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Chronic ketamine produces altered distribution of parvalbumin-positive cells in the hippocampus of adult rats

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Abstract

The underlying mechanisms of schizophrenia pathogenesis are not well understood. Increasing evidence supports the glutamatergic hypothesis that posits a hypofunction of the N-methyl D-aspartate (NMDA) receptor on specific gamma amino-butyric acid (GABA)-ergic neurons may be responsible for the disorder. Alterations in the GABAergic system have been observed in schizophrenia, most notably a change in the expression of parvalbumin (PV) in the cortex and hippocampus. Several reports also suggest abnormal neuronal migration may play a role in the etiology of schizophrenia. The current study examined the positioning and distribution of PV-positive cells in the hippocampus following chronic treatment with the NMDA receptor antagonist ketamine. A robust increase was found in the number of PV-positive interneurons located outside the stratum oriens (SO), the layer where most of these cells are normally localized, as well as an overall numerical increase in CA3 PV cells. These results suggest ketamine leads to an abnormal distribution of PV-positive cells, which may be indicative of aberrant migratory activity and possibly related to the Morris water maze deficits observed. These findings may also be relevant to alterations observed in schizophrenia populations.

Keywords

ketamine; schizophrenia; parvalbumin; hippocampus

Introduction

Schizophrenia is a severe neuropsychiatric disorder for which the underlying mechanisms are not well understood [35]. Post-mortem investigations of patients with schizophrenia have identified disruptions in glutamatergic signaling, most notably a hypofunction of the *N*-methyl D-aspartate (NMDA) glutamate receptor [1,4,6,11,13]. Abnormal activity of NMDA receptors on gamma amino-butyric acid (GABA)-ergic interneurons in particular has been observed in the brains of schizophrenic patients [49]. A reduction in the expression of the calcium-binding protein parvalbumin (PV) in fast-spiking GABAergic interneurons is another consistent pathological feature of the disorder [2,15,29,50]. This change is commonly reported as a decrease in mRNA expression or the number of PV-positive cells [2,15,29], while more recent reports suggest the reduction is in the mean PV intensity per

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cell [25,40,48]. These findings collectively suggest that aberrant GABA functioning may play an influential role in aspects of schizophrenia.

Neurodevelopmental hypotheses of schizophrenia indicate abnormal migration of newborn neurons may play a role in the disorder [18]. The expression of reelin, a protein implicated in neuronal migration during development [9,16], shows profound reductions in post-mortem brains of schizophrenia patients [17], particularly in the prefrontal cortex [14] and hippocampus [12]. Genetic linkage studies with schizophrenia patients have reported additional risk factors tied to migratory regulation such as MDGA1 [20,30] and Disrupted-in-Schizophrenia-1 (DISC1) [7,45]. DISC1 in particular has been implicated in normal neuronal migration in the hippocampus [10,24,27], suggesting DISC1 mutations may impair migration and alter network function in schizophrenia.

Sub-anesthetic doses of noncompetitive NMDA receptor antagonists, such as phencyclidine (PCP) and ketamine, produce neurological and behavioral alterations consistent with schizophrenia in humans [19,28,47]. Investigations of disease processes in rodents have also benefitted from pharmacological approaches with these drugs [3,8,37,44]. Modeling aspects of schizophrenia in various animal systems has demonstrated heterotopic expression of newborn neurons during development [21,33] and adulthood [31,36]; however, the types of abnormally migrated neurons have not been well elucidated. Based on the altered expression of PV in schizophrenic brains, we examined the distribution and localization of PV-positive neurons within the CA3 region of the hippocampus and cortex following chronic administration of ketamine. In this exploratory study, we observed differences in the number and positioning of the PV-positive cells which may be indicative of migratory deficits, and could be linked to altered connectivity.

Methods

Subjects

Forty male Sprague-Dawley rats (n=10) from Charles River Laboratories (Hollister, CA, USA) weighing between 250 and 350 g were pair-housed in a standard animal facility with a 12–12h light-dark cycle, and with food and water available *ad libitum.* All procedures were performed in accordance with the institutional Animal Care and Use Committee and NIH guidelines for ethical treatment of research subjects.

Drugs

Ketamine HCl (Henry–Schein, Indianapolis, IN) was diluted in physiological saline (VWR, Bridgeport, NJ) to achieve a final concentration of 8 mg/ml as has been previously demonstrated to impair sensorimotor gating and spatial learning [42]. Ketamine or saline was administered subcutaneously once daily at a dose of 1 ml/kg of body weight beginning on the first day of behavioral testing through the completion of testing, a total of 18 days consistent with previous investigations [42].

Morris Water Maze

The Morris water maze (MWM) was conducted as described previously [42]. In experiment 1, subjects underwent 5 days of acquisition followed by a probe trial an average of 5 hours later. Ketamine-administered rats were then retrained for 7 additional days in an effort to determine if equivalent performance to controls could be achieved prior to 3 days of reversal training and 2 days of visible training. Based on the data from the first experiment a second experiment was performed to replicate and verify tissue results. In experiment 2, small variations were made in reversal training in order to parse out ketamine-induced deficits, but overall number of days of drug administration and training days was consistent.

Immunohistochemistry

Half of the animals run in each of the Morris water maze (n=5) experiments were randomly selected for transcardial perfusion with 4% paraformaldehyde following CO_2 asphyxiation. Brains were then removed and placed in 4% paraformaldehyde at 4° C for 48 hours before being moved to a 30% sucrose solution until sectioning. Whole brains were sectioned at a thickness of 15 μm on a cryostat and sections were stored at 4° C until the immunohistochemistry (IHC) experiments. Sections were placed in plastic wells and remained free floating until the completion of the IHC procedure. Sections were initially blocked for 45 minutes in a 5% normal goat serum (NGS) solution and then incubated overnight at room temperature with a primary monoclonal antibody raised in mouse directed against PV (1:1000; Sigma-Aldrich, St. Louis, MO). Following five washes, fluorescent labeling was performed with Alexafluor 488 anti-mouse secondary antibody (1:2000; Invitrogen, Grand Island, NY) for 45 minutes at room temperature. Following five washes, sections were mounted onto slides for fluorescent imaging.

Serial sections beginning at the anterior hippocampus (2.5 mm posterior of Bregma) were evaluated by two independent observers blind to treatment. PV-positive neuron number and positioning were examined in the CA3 region of the hippocampus due to their abundance and typical localization in this area. PV-positive neuron number was also examined in the retrosplenial cortex, directly superior to the hippocampus. For each individual section, the area of interest, encompassing the CA3 region medial to and including the stratum oriens (SO), was determined by alignment of the outer shell of the CA3 region of the hippocampus along the border of the field of view using a 10X objective. All images were captured at an objective of 10X using a Zeiss Axioskop II Plus microscope (Carl Zeiss MicroImaging, Inc, Thornwood, NY). A cell was determined to be outside the SO if no part of the cell fell within the clearly defined SO layer. A minimum of six sections per subject was utilized to determine the number and location of PV-positive cells.

Statistical Analyses

MWM acquisition and visible training data were analyzed using the SPSS statistical software package by a repeated measures analysis of variance (ANOVA), while probe trial data were analyzed with one-way ANOVA. One-way ANOVA was also performed to detect differences in the amount or distribution of PV-positive cells in the hippocampus between groups. Tukey post-hoc comparisons were performed to analyzed probe within group probe trial performance.

Results

Morris Water Maze

Experiment 1—Ketamine produced a deficit in MWM consistent with previous investigations [5,42]. Significant deficits were observed in acquisition training versus saline ($F_{1,78} = 40.04$, $p<0.01$; see figure 1A). During the probe trial (see figure 1B), ketamine-administered rats did not perform a selective search ($F_{3,36} = 6.118$, $p<0.01$; Tukey post-hoc analyses of quadrant revealed that animals did not spent significantly more time in the target quadrant than the adjacent left ($p=0.997$) or opposite quadrant ($p=0.661$)), whereas rats administered saline did show a preference for the target quadrant ($F_{3,36} = 29.635$, $p<0.01$; Tukey post-hocs indicated target versus each quadrant at $p<0.01$).

Experiment 2—Ketamine produced similar impairments in experiment 2 with a significant deficit during acquisition ($F_{1,78} = 64.741$, $p<0.01$; data not shown) and the probe trial ($F_{3,36} = 4.892$, $p<0.01$; Tukey post-hocs revealed that rats spent significantly more time in the opposite quadrant than the target quadrant ($p<0.01$).

Immunohistochemistry

Cell counts for immunofluorescent PV-positive cells from both experiments were performed within the left and right CA3 region of the hippocampus and left and right cortices to assess changes in number. For the hippocampus, representative images for saline and ketamine are displayed in figure 2A and 2B, respectively. Ketamine produced an increase in the total number of PV-positive neurons in CA3 compared to controls in experiment 1 ($F_{1,45} = 8.169$, $p<0.01$; see figure 2C) and experiment 2 ($F_{1,45} = 9.609$, $p<0.01$; see figure 2E). Ketamine also produced a change in the localization of these neurons. The number of PV-positive cells outside the SO was significantly greater following chronic ketamine administration as compared to saline controls in experiment 1 ($F_{1,45} = 7.659$, $p<0.01$; see figure 2D) and experiment 2 ($F_{1,45} = 7.921$, $p<0.01$; see figure 2F).

Cell counts were also performed in the retrosplenial cortex; representative images are depicted in figure 3A and 3B, respectively. No significant differences were observed between groups in the number of PV-positive neurons in the cortex in experiment 1 ($F_{1,45} = 0.107$, $p=.745$; see figure 3C) or experiment 2 ($F_{1,45} = 1.276$, $p=.264$; see figure 3D), suggesting the ketamine-induced changes are region-specific. Table 1 depicts the raw cell count data from both experiments.

Discussion

The current study investigated the expression and positioning of PV-positive cells in the hippocampus following chronic ketamine administration and a spatial learning task. Our findings reveal an increase in number and a shift in the precise localization of these GABAergic neurons, which may be indicative of abnormal migratory activity. The significant increase in the number of PV-positive neurons in CA3 in two distinct experiments is in contrast to findings of decreased hippocampal PV density in animal models [22,38] and schizophrenia populations [26]. The increased number of PV cells reported here suggests ketamine may alter neurogenesis in these studies, as previously reported [23], resulting in the increased number and aberrant positioning in CA3. This interpretation is supported by the lack of a ketamine-induced increase in number in the cortex. An overall increase the in total number of PV-positive neurons specifically in the hippocampus is particularly interesting as it may related to the spatial learning and memory deficits. The consequence of increased PV-positive neurons is difficult to estimate, however, alterations in overall network function would be likely if these neurons are functional. The increased number of PV-positive cells outside the SO in the ketamine-treated group suggests a heterotopic distribution of newborn neurons in the CA3 region of the hippocampus. These neuronal displacements could lead to altered connectivity within the hippocampus and disrupted network activity, a phenomenon that may be occurring in schizophrenia [46].

The location of PV neurons within the hippocampus is generally restricted to the SO and stratum pyramidale with sparse distribution in other layers such as the stratum radiatum [32,34,43]. The heterotopic nature of PV-positive neurons observed in the current study suggests there may be disrupted migration following chronic ketamine administration. The protein reelin, which regulates the migration and positioning of immature neurons, is only expressed in GABAergic cells in the adult rat hippocampus [39]. These findings, along with post-mortem studies from schizophrenia brains showing reductions in PV [2,15,29] and reelin expression [12,14,17], may present a link between PV-mediated network dysfunction and abnormal migration.

Previous reports suggest the NMDA receptor plays an integral role in regulating the migration of newborn neurons in the adult hippocampus [36] and developing cortex [41]. Our findings suggest that chronic NMDA receptor blockade with ketamine may impair

neuronal migration. The current study, as well as previous studies from our laboratory, has demonstrated that ketamine produces robust impairments in sensorimotor gating, spatial learning, and emotional learning and memory [5,42]. It is possible that aberrant network function due to migratory deficits may be important in these cognitive impairments. Future studies may be able to elucidate if abnormal migration plays any role in these deficits.

Although the data reported here suggest the altered distribution of PV-positive neurons may be a result of aberrant migration, more studies are necessary to confirm this hypothesis. The co-administration of 5-bromo-2-deoxyuridine (BrDU) with ketamine may allow a clearer picture of whether these heterotopic PV-positive cells are newborn neurons; previous studies suggest ketamine enhances neurogenesis, though without altering newborn cell location or showing BrDU-PV co-localization in the dentate gyrus [23]. Furthermore, more extensive stereological analyses in future studies may be able to detect quantitative differences produced by ketamine. Additional investigations are needed to determine if the above changes persist once ketamine administration and behavioral testing have been completed similar to previous work [23]. Despite these limitations, the current study strengthens the link between ketamine-induced disruptions in PV and schizophrenia.

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Research Highlights

- Ketamine SC at 8mg/kg impaired spatial learning consistent with previous findings.
- Ketamine induced a significant increase in the number of PV+ neurons in CA3 field of hippocampus.
- Ketamine induced a significant increase in PV+ neurons outside the SO of the hippocampus.

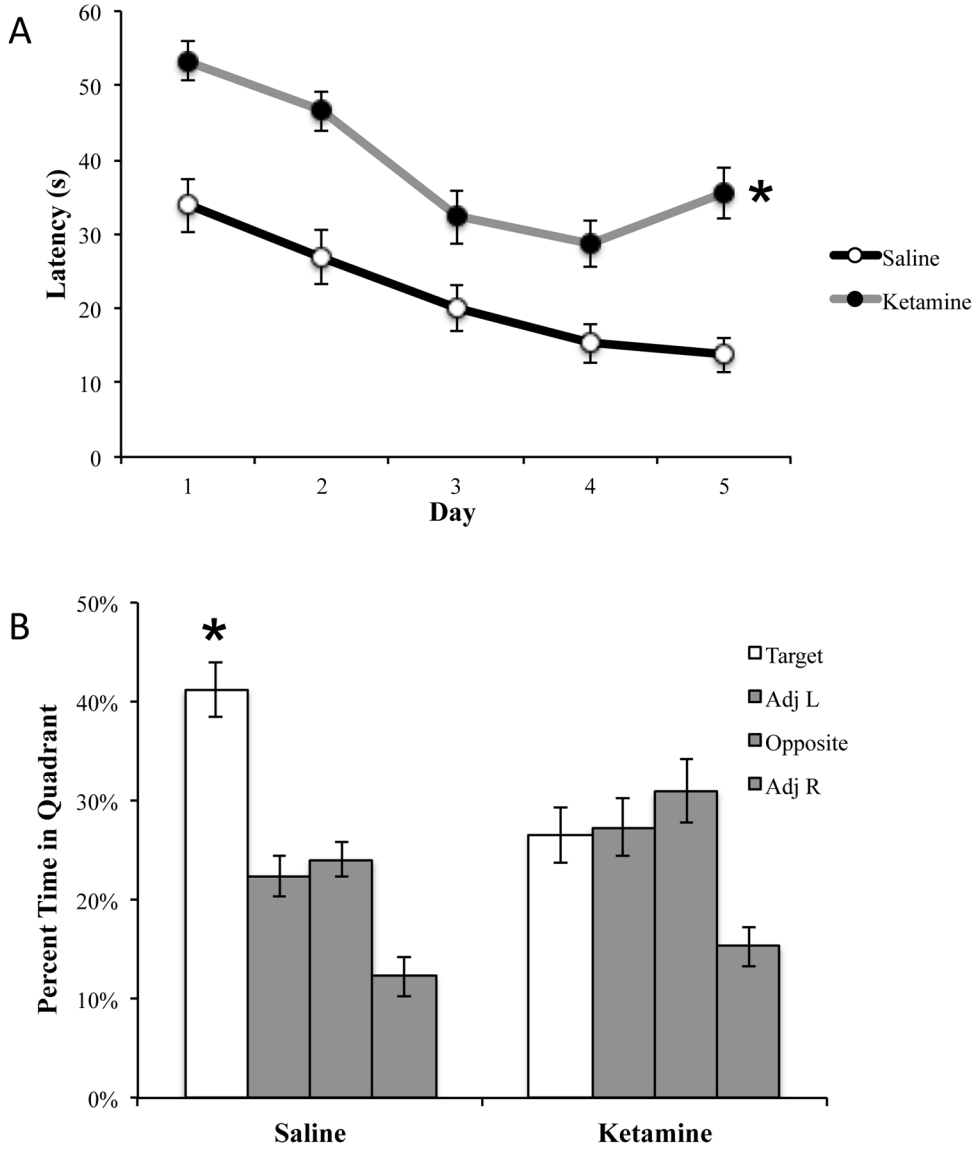

Figure 1.

Ketamine produced deficits in the Morris water maze. (A) Ketamine-treated rats displayed significantly longer latency to find the platform during acquisition. (B) Saline-treated rats exhibited a selective search on the probe trial, indicating a significant preference for the target quadrant, while ketamine produced a deficit. Saline: n=10; ketamine: n=10; *p<0.01

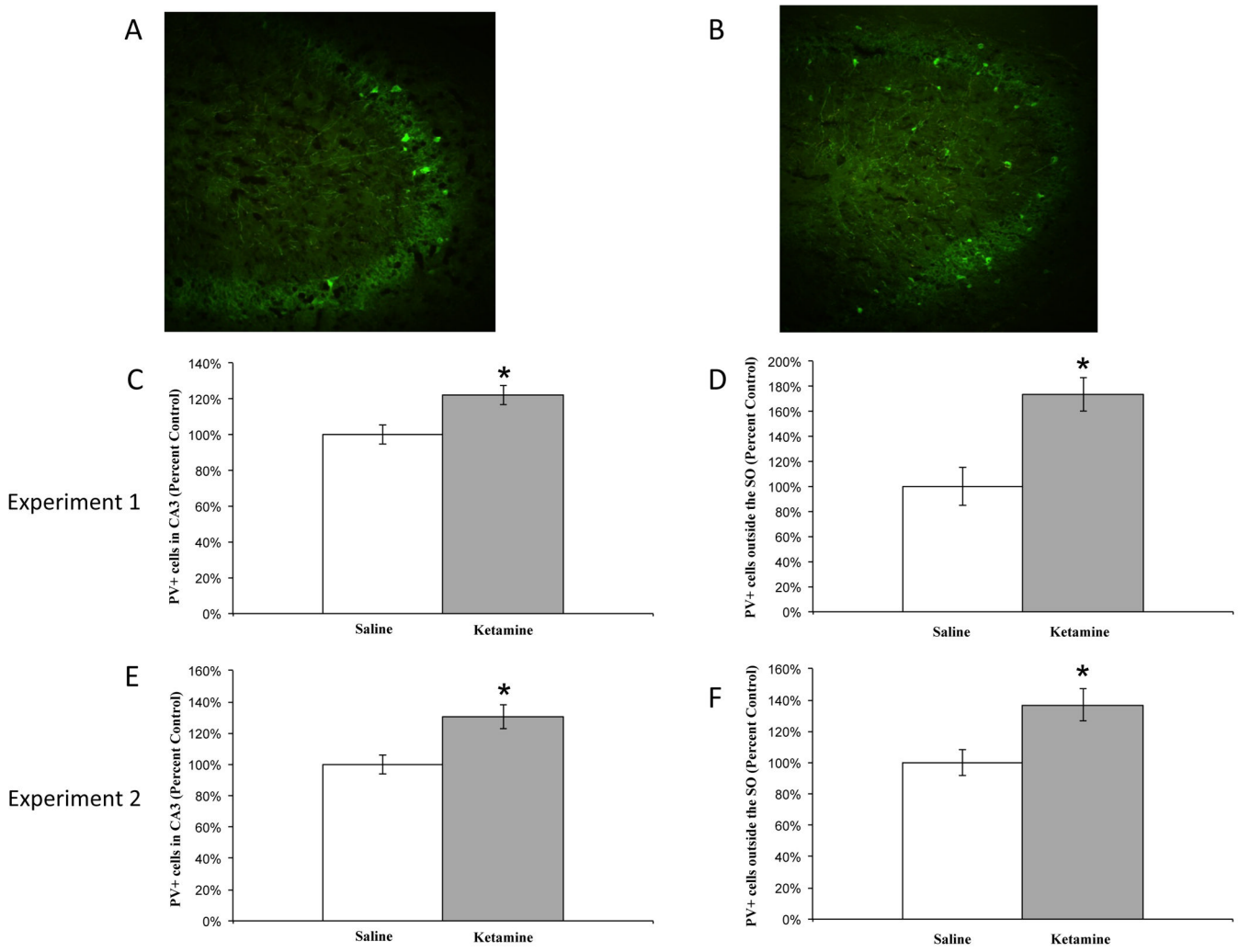

Figure 2.

Number and positioning of PV-positive neurons in the CA3 region of hippocampus. (A) Representative image of saline-treated subject. (B) Representative image of ketamine-treated subject. Ketamine produced a significant increase in PV-positive neurons in CA3 in experiment 1 (C) and experiment 2 (E) compared to saline. Ketamine also led to a percent increase in these cells outside the stratum oriens as compared to saline in experiment 1 (D) and experiment 2 (F). Saline: n=10; ketamine: n=10; *p<0.01

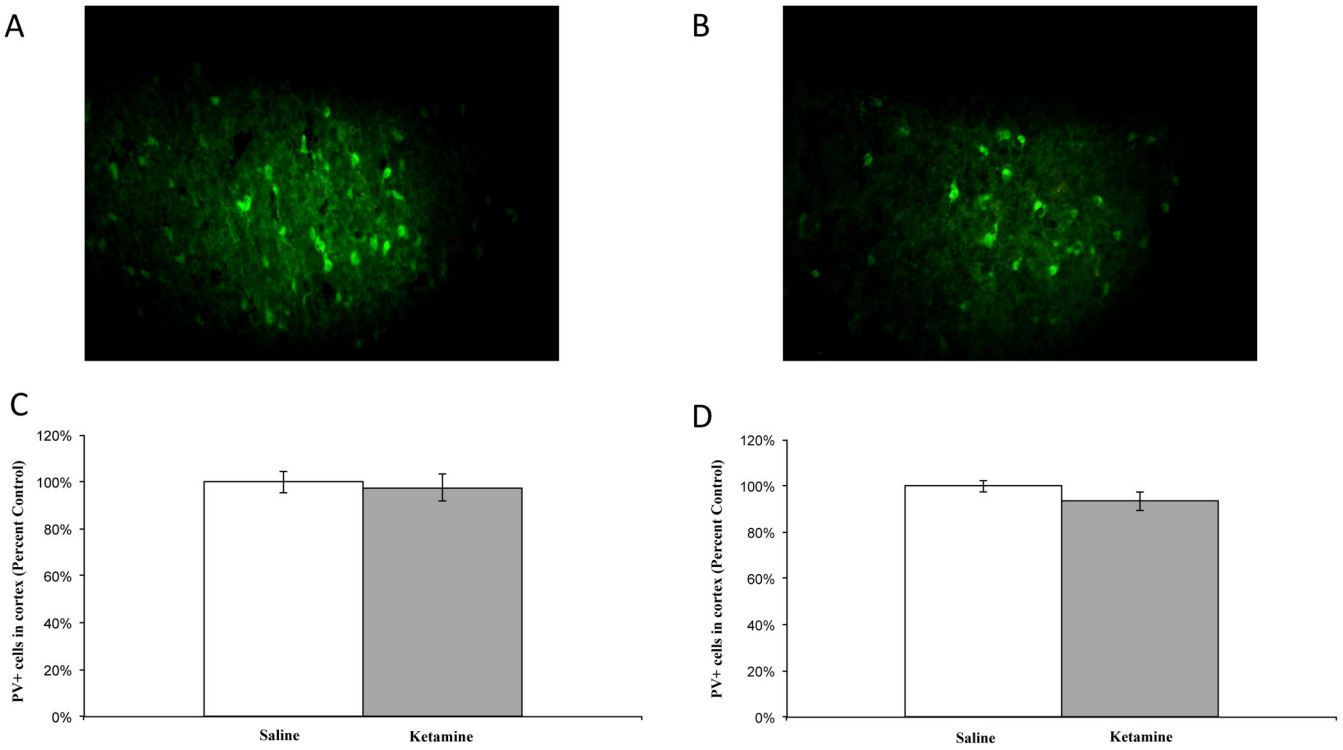

Figure 3.

PV-positive neurons in the cortex. (A) Representative image of saline-treated subject. (B) Representative image of ketamine-treated subject. No significant differences were observed in PV-positive neurons in the cortex in experiment 1 (C) or experiment 2 (D), $p>.05$. Saline: n=5; ketamine: n=5.

Table 1

PV + cell count data from experiments 1 and 2 (expressed as mean ± SEM).

Experiment	Group	CA3	CA3 outside SO	Cortex
1	Saline	26.71 ± 1.46	3.50 ± 0.52	64.13 ± 2.94
	Ketamine	32.61 ± 1.46	6.09 ± 0.78	62.59 ± 3.70
2	Saline	24.65 ± 0.65	3.65 ± 0.30	66.88 ± 1.70
	Ketamine	36.33 ± 2.20	5.00 ± 0.37	62.50 ± 2.70