non-dopaminergic symptoms in schizophrenia patients, such as deficits in cognition (Pantelis et al., 1997). These data are also consistent with recent demonstrations examining the early postnatal interneuron-specific knockdown of the NMDA receptor. Specifically, these mice demonstrate reductions in PV expression and increases in pyramidal neuron activity which are associated with behavioral deficits consistent with a schizophrenia-like phenotype; including deficits in pre-pulse inhibition of startle, novelty-induced hyperlocomotion, a decrease in saccharine preference, and deficits in spatial working memory (Belforte et al., 2010). Collectively, we demonstrate that a knockdown of PV expression in the vHipp is sufficient, in and of itself, to produce the aberrant dopamine neuron activity and behavioral hyper-responsivity to psychomotor stimulants that is thought to contribute to psychosis in schizophrenia patients.

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Contributors

Dr. Lodge designed the study and assisted with the manuscript preparation. Drs. Boley and Perez assisted with the study design and performed all of the experiments, analyzed the data and participated in writing the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Lodge reports receiving consulting fees from Dey Pharmaceuticals, while Boley and Perez have no disclosures nor conflicts of interest.

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N/A.

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