



Endocannabinoid Signaling Contributes to Experience-Induced Increase of Synaptic Release Sites From Parvalbumin Interneurons in Mouse Visual Cortex

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During postnatal development of the visual cortex between eye-opening to puberty, visual experience promotes a gradual increase in the strength of inhibitory synaptic connections from parvalbumin-positive interneurons (PV-INs) onto layer 2/3 pyramidal cells. However, the detailed connectivity properties and molecular mechanisms underlying these developmental changes are not well understood. Using dual-patch clamp in brain slices from G42 mice, we revealed that both connection probability and the number of synaptic release sites contributed to the enhancement of synaptic strength. The increase of release site number was hindered by dark rearing from eye-opening and rescued by 3-days re-exposure to the normal visual environment. The effect of light re-exposure on restoring synaptic release sites in dark reared mice was mimicked by the agonist of cannabinoid-1 (CB1) receptors and blocked by an antagonist of these receptors, suggesting a role for endocannabinoid signaling in light-induced maturation of inhibitory connectivity from PV-INs to pyramidal cells during postnatal development.

Keywords: parvalbumin interneuron, cannabinoid, postnatal development, connectivity, synaptic strength, perisomatic inhibition, visual cortex

INTRODUCTION

Parvalbumin-expressing interneurons (PV-INs) are the prominent subtype of interneurons in the cortex (Rudy et al., 2011). Distinct anatomical and functional features allow PV-INs to provide fast feedforward and feedback inhibition. PV basket cells form perisomatic inhibitions onto pyramidal cells (Tremblay et al., 2016), highly connected with neighbor pyramidal cells and themselves (Holmgren et al., 2003; Packer and Yuste, 2011; Avermann et al., 2012; Gu et al., 2013; Pfeffer et al., 2013), and are uniquely poised to control network firing (Rudy et al., 2011; Bridi et al., 2020b).

PV-INs are crucial for several cortical functions. They are essential for gain control (Atallah et al., 2012), play a role on feature selectivity (Lee et al., 2012; Duan et al., 2017; Goel et al., 2018), participate in gamma rhythms (Cardin et al., 2009; Sohal et al., 2009). Importantly, in the visual

cortex the protracted development of perisomatic inhibition has been implicated in the gating and control of ocular dominance plasticity during the critical period (Huang et al., 1999; Fagiolini et al., 2004; for reviews see Jiang et al., 2005; van Versendaal and Levelt, 2016; Choi, 2018; Hensch and Quinlan, 2018).

In the visual cortex, perisomatic inhibition develops postnatally and its maturation is completed at the beginning of puberty (~5 weeks of age). This maturation involves the increase in the number of synapses (Huang et al., 1999; Chattopadhyaya et al., 2004; Kreczko et al., 2009) and also an increase in the strength (Morales et al., 2002; Jiang et al., 2010a; Tatti et al., 2017). There is abundant evidence that this process depends on visual experience (Benevento et al., 1995; Morales et al., 2002; Chattopadhyaya et al., 2004; Katagiri et al., 2007; Kreczko et al., 2009; Jiang et al., 2010b). However, the underlying molecular mechanisms and its consequences for the functional circuitry are not clear. Here we show that the experience developmental increase in the strength of perisomatic inhibition reflects the increase in the number of PV-IN→Pyr connections and in the number of synapses per connection, without changes in the quantal size of quantal content. This change can be mimicked by the agonist of CB1 receptors and blocked by an antagonist of CB1 receptors. Our findings provide evidence that endocannabinoid may be involved in experience induced maturation of inhibitory synapse number during development.

MATERIALS AND METHODS

Animals

G42 mice were obtained directly from Dr. J. Z. Huang (Cold Spring Harbor Laboratory) *via* Dr. Bernardo Rudy. Offspring were produced from homozygous or heterozygous breeding pairs. Either sex of mice was used in this study. Normally reared mice were reared in a 12-h light/dark cycles. Dark reared mice were reared in a dark room with light completely blocked. I.P. injections in dark reared mice were performed with the help of a night vision goggle in the darkroom. All procedures were approved by the Institutional Animal Care and Use Committee at the Johns Hopkins University.

Brain Slice Preparation

Acute visual cortical slices (300 μ m) from G42 mice were prepared as previously described (Jiang et al., 2010b; Gu et al., 2013; Huang et al., 2013; Gao et al., 2017; Bridi et al., 2020b). Briefly, slices were cut in the ice-cold dissection buffer containing (in mM): 212.7 sucrose, 5 KCl, 1.25 NaH_2PO_4 , 10 MgCl_2 , 0.5 CaCl_2 , 26 NaHCO_3 , 10 dextrose, bubbled with 95% O_2 /5% CO_2 (pH 7.4). Slices were then transferred into a recovery chamber containing normal artificial cerebrospinal fluid (ACSF) and recovered for 30 min in a 30°C water bath. After that, the slices were recovered in the room temperature for at least an additional 30 min before recording. Normal ACSF was similar to the dissection buffer except that the concentrations of MgCl_2 and CaCl_2 were 1 mM and 2 mM, respectively, and sucrose was replaced by NaCl (124 mM).

Dual-Patch Clamp

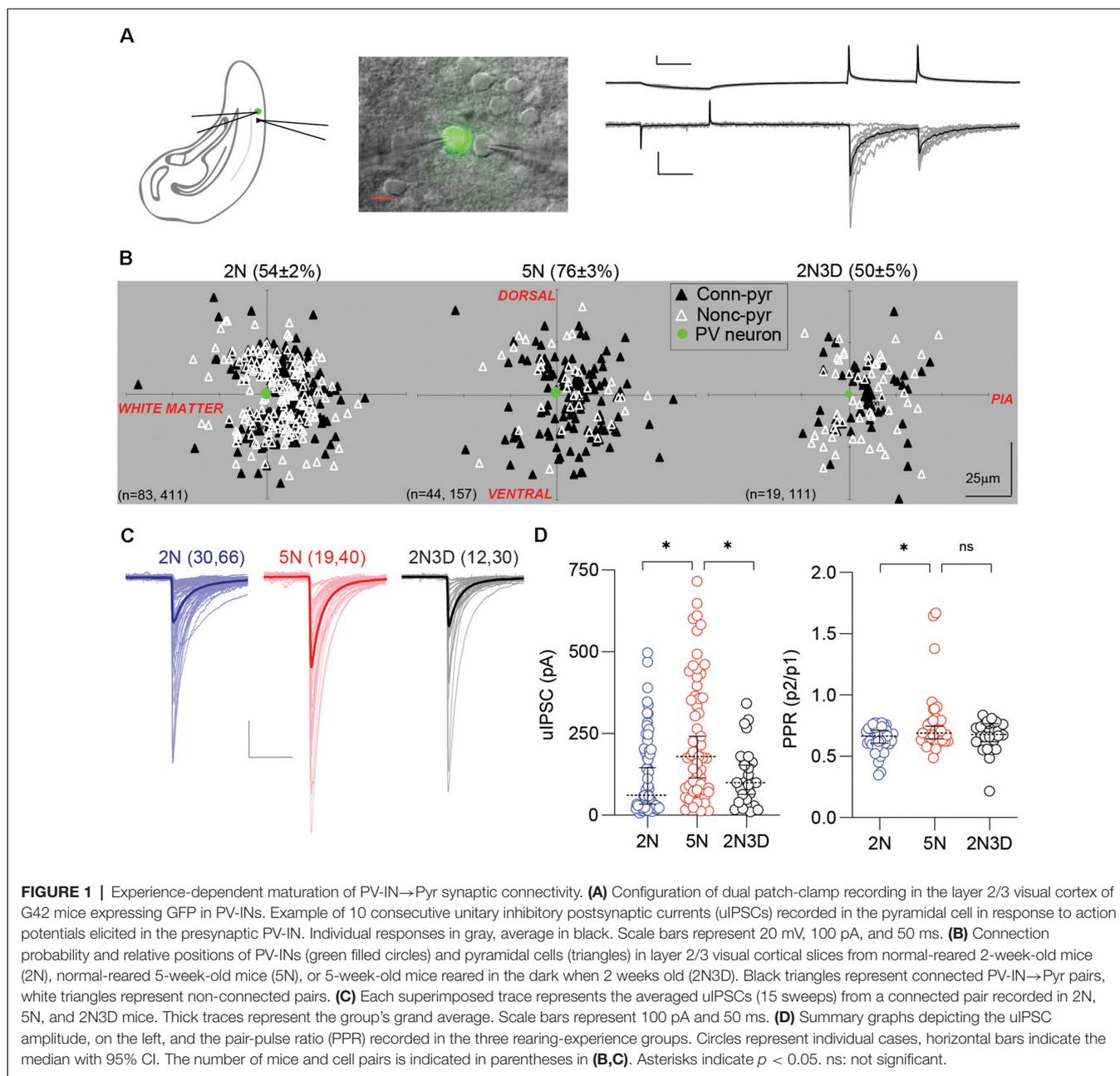
Two types of internal solution were used for dual-patch clamp in this study: a K-based internal solution (in mM: 130 Kgluconate, 10 KCl, 0.2 EGTA, 10 HEPES, 0.5 NaGTP, 4 MgATP, and 10 Na_2 -Phosphocreatine; pH adjusted to 7.25 with KOH, 280–290 mOsm), and a CsCl-based internal solution (in mM: 120 CsCl, 8 NaCl, 10 HEPES, 2 EGTA, 5 QX-314, 0.5 Na_2 GTP, 4 MgATP, and 10 Na_2 -Phosphocreatine; pH adjusted to 7.25 with CsOH, 280–290 mOsm). As previously described (Jiang et al., 2010b; Gu et al., 2013; Huang et al., 2013; Gao et al., 2017; Bridi et al., 2020b), in the layer 2/3 of the visual cortex, PV-INs were identified by fluorescence and recorded under current clamp with pipettes containing the K-based internal solution. Pyramidal cells were visually identified by their pyramidal looking soma and clear apical dendrite (Jiang et al., 2007) and recorded under voltage clamp with pipettes filled with the CsCl-based internal solution. Patch-clamp recordings were performed at 30°C. Only cells with membrane potentials < -60 mV, series resistance < 20 M Ω were studied. Patch-clamp properties were monitored with 100-ms negative voltage or current commands (-2 mV and -40 pA for voltage and current clamp, respectively) delivered every 20–30 s. Cells were excluded if series resistance changed $> 15\%$ over the experiment. Data were filtered at 2 kHz and digitized at 10 kHz using Igor Pro (WaveMetrics). Synaptic currents were recorded from pyramidal cells holding at -60 mV in the presence of 20 μ M 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and 100 μ M 2-amino-5-phosphonovaleric acid (APV) and evoked PV-INs firing every 20 s by a depolarized current with 2 ms pulses delivered in pairs [inter-stimulus interval (ISI): 100 ms] to compute paired-pulse ratio (PPR = P_2/P_1 , where P_1 and P_2 are the amplitudes of the responses to the first and second stimulation, respectively; **Figure 1A**). Spike features in PV-INs were calculated as previously described (Bridi et al., 2017). The distance between the cell pair of PV-IN and pyramidal cell and the position of the cell pairs in the brain slices were recorded.

Chemicals and I.P. Injection

WIN 55,212-2 (WIN), AM251, DL-AP5, and CNQX were purchased from Sigma and the R&D system. CB1 receptor antagonist and agonist, WIN and AM251 were dissolved in the vehicle solution [10% Tween 80, 20% DMSO, and 70% saline (0.9% NaCl)] to a final concentration of 1 mg/ml for systematic injection (I.P.). To minimize variability in these experiments the control and treated mice came from the same litter and were housed together. On the day of the experiment we tested one control and one treated mice and the order of sacrifice was alternated every day.

Data Analysis and Statistics

The mean-variance analysis was performed on responses evoked by 15 stimulus trains (5 or 10 stimuli at 30–50 Hz) delivered at 20 s intervals. The unitary inhibitory postsynaptic current (uIPSC) amplitude was measured for each stimulus, and the mean (I) and variance (var) were plotted against each other. Synaptic parameters including the number of release sites (N)



and the quantal size (q) were obtained by fitting the data to the parabola: $var = q \cdot I - I^2/N$ as previously described (Scheuss and Neher, 2001; Gu et al., 2013). We previously validated using this approach to evaluate parameters in PV-IN→Pyr connections (Gu et al., 2013). We considered only those cases in which the R^2 value of the fit was >0.5 .

For comparison in connection probability, a χ^2 test was applied to determine variation, and a Fisher's Exact p -value was used to determine the significance. For other two-group comparisons, significance was examined by unpaired two-tailed t -tests or Mann-Whitney ($M-W$) tests based on the normality of dataset using the D'Agostino-Pearson omnibus normality test. For multiple groups (more than two) comparisons, one way

ANOVA test followed by Holm-Sidak's multiple comparisons test (normally distributed data), or Kruskal-Wallis test followed by Dunn's multiple comparisons test (non-normal distributed data) were used to determine statistical significance. $P < 0.05$ was considered as statistical significance. Statistical outliers in the amplitude of uIPSCs were detected using pre-established criteria (ROUT test) and excluded from analysis (**Supplementary Table S1**).

RESULTS

During postnatal development, in the period between eye-opening to puberty, visual experience promotes a ~ 3 -fold

increase in the strength of GABAergic perisomatic inhibition onto layer 2/3 pyramidal cell (Huang et al., 1999; Morales et al., 2002; Chattopadhyaya et al., 2004; Lu et al., 2014). It is unclear whether this increase in perisomatic inhibition reflects an increase in connectivity, i.e., more interneurons contacting a given pyramidal cell, an increase in the potency of these contacts, or both. Since parvalbumin-positive inhibitory interneurons (PV-INs) contribute the majority of perisomatic inhibitory inputs (Kruglikov and Rudy, 2008), we addressed these questions by performing paired recordings of pyramidal cells (Pyr) and PV-INs in the layer 2/3 of acute visual cortical slices of G42 mice, a line that expresses GFP in PV-INs (Chattopadhyaya et al., 2004).

Experience-Dependent Developmental Increase in PV-IN→Pyr Connectivity

We compared the PV-IN→Pyr connectivity in visual cortical slices from three groups of G42 mice that differed in age and visual experience: normally-reared 2-week-old mice (2N, postnatal days 14–16), normally-reared 5-week-old mice (5N, postnatal days 35–37) and 5-week-old mice reared in the dark when 2 weeks old (2N3D, postnatal days 35–37). Action potentials were induced in the PV-INs and the uIPSCs were recorded in pyramidal cells (see “Materials and Methods” section; **Figure 1A**). As shown in **Figure 1B**, the connection probability of the PV-IN→Pyr pairs increased significantly between 2 and 5 weeks of age in normal reared mice (2N: 0.54 ± 0.02 , $n = 411$ pairs, 83 mice; 5N: 0.76 ± 0.04 , $n = 157$ pairs, 44 mice; $p < 0.0001$; Fisher’s exact test), and this developmental increase did not occur in mice reared in the dark for 3 weeks (2N3D: 0.50 ± 0.05 , $n = 111$ pairs, 19 mice; 5N vs. 2N3D: $p < 0.0001$; 2N vs. 2N3D: $p = 0.5205$; Fisher’s exact test). Similarly, in connected PV-IN→Pyr pairs the amplitude of uIPSCs also increased from postnatal 2 weeks to 5 weeks in normally reared mice, and it did not occur in mice reared in the dark (statistic value = 15.53, $p = 0.0004$, Kruskal–Wallis test; 2N vs. 5N: $p = 0.0004$; 5N vs. 2N3D: $p = 0.0176$; Dunn’s multiple comparison test; **Figures 1C,D**). We also measured the PPR (P2/P1) of the uIPSCs as an indicator of presynaptic release probability. The PPR of uIPSCs was larger in 5N mice compared to 2N mice but visual deprivation after eye-opening did not significantly affect this increase (statistic value = 5.55, $p = 0.0623$, Kruskal–Wallis test; 2N vs. 5N: $p = 0.0383$; 5N vs. 2N3D: $p = 0.8013$; Dunn’s multiple comparison; **Figure 1D**). These results indicate that during postnatal maturation, PV-INs connect with more nearby pyramidal cells and with stronger connections. Those changes require visual experience.

Developmental Increase of uIPSCs Amplitude Reflects Release Sites per PV-IN→Pyr Connection

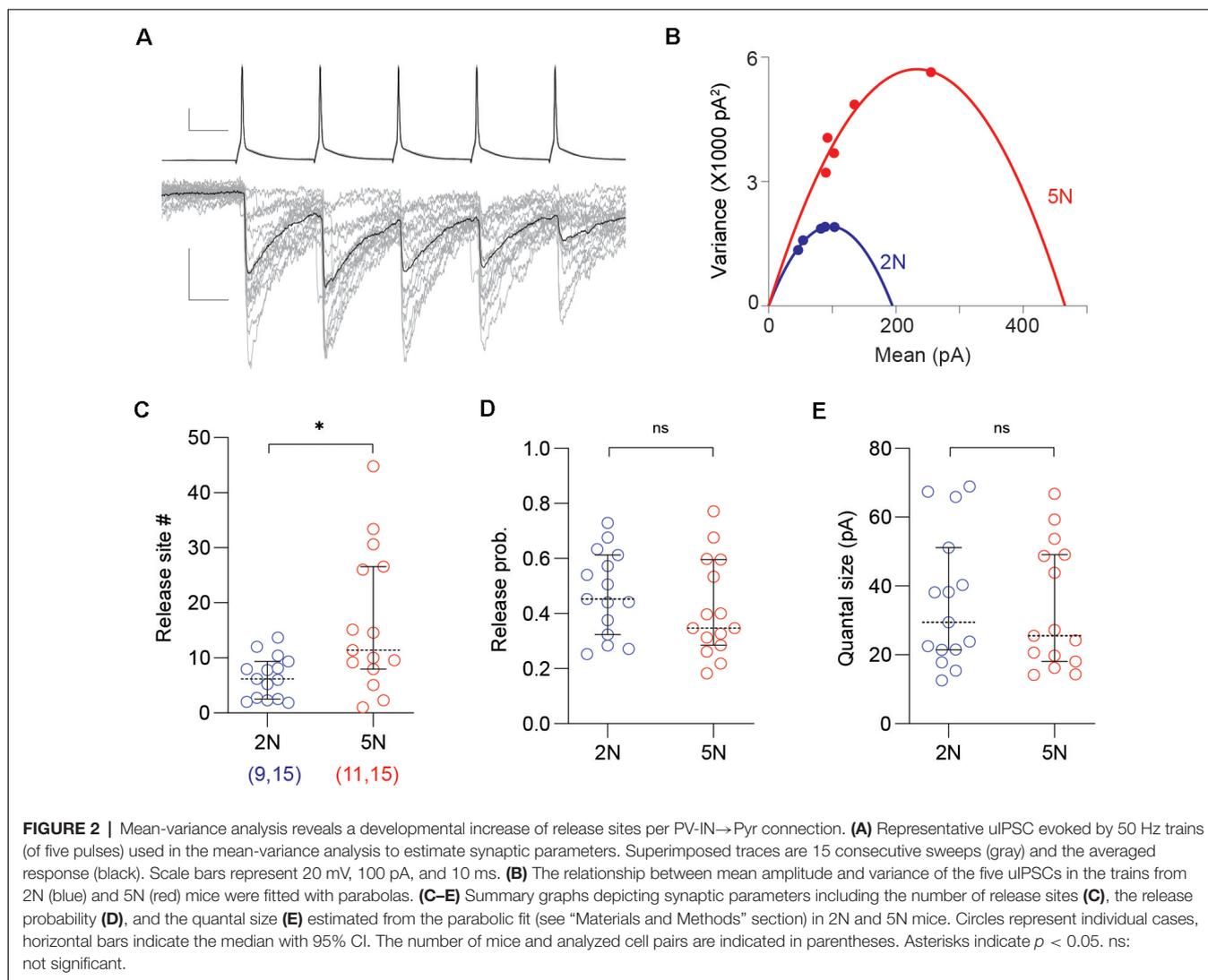
To further understand the maturation of synaptic properties in connected PV-IN→Pyr cell pairs, we used mean-variance analysis to estimate the quantal parameters from uIPSCs, including the number of the synaptic release site, the release probability, and the quantal size (**Figures 2A,B**). This approach

was validated in our previous publication (Gu et al., 2013). We found that the number of release site significantly increased from 2N to 5N (2N: $n = 15$ pairs, nine mice; 5N: $n = 15$ pairs, 11 mice; $t_{(28)} = 2.889$, $p = 0.0074$, unpaired t -test; **Figure 2C**), but not the release probability ($t_{(28)} = 0.9500$, $p = 0.3502$, unpaired t -test; **Figure 2D**) or the quantal size ($t_{(28)} = 0.3182$, $p = 0.7527$, unpaired t -test; **Figure 2E**). These results indicated that the developmental increase in the uIPSC amplitude can be attributed to an increase in the number of release sites, probably reflecting more synaptic contacts per PV-IN→Pyr pairs.

Light Exposure via Endocannabinoid Signaling Increases the uIPSC Amplitude and the Number of Synaptic Release Sites in Dark-Reared Mice

Previously we showed that brief exposure to normal light environment can rescue alterations in GABAergic release induced by prolonged dark-rearing (Jiang et al., 2010b). We asked, therefore, whether a brief exposure to light can restore the strength of PV-IN→Pyr connectivity in 2N3D mice. In six light-exposed mice (2N3D + L), the proportion of connected pairs was still low (only 17 out of 34 connected pairs) and comparable to the proportion observed in six non-exposed 2N3D mice (12 out of 32 pairs; $p = 0.3325$, Fisher exact test). In contrast, the exposure to light did increase significantly the amplitude of uIPSCs in the connected PV-IN→Pyr pairs (2N3D + L: 559.7 ± 118.1 pA, $n = 16$ pairs, six mice; 2N3D: 176.3 ± 36.3 pA, $n = 12$ pairs, six mice; $U = 38$, $p = 0.0061$, M–W test; **Figures 3A,B**). In a subset of these connected PV-IN→Pyr cell pairs we performed the Mean-variance analysis as showed in **Figure 2**. We found that light exposure increased the number of release sites (2N3D + L: 20.7 ± 5.7 , $n = 10$ pairs; 2N3D: 6.6 ± 1.1 , $n = 9$ pairs; $t_{(17)} = 2.288$, $p = 0.0352$, unpaired t -test; **Figure 3C**), but did not change the release probability (2N3D + L: 0.63 ± 0.03 ; 2N3D: 0.57 ± 0.06 ; $U = 40$, $p = 0.7197$, M–W test; **Figure 3D**) or quantal size (2N3D + L: 52.8 ± 5.5 pA; 2N3D: 51.3 ± 10.0 pA; $t_{(17)} = 0.1470$, $p = 0.8849$, unpaired t -test; **Figure 3E**).

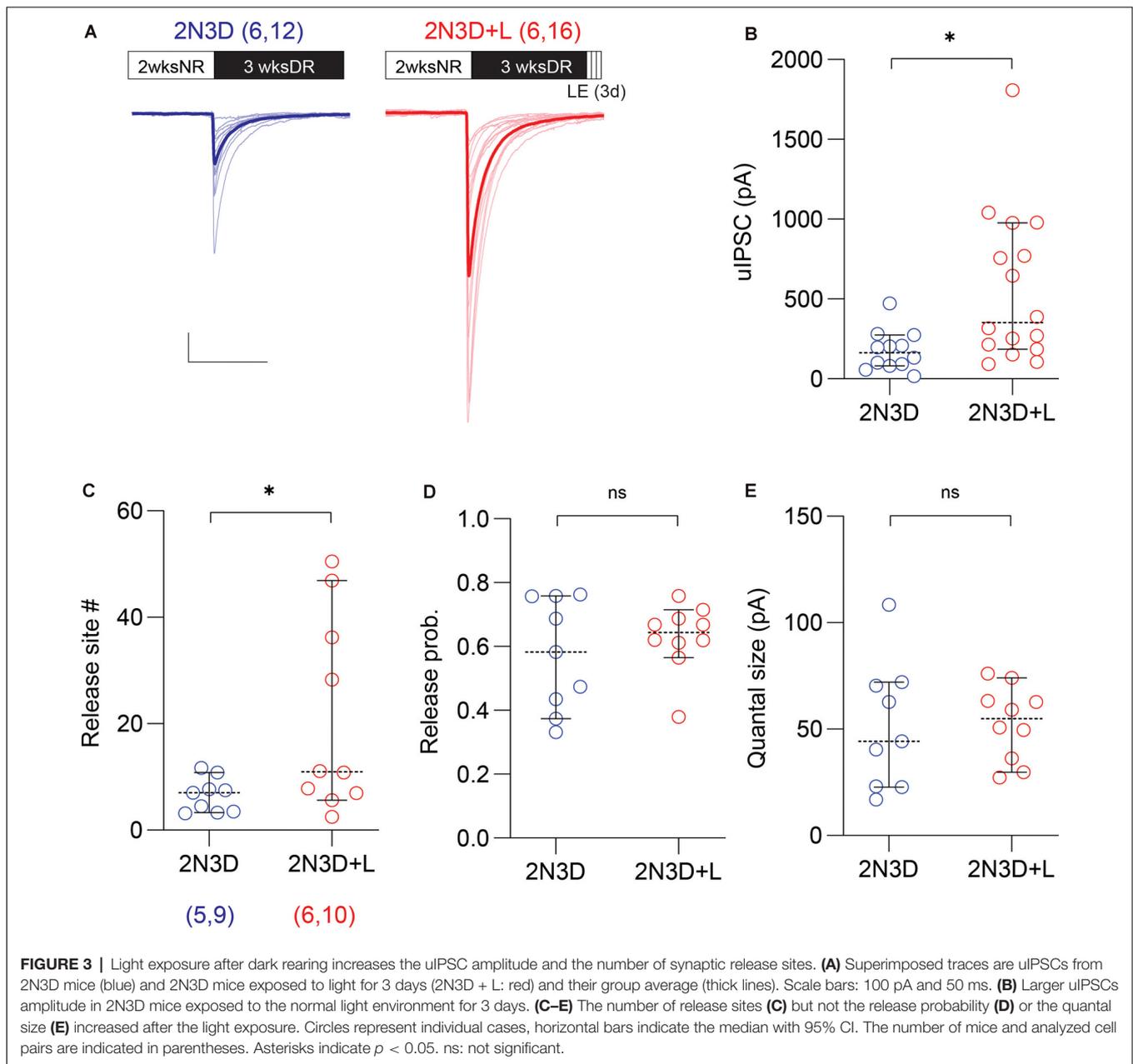
Next, we explored possible molecular mechanisms contributing to the rapid recovery of the uIPSC amplitude and the number of release sites induced by light exposure. Previously we reported that endocannabinoid signaling plays a role in the experience-dependent maturation of short-term plasticity of GABAergic synaptic transmission in the layer 2/3 visual cortex (Jiang et al., 2010a,b; Sun et al., 2015). Therefore, we examined the role of endocannabinoid signaling in the rapid recovery of the uIPSCs amplitude and the number of release sites induced by light re-exposure in the dark reared mice. To that end, we tested whether the effects of light exposure can be respectively mimicked and prevented by cannabinoid agonists and antagonists. First, we evaluated in the 2N3D mice the effects of the agonist of cannabinoid-1 (CB1) receptor WIN injected systemically in the last 3 days of dark rearing (10 mg/kg, I.P. injection twice per day). We found that in 2N3D mice injected with WIN, the uIPSC



amplitude was larger than that in the control 2N3D mice injected with vehicle (2N3D + WIN: 411.3 ± 57.1 pA, $n = 22$ pairs, seven mice; 2N3D + Veh: 218.0 ± 50.4 pA, $n = 20$ pairs, six mice; $U = 120$, $p = 0.0111$, M–W test; **Figures 4A,B**). Similarly, the variance analysis revealed a larger number of synaptic release sites in the WIN-injected 2N3D mice (2N3D + WIN: 20.6 ± 4.1 , $n = 14$ pairs; 2N3D + Veh: 8.9 ± 1.6 , $n = 16$ pairs; $U = 44$, $p = 0.0039$, M–W test; **Figure 4C**), but no differences either in the quantal size (2N3D + WIN: 49.3 ± 6.4 pA; 2N3D + Veh: 42.5 ± 6.6 pA; $t_{(28)} = 0.7307$, $p = 0.4710$, unpaired t -test; **Figure 4E**) or in the computed release probability (2N3D + WIN: 0.48 ± 0.06 ; 2N3D + Veh: 0.60 ± 0.04 ; $t_{(28)} = 1.658$, $p = 0.1085$, unpaired t -test; **Figure 4D**). We also found that WIN injection did not change the spike features or membrane properties in PV-INs or pyramidal cells (**Supplementary Table S2**).

We considered the possibility that WIN injections may alter the PV-IN→Pyr connectivity in normally reared mice. To that end, we repeated the 3-day WIN treatment (10 mg/kg,

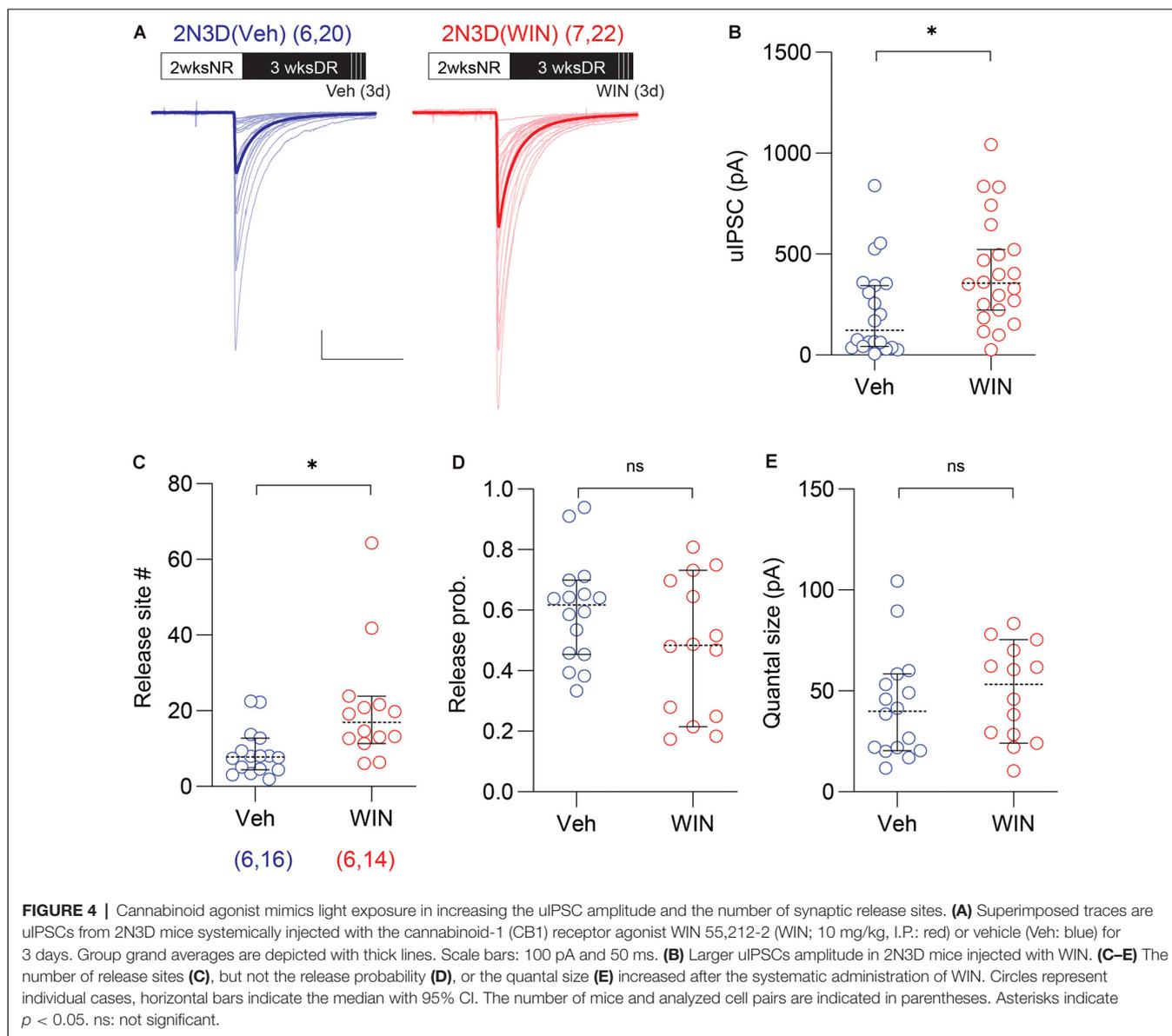
I.P. injection twice per day) in 5N mice, and found that in WIN injected mice the proportion of connected PV-INs→Pyr pairs was comparable to that of 5N mice injected with vehicle (5N + WIN: 26 out of 35 pairs; 5N + Veh: 26 out of 35 pairs; $p > 0.9999$, Fisher exact test). In a similar manner, there were no differences in the uIPSC amplitude (5N + WIN: 238.3 ± 46.6 pA, $n = 23$ pairs, seven mice; 5N + Veh: 390.1 ± 71.2 pA, $n = 24$ pairs, seven mice; $U = 200$, $p = 0.1086$, M–W test; **Figures 5A,B**), the number of release site (5N + WIN: 15.8 ± 2.7 , $n = 16$ pairs; 5N + Veh: 19.9 ± 4.1 , $n = 13$ pairs; $U = 91$, $p = 0.5890$, M–W test; **Figure 5C**), the release probability (5N + WIN: 0.41 ± 0.06 ; 5N + Veh: 0.49 ± 0.07 ; $t_{(27)} = 0.9182$, $p = 0.3666$, unpaired t -test; **Figure 5D**), or the quantal size (5N + WIN: 47.7 ± 7.2 pA; 5N + Veh: 52.6 ± 4.0 pA; $t_{(27)} = 0.5484$, $p = 0.5879$, unpaired t -test; **Figure 5E**), after 3-day WIN injection in 5-week-old normally reared mice. The WIN injection in 5N mice modestly affected intrinsic firing properties: it decreased the spike threshold voltage, trough voltage, and upstroke/downstroke ratio, and



increased the input resistance and spike downstroke of PV-INs (**Supplementary Table S3**).

Finally, in a complementary set of studies, we tested whether the CB1 antagonist AM251 prevents the increase of PV-IN→Pyr strength in 2N3D mice re-exposed to normal light/dark cycles for 3 days. In these 2N3D + L mice, we injected AM251 daily during the light exposure (10 mg/kg, I.P. injection twice per day, started 1 day before the light re-exposure). Compared to vehicle-injected mice, the mice injected with AM251 showed smaller uIPSC amplitude (2N3D + L + AM251: 106.4 ± 18.7 pA, $n = 21$ pairs, six mice; 2N3D + L + Veh: 391.6 ± 52.2 pA, $n = 24$ pairs, six mice; $U = 64$, $p < 0.0001$, M–W test; **Figures 6A,B**), and a smaller number of release sites (2N3D + L + AM251: 9.4 ± 1.5 pA,

$n = 14$ pairs; 2N3D + L + Veh: 15.8 ± 2.4 pA, $n = 19$ pairs; $U = 78$, $p = 0.0461$, M–W test; **Figure 6C**), but without changes in either the release probability (2N3D + L + AM251: 0.43 ± 0.06 ; 2N3D + L + Veh: 0.52 ± 0.04 ; $t_{(31)} = 1.43$, $p = 0.1626$, unpaired t -test; **Figure 6D**) or the quantal size (2N3D + L + AM251: 42.7 ± 5.0 pA; 2N3D + L + Veh: 53.3 ± 4.3 pA; $t_{(31)} = 1.599$, $p = 0.1199$, unpaired t -test; **Figure 6E**). Altogether the results indicate that after a long period of dark rearing, the reduced strength of the PV-IN→Pyr connections, but not the lowered probability of connections, can be rapidly restored by brief exposure to light, in a process that can be mimicked by CB1 agonists, and prevented by CB1 antagonists. The AM251 injections did not change the spike



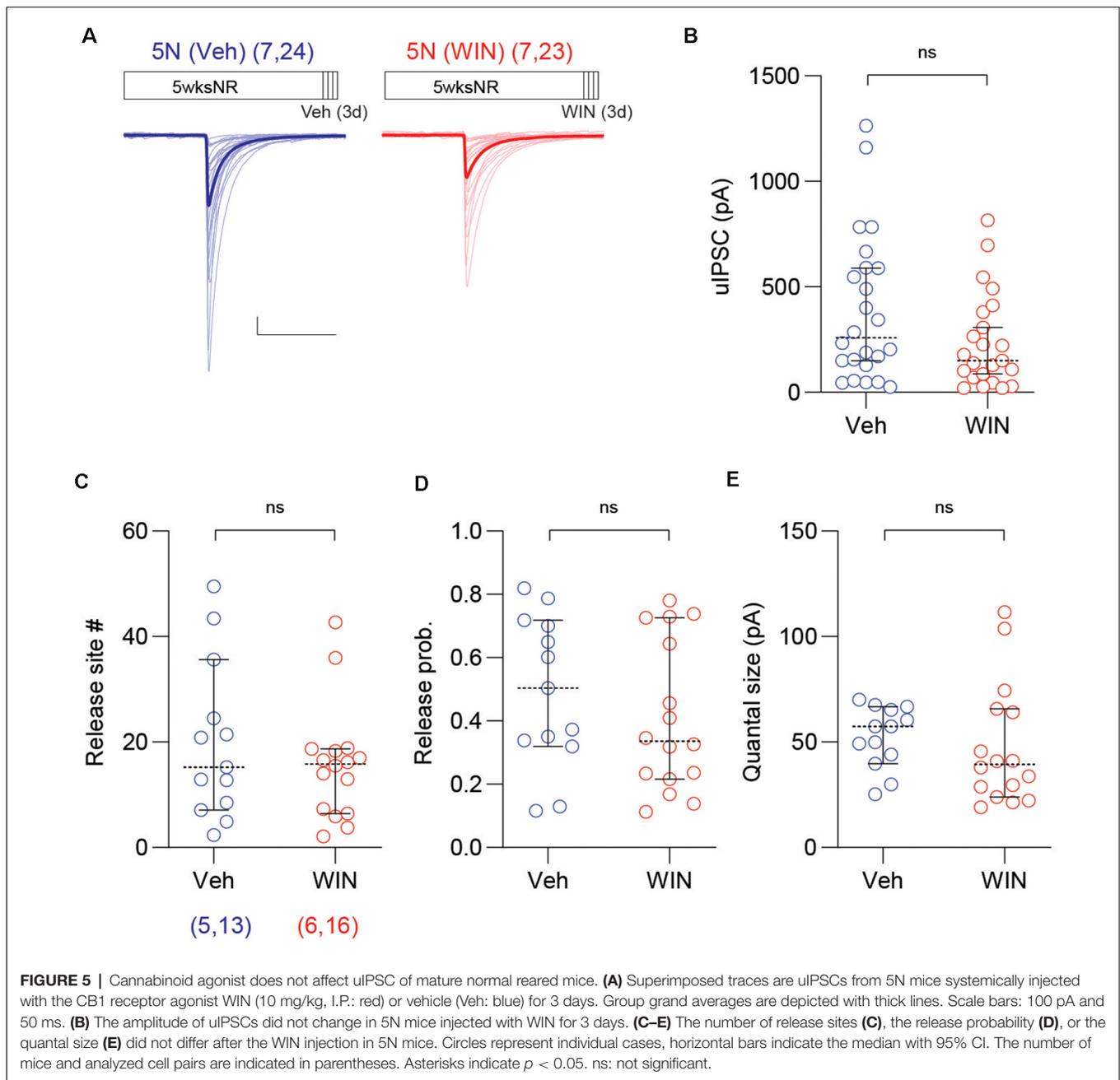
features or membrane properties in PV-INs or pyramidal cells (**Supplementary Table S4**).

DISCUSSION

Our analysis of PV-IN circuitry in the G42 line revealed that the potency and abundance of PV-IN→Pyr connections both increase during postnatal development. Dark rearing since eye-opening arrest both processes, and in the deprived mice the potency of PV-IN→Pyr inputs, although not the connectivity levels, can be rapidly restored by brief light exposure. We surmise that at the quantal level, the developmental/experience increase in potency reflects the addition of release sites without overt changes in release probability or quantal size, in a process that requires cannabinoid signaling.

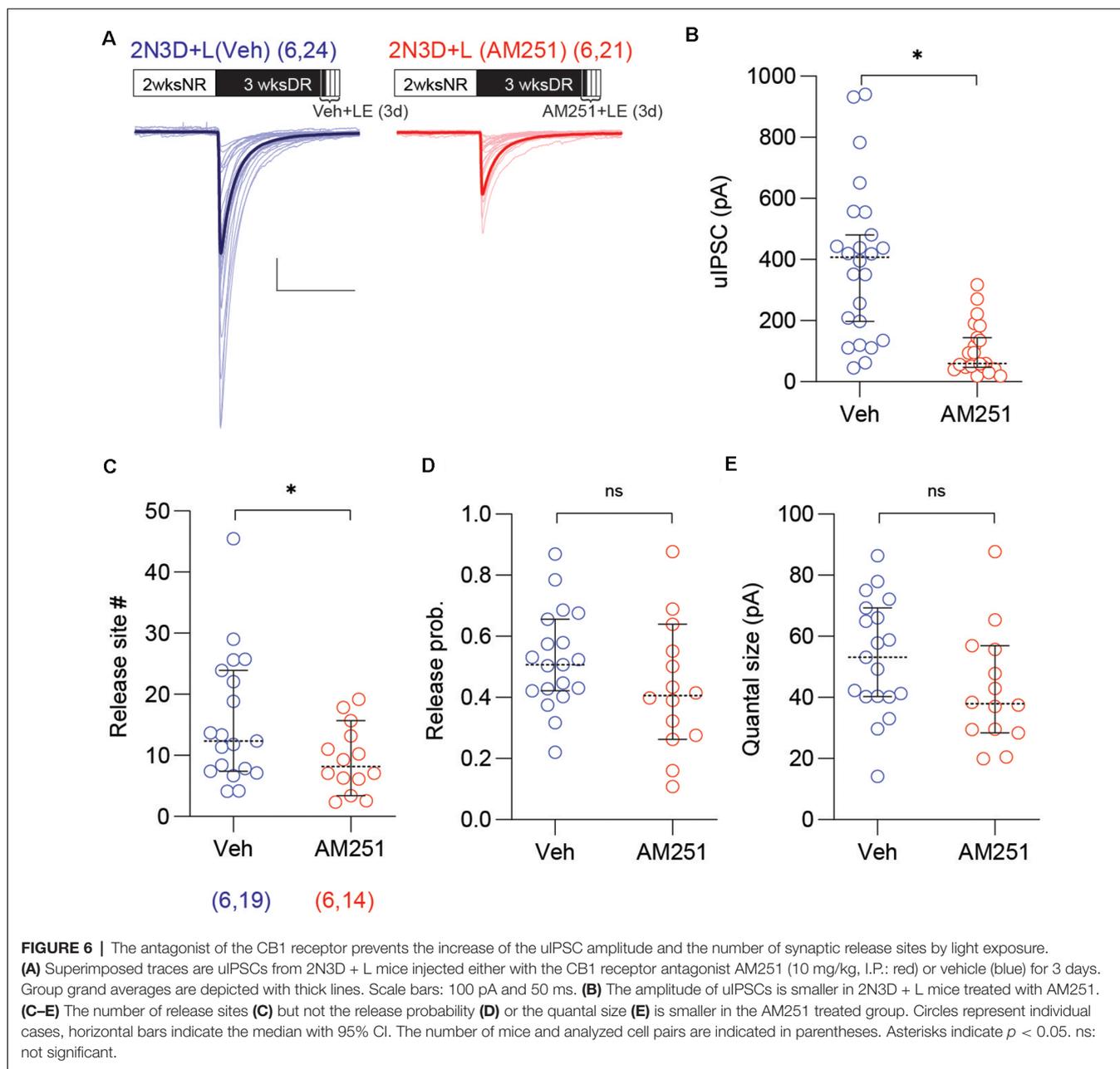
PV-INs were identified based on the fluorescence in acute brain slices of G42 mice in this study. These mice are BAC transgenic mice that express GFP under GAD67 gene promoters exclusively in PV-INs (Chattopadhyaya et al., 2004), but only in a subset of them (Chattopadhyaya et al., 2004; Sippy and Yuste, 2013; Large et al., 2016). PV-positive interneurons are comprised of two subtypes of fast-spiking interneurons, basket cells, and chandelier cells, with distinct anatomical and functional features (Povysheva et al., 2013; Taniguchi et al., 2013; Inan and Anderson, 2014; Miyamae et al., 2017). Although chandelier cells are far less common than basket cells, we can't rule out that we recorded a mixture of these two subtypes of fast-spiking interneurons.

We found that the connection probability and the unitary strength of PV-IN→Pyr connections in layer 2/3 cortex increased during development, which is in agreement with



previous reports of a protracted maturation of PV-IN circuits in the visual cortex (Chattopadhyaya et al., 2004; Lazarus and Huang, 2011; Lu et al., 2014), dentate gyrus (Doischer et al., 2008), and prefrontal cortex (Yang et al., 2014). The increase in input strength resulted from the increased number of synaptic release sites rather than quantal size or release probability. The mean-variance analysis indicated a 2-fold increase in synaptic release sites per PV-IN→Pyr connection from the 2nd to the 5th week (from ~10 to ~20 release sites; **Figure 2B**). On the other hand, the PV-IN→Pyr connection probability increases 1.5 times from 2-week-old to 5-week-old (from ~50% to ~75%; **Figure 1B**), which should yield a ~3-fold increase

in the total number release sites onto each pyramidal cell during this developmental period. This estimation matches the 3-fold developmental increase in the magnitude of the maximal evoked IPSCs in pyramidal cells (Morales et al., 2002), and it also matches the ~3-fold developmental increase in perisomatic boutons onto pyramidal cells reported in anatomical studies (Chattopadhyaya et al., 2004; Kreczko et al., 2009). Notably, the developmental increase in all of these measures of GABAergic strength, number of release sites, maximal IPSC, and number perisomatic GABAergic boutons, can be arrested early dark rearing. There are apparent discrepancies, however. In adult mice, each pyramidal cell in layer 2/3 visual cortex



has connections from about 14 PV-INs (Safari et al., 2017). Considering an average of ~ 20 release sites per connection (Figure 2), this would yield ~ 280 release sites per adult pyramidal cells, which far exceed ~ 22 perisomatic GAD puncta observed in the adult layer 2/3 pyramidal cells (Kreczko et al., 2009). This may indicate multivesicular release in PV-IN inhibitory synapses, as reported in hippocampal GABAergic synapses, where there is a fivefold discrepancy between the numbers of functionally determined release sites and structurally identified active zones (Biro et al., 2006). Finally, it is worth pointing out that from a functional point of view, increases in release sites without changes in release probability could be a way to strengthen inhibitory output without altering the dynamic

properties of release, which in the case of PV-INs, are uniquely tuned to maintain the performance over a wide range of firing activity (Bridi et al., 2020b). In turn, this idea concurs with the notion of a need for mechanisms that change overall network inhibition without compromising the temporal dynamics of synaptic inhibition (Gao et al., 2017).

Our results with CB1 ligands support a role for endocannabinoid signaling in the visually-driven increase of PV-IN \rightarrow Pyr release sites. This is consistent with studies showing altered PN-Ins circuits in CB1 KO mice (Fitzgerald et al., 2012; Aso et al., 2018). The underlying mechanisms remain unknown. Early immunohistochemistry studies reported that CB1 and parvalbumin are expressed in the largely distinct

non-overlapping interneuron population (Katona et al., 1999; Wedzony and Chocyk, 2009), which argues against a direct cannabinoid action on PV-INs. Later studies, however, did report CB1 expression in PV-INs in a variety of brain structures (McDonald and Mascagni, 2001; Fusco et al., 2004; Freiman et al., 2006; Narushima et al., 2006; Uchigashima et al., 2007; Horne et al., 2013; Rivera et al., 2014; Holley et al., 2019). Moreover, CB1 agonists do affect PV-IN synaptic transmission in the cortex (Jiang et al., 2010b). Nevertheless, indirect mechanisms are also plausible. For example, activation of CB1 receptors on glia can affect synaptic transmission between neurons (reviewed by Castillo et al., 2012; Metna-Laurent and Marsicano, 2015). Similarly, systemic delivery of cannabinoids increases the BDNF levels in PFC and hippocampus (Sales et al., 2019), and BDNF is a key mediator in CB1 receptor-dependent protection against excitotoxicity (Khaspekov et al., 2004).

Multiple mechanisms have been implicated in the maturation of inhibitory synapses made PV-INs. Some of them promote maturation, like BDNF (Huang et al., 1999; Gianfranceschi et al., 2003; Jiao et al., 2011). GABA (Chattopadhyaya et al., 2007), OTX2 (Sugiyama et al., 2008), NPAS4 (Lin et al., 2008), SynGAP1 (Berryer et al., 2016) while others, such as HDAC1 (Koh and Sng, 2016), polysialic acid (PSA; Di Cristo et al., 2007) and p75 neurotrophin receptor (p75NR; Baho et al., 2019) negatively regulate the maturation of inhibitory synapses from PV-INs. Our study provides evidence for the role of endocannabinoid signaling in the experience-dependent increase of release sites in PV-INs.

Although acute applications of CB1 agonists promote long-term depression of GABAergic transmission (reviewed by Chevalerey et al., 2006), the current observation that systemic and prolonged exposure to cannabinoids strengthen PV-IN→Pyr output complements previous findings that cannabinoids increase the fidelity of PV-IN→Pyr transmission (Jiang et al., 2010b) and play a role in the sleep-dependent enhancement of GABAergic inhibition (Bridi et al., 2020a). The positive effect of cannabinoids on the number of release sites makes this mechanism an attractive target to increase the strength of GABAergic circuitry for therapeutic purposes. Unlike other

signaling mechanisms that promote PV-IN output, like BDNF for example, cortical CB1 receptors can be readily accessed by small molecules capable of crossing the blood-brain barrier. In this context, it will be of interest to determine whether the beneficial effects of cannabidiol in models of Alzheimer's disease (Aso et al., 2018) and autism spectrum disorder (Fleury-Teixeira et al., 2019) are partly due to an increase in PV-IN release sites.

DATA AVAILABILITY STATEMENT

The datasets for generating figures of this study are available in the **Supplementary Materials**.

ETHICS STATEMENT

The animal study was reviewed and approved by IACUC at the Johns Hopkins University.

AUTHOR CONTRIBUTIONS

SH conducted experiments and analyzed data. SH and AK designed experiments, interpreted results, and wrote the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fncel.2020.571133/full#supplementary-material>.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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