Research report

The serotonin reuptake inhibitor citalopram suppresses activity in the neonatal rat barrel cortex *in vivo*

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ABSTRACT

Inhibition of serotonin uptake, which causes an increase in extracellular serotonin levels, disrupts the development of thalamocortical barrel maps in neonatal rodents. Previous *in vitro* studies have suggested that the disruptive effect of excessive serotonin on barrel map formation involves a depression at thalamocortical synapses. However, the effects of serotonin uptake inhibitors on the early thalamocortical activity patterns in the developing barrel cortex *in vivo* remain largely unknown. Here, using extracellular recordings of the local field potentials and multiple unit activity (MUA) we explored the effects of the selective serotonin reuptake inhibitor (SSRI) citalopram (10–20 mg/kg, intraperitoneally) on sensory evoked activity in the barrel cortex of neonatal (postnatal days P2-5) rats *in vivo*. We show that administration of citalopram suppresses the amplitude and prolongs the delay of the sensory evoked potentials, reduces the power and frequency of the early gamma oscillations, and suppresses sensory evoked and spontaneous neuronal firing. In the adolescent P21-29 animals, citalopram affected neither sensory evoked nor spontaneous activity in barrel cortex. We suggest that suppression of the early thalamocortical activity patterns contributes to the disruption of the barrel map development caused by SSRIs and other conditions elevating extracellular serotonin levels.

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1. Introduction

The primary somatosensory cortex in rodents contains a somatotopic map where each whisker is represented in a discrete cytoarchitectural L4 unit, the "barrel" (Woolsey and Van der Loos, 1970; Petersen, 2007; Fox, 2008). During development, the barrel map forms in the first postnatal week, which is also the critical period for barrel map plasticity (for reviews, (O'Leary et al., 1994; Erzurumlu and Kind, 2001; Lopez-Bendito and Molnar, 2003; Feldman and Brecht, 2005; Fox, 2008; Feldman, 2009; Erzurumlu and Gaspar, 2012). During this time, the barrel cortex displays enhanced plasticity at thalamocortical synapses (Isaac et al., 1997; Feldman et al., 1998) and unique spontaneous and sensory-driven activity patterns that are thought to participate in the activity-dependent formation of the topographic thalamocortical barrel maps (Minlebaev et al., 2007, 2009; Yang et al., 2009; Minlebaev et al., 2011; Yang et al., 2013). Among the various signalling mechanisms which are involved in the development of the barrel map, serotonin and glutamate signalling were found to be critical in barrel map formation. An increase in extracellular serotonin levels through a pharmacological blockade of serotonin transporters during the critical period using selective serotonin uptake inhibitors (SSRIs) or genetic deletion of serotonin transporters, as well as through genetic deletion of monoamine oxidase A (MAOA) prevents formation of the whisker-related barrel patterns (Cases et al., 1996; Persico et al., 2001; Salichon et al., 2001; Toda et al., 2013; for review, see van Kleef et al., 2012). Defective barrel phenotypes and/or alteration in the functional organization of cortical columns have also been observed after pharmacological blockade of glutamatergic signalling in the barrel cortex (Fox et al., 1996; Mitrovic et al., 1996) and in mutant mice with genetic blockade of cortical NMDA receptors (Iwasato et al., 2000; Lee et al., 2005) and the metabotropic glutamatergic pathway including the mGluR5

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receptor and phospholipase C-β (Hannan et al., 1998, 2001; Spires et al., 2005; Ballester-Rosado et al., 2010).

Electrophysiological studies using thalamocortical slices *in vitro* revealed that serotonin, acting through presynaptic receptors, strongly reduces glutamate release and inhibits thalamocortical synaptic transmission in neonatal mice and rats, and that serotoninergic control over thalamocortical transmission is a developmentally transient mechanism (Rhoades et al., 1994; Laurent et al., 2002). These findings suggested that serotonin mediated inhibition of thalamocortical transmission alters activity-dependent mechanisms in the developing thalamocortical circuit and contributes to the defective development of the barrel map under conditions of increased extracellular serotonin levels. However, the effects of increased endogenous serotonin on the early activity patterns in the developing barrel cortex remain unknown. In this study, we addressed this question by exploring the effects of the SSRI citalopram, an agent which increases extracellular serotonin levels, on spontaneous and sensory evoked activity in the barrel cortex of neonatal rats *in vivo*. We found that this agent strongly inhibits early activity patterns in the neonatal barrel cortex, this is compatible with the hypothesis that excessive serotonin mediated malformations in barrel maps involve inhibition of the activity-dependent mechanisms of barrel map development.

2. Materials and methods

2.1. Ethical approval

This work has been carried out in accordance with EU Directive 2010/63/EU for animal experiments, and all animal-use protocols were approved by the French National Institute of Health and Medical Research (INSERM, protocol N007.08.01) and Kazan Federal University on the use of laboratory animals (ethical approval by the Institutional Animal Care and Use Committee of Kazan State Medical University N9-2013).

2.2. Surgery

Wistar rats of either sex from postnatal day P2 (P0 = day of birth) till postnatal day P29 were used. Surgery was performed under a combination of urethane (1 g/kg, i.p.) and isoflurane anesthesia. In brief, the skull of the animal was cleaned of skin and periosteum. The skull was covered by dental cement (Grip Cement, Caulk Dentsply, DE, USA) except for a 4–9 mm window above the barrel cortex. A metal ring was fixed to the nasal and occipital bones of the rat's head by dental cement. After surgery, the animals were warmed, and left for one hour to recover. During recordings, the head was fixed to the ball-joint holder by the attached metal ring; animals were surrounded by a cotton nest and heated via a thermal pad (35–37 °C). A chlorided silver wire, placed in the visual cortex, served as the ground electrode.

2.3. Extracellular recordings

Extracellular local field potentials (LFP) and multiple unit activity (MUA) were recorded from single barrel column using 16-site linear silicon probes (50 μm separation distance between recording sites, Neuronexus Technologies, MI). The skull was drilled above the barrel cortex (AP −0.3 to −1 mm; lateral 3–4 mm from bregma), and dura mater was carefully dissected using a 27G needle. Electrodes were inserted at a depth of 700–1000 μm (depending on animal's age) vertically to the cortical surface. The signals from extracellular recordings were amplified and filtered (x10,000; 0.2 Hz–10 kHz) using a DigitalLynx (Neuralynx, USA) amplifier, digitized at 32 kHz and saved on a PC for post-hoc analysis. Principal whisker (PW) was identified by the shortest latency MUA responses in layer 4

evoked by brief (2 ms) single whisker deflection. The whiskers were trimmed to a length of 0.8–1.5 mm and were stimulated using piezo actuator at 10–20 s intervals. A needle (22G) was glued to the end of piezo actuator (Noliac, Denmark) and the tip of the whisker was inserted 0.5 mm into the blunt tip of the needle, so that the whisker rested snugly inside. During recordings of spontaneous activity PW was released from the needle. Spontaneous (n = 4 rats) and sensory evoked (n = 5 rats) activity was recorded for 1 h after injection of 50 μl normal saline (i.p.). Then the rats were injected with a 50 μl citalopram solution in normal saline prepared from a 1% stock solution of citalopram hydrobromide (Sigma) in 45% ethanol at a dosage of 10–20 mg/kg and recorded for 2–3 h. Under these recording conditions, our previous studies did not reveal any significant change in sensory evoked and spontaneous activity in control or saline-injected animals during 3–4 h recordings period (Minlebaev et al., 2011; Lebedeva et al., 2015).

2.4. Data analysis

Raw data were preprocessed using a custom-developed routines in MATLAB environment (MathWorks, USA). The wide-band signal was downsampled to 1000 Hz and used as the local field potential (LFP) signal. Positive polarity is shown as up in all figures. For action potential detection, the raw wide-band signal was filtered (bandpass 300–3000 Hz) and negative events exceeding 5 standard deviations calculated over the most silent 1 s length segment of the filtered trace were considered as spikes (MUA). Sensory evoked potentials (SEPs) were detected as the first LFP troughs of sensory evoked responses in L4. For the analysis of sensory evoked oscillations, 500 ms periods following SEPs were used. Local field potentials and extracellular units were analyzed by custom-written, MATLAB-based programs. Spectral analysis was carried out using Chronux toolbox procedures. Spectral power and coherence were estimated using direct multi-taper estimators (5 tapers, time-bandwidth product 3, and padding factor 2) or continuous wavelet transformation with the Morlet mother wavelet. Spontaneous bursts (LFP-splashes such as gamma-, spindle-bursts and sharp potentials) were detected with the following steps: (1) the LFP signal was bandpass filtered (5–100 Hz), (2) segments of negative troughs with amplitude greater than 6 standard deviations were detected from the filtered signal, (3) LFP-splashes with a length of more than 200 ms associated with spikes were counted. Current-source density (CSD) analysis across cortical depth was used to eliminate volume conduction and localize synaptic currents. CSD was computed according to a differential scheme for the second spatial derivative (along recording sites) and smoothed with a triangular kernel of length.

2.5. Statistics

Statistical analysis was performed using the Matlab Statistics toolbox. The two-side Wilcoxon rank sum test was performed to assess the significance of differences between groups of data with the level of significance kept at $p < 0.05$.

3. Results

In the present study we explored the effect of the SSRI citalopram on spontaneous and sensory evoked cortical activity using multisite silicone probe recordings of the local field potential (LFP) and multiple unit activity (MUA) from whisker representations in the primary somatosensory barrel cortex of urethane-sedated (1 g/kg, i.p.), head restrained rats of two age groups, P2-5 and P21-29.

In P2-5 animals, a brief (2 ms) mechanical stimulation of the principal whisker evoked complex responses consisting of the
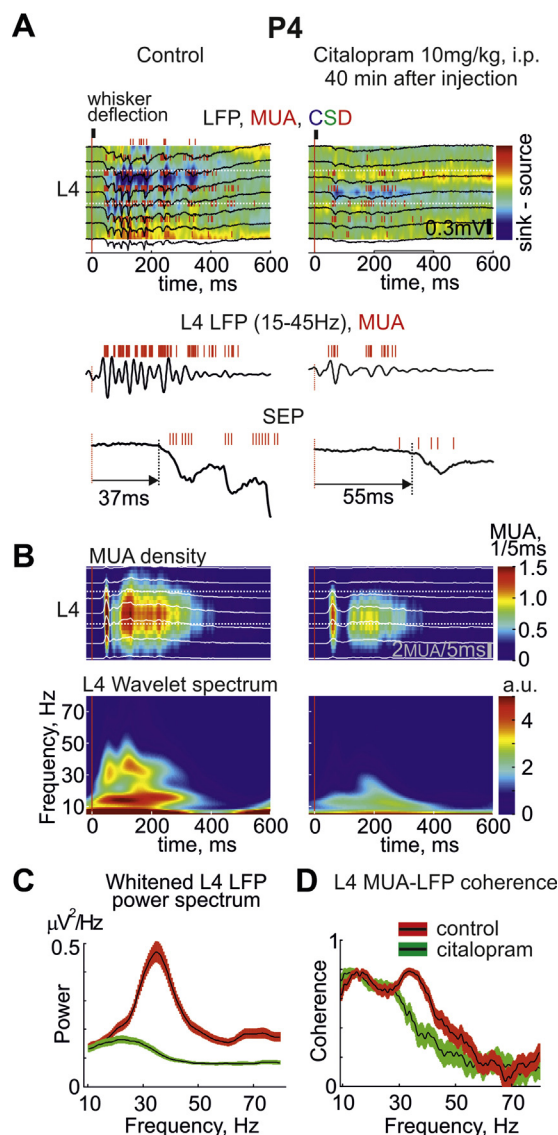
Fig. 1. Effects of citalopram on sensory evoked responses in the barrel cortex of neonatal rats.
(A) Sensory responses evoked by the principal whisker deflection at different cortical depths in the corresponding cortical column of a P4 rat barrel cortex (LFP-black traces; MUA-red bars overlaid on color coded current source density plot (CSD) in control conditions (left) and 40 min after citalopram injection (10 mg/kg, right). Stimulus onset is indicated by vertical red lines. Layer 4 borders are indicated by white dashed lines. Shown below, are corresponding gamma bandpass filtered LFP signals in L4 and SEPs on an expanded time scale. Note a reduction in SEP amplitude and an increase in SEP onset delay, and a reduction in gamma oscillation power and frequency after administration of citalopram. (B) Corresponding stimulus-triggered average for MUA across layers (top) and L4 LFP wavelet spectrum (bottom) (n = 120 responses). (C–D) Averaged power spectral density of whitened L4 LFP (C) and MUA-LFP coherence (D) for a 500 ms window after SEP before and after citalopram administration. Shaded areas show confidence intervals.

initial sensory evoked potential (SEP) occurring at a latency of 48 ± 7 ms after the stimulus onset with an amplitude of $311 \pm 80 \,\mu V$ (mean $\pm$ SE, n = 5; P2-5 rats), followed by gamma- and spindle-burst oscillations (Fig. 1A). In keeping with the results of previous studies, both SEP and the following sensory-evoked activity bursts were associated with maximal LFP signals, current sinks and MUA in L4 (Fig. 1A,B) (Yang et al., 2009; Minlebaev et al., 2011; Yang et al., 2013; Gerasimova et al., 2014; Mitrukhina et al., 2015).The power spectral density of sensory evoked early gamma oscillations (EGOs), calculated from a 500 ms period following SEPs, revealed a peak at 37 ± 2 Hz and with an integral EGOs' power in the gamma (30–80 Hz) frequency band of $6.58 \pm 2.67 \,\mu V^2/Hz$ (Fig. 1C). Neuronal firing was essentially locked to the troughs of oscillations and MUA-LFP coherence analysis revealed two peaks at 40 ± 4 Hz and 17 ± 1 Hz, characteristic of EGOs and spindle-burst oscillations, respectively (Fig. 1D).

Citalopram (10–20 mg/kg, i.p.) exerted multiple and essentially suppressive effects on the sensory evoked responses in the barrel cortex of neonatal rat pups. These effects developed relatively slowly and were quantified 100–180 min after drug administration. The effects of citalopram on SEPs included a more than two-fold reduction in SEPs' amplitude to $119 \pm 31 \,\mu V$ ($40 \pm 6\%$ of the control values) and an increase in SEP onset latency to 65 ± 11 ms ($138 \pm 4\%$ of the control values; n = 5; P2-7 rats; Fig. 1 & Fig. 2). SEP-driven L4 MUA also reduced from 5.25 ± 0.87 to 3.78 ± 1.03 spikes/20 ms (67% of control values). Citalopram also strongly, by nearly fivefold, decreased EGOs' power to $1.00 \pm 0.37 \,\mu V^2/Hz$ (21% of control values) and slowed down EGO frequency, shifting them to the beta/gamma border range (peak frequency 30 ± 2 Hz) (Fig. 1 & Fig. 2). This was also associated with a nearly twofold reduction in neuronal firing during sensory evoked oscillatory bursts from 44.8 ± 9.8 to 25.0 ± 7.3 spikes per 500 ms period following SEP
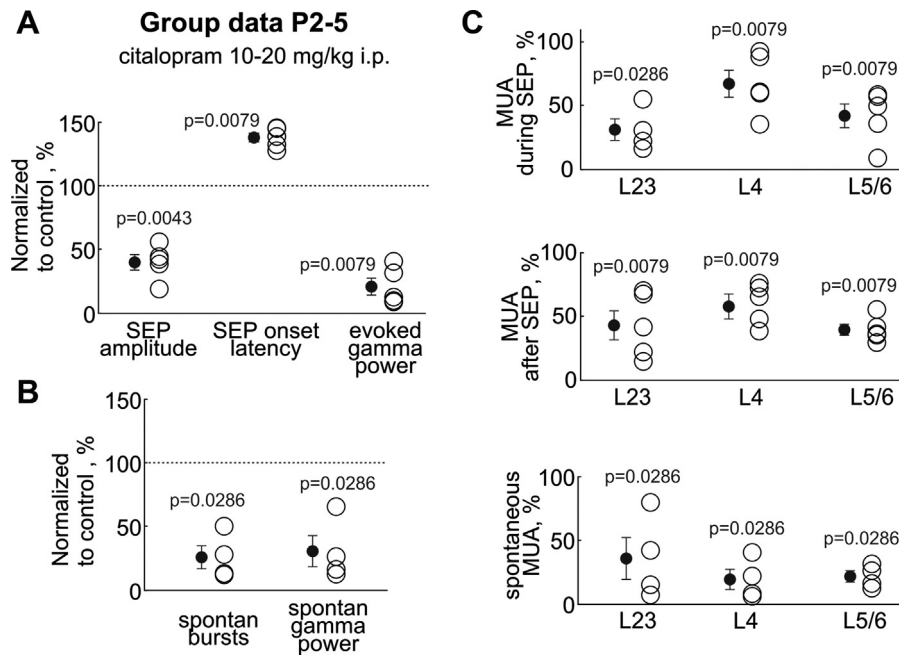
Fig. 2. Group data on the effects of citalopram on spontaneous and sensory evoked activity in the barrel cortex of neonatal rats.
(A–C) Effects of citalopram on (A) sensory evoked LFP responses, (B) frequency of spontaneous activity bursts and gamma power of spontaneous bursts, (C) MUA during and after SEP and overall spontaneous MUA across layers in the neonatal rat barrel cortex after administration of citalopram (10–20 mg/kg) normalized to the control values. Each open circle corresponds to an individual rat. Black circles show mean ± standard error. Pooled data from five P2-5 rats.

($58 \pm 10\%$; n = 5; P2-5 rats). Suppression of sensory evoked MUA responses was also observed in supragranular and infragranular layers (Fig. 1B, Fig. 2C).

Citalopram also strongly suppressed spontaneous activity in the neonatal rat barrel cortex. In control conditions, spontaneous activity was organized in intermittent bursts occurring at 5.17 ± 3.25 bursts/min (n = 4; P2-5 rats) and associated with gamma and spindle oscillations and bursts of MUA, similarly to previously described findings (Khazipov et al., 2004; Minlebaev et al., 2007; Yang et al., 2009) (Fig. 3). Citalopram (10–20 mg/kg) reduced spontaneous burst frequency to 0.76 ± 0.39 bursts/min (Fig. 2). Overall spontaneous L4 MUA was also strongly reduced by citalopram from 1.99 ± 0.85 to 0.24 ± 0.07 spikes/s as well as MUA in supra- and infragranular layers (Fig. 2C). Similarly to the effects on sensory evoked EGOs, L4 LFP power in the gamma range (30–80 Hz) was reduced after administration of citalopram from 0.94 ± 0.10 to $0.17 \pm 0.04 \, \mu V^2$/Hz ($30 \pm 12\%$ of control values; n = 4; P2-5 rats).

Previous studies using brain slices *in vitro* showed that inhibitory effects of serotonin on thalamocortical synaptic transmission are limited to the neonatal period and that they wane during the adolescent period (Rhoades et al., 1994; Laurent et al., 2002). Therefore, we also explored the effects of citalopram, using similar experimental setup, on spontaneous and sensory evoked activity in barrel cortex of adolescent animals (Fig. 4). We found that citalopram (20 mg/kg, i.p.) barely affected activity in these animals including little change in SEP's amplitude (before and after citalopram administration, respectively: 874 ± 207 and $808 \pm 204 \, \mu V$), SEP onset latency (6.9 ± 0.5 and 6.8 ± 0.6 ms), SEP-driven MUA in L4 (5.6 ± 0.7 and 6.2 ± 0.7 spikes/20 ms) and L4 MUA during 500 ms period following SEP (25.4 ± 4.1 and 25.4 ± 3.6 spikes/500 ms) (n = 4; P21-29 rats; p > 0.05 for all parameters; Fig. 4A,C). Citalopram also did not significantly affect spontaneous activity: ongoing L4 MUA was of 29.7 ± 7.1 and 38.4 ± 6.6 spikes/s ($151 \pm 34\%$ of the control values) before and after citalopram administration (n = 4; p > 0.05; Fig. 4B,C). We also did not observe any significant change in spontaneous and sensory evoked activity in other cortical layers (Fig. 4C).

4. Discussion

In the present study, we addressed the effects of the SSRI citalopram on sensory evoked and spontaneous activity in the barrel cortex of P2-29 rats using intracortical recordings of EEG and neuronal firing. Our main finding is that specifically during the postnatal period, when the thalamocortical barrel map is formed and refined through activity-dependent mechanisms, inhibition of serotonin uptake with citalopram strongly suppresses spontaneous cortical activity and inhibits sensory evoked oscillatory bursts. These findings support the hypothesis that defective development of barrel map under the conditions of increased extracellular serotonin levels involves inhibition of the activity-dependent mechanisms.

The suppressive effects of citalopram on spontaneous and sensory evoked activity in the neonatal barrel cortex are in agreement with serotonin-mediated suppression of glutamate release from presynaptic thalamic terminals during the neonatal period (Rhoades et al., 1994; Laurent et al., 2002). Previous patch-clamp and pharmacological studies have shown that generation of the early activity bursts in the neonatal rat barrel cortex primarily depends on glutamatergic synaptic transmission (Minlebaev et al., 2007, 2009). The origin of the glutamatergic drive to the barrel cortex during this period is essentially thalamic, with a developmental recruitment of the local excitatory and inhibitory cortical networks only by the end of the first postnatal week (Daw et al., 2007; Minlebaev et al., 2011; Yang et al., 2013). During the postnatal period, thalamic axonal terminals transiently express serotonin receptors, through which exogenous serotonin strongly reduces synaptic glutamate release, as has been shown in thalamocortical slices *in vitro* (Rhoades et al., 1994; Laurent et al., 2002). In the present study, blockade of serotonin uptake using citalopram, which increases extracellular serotonin levels (Tohgi et al., 1995), reduced SEP amplitude, oscillation power and neuronal excitation *in vivo*. These effects of citalopram likely involve progressive accumulation of extracellular serotonin levels after serotonin uptake blockade, and a depression of glutamate release from the thalamic
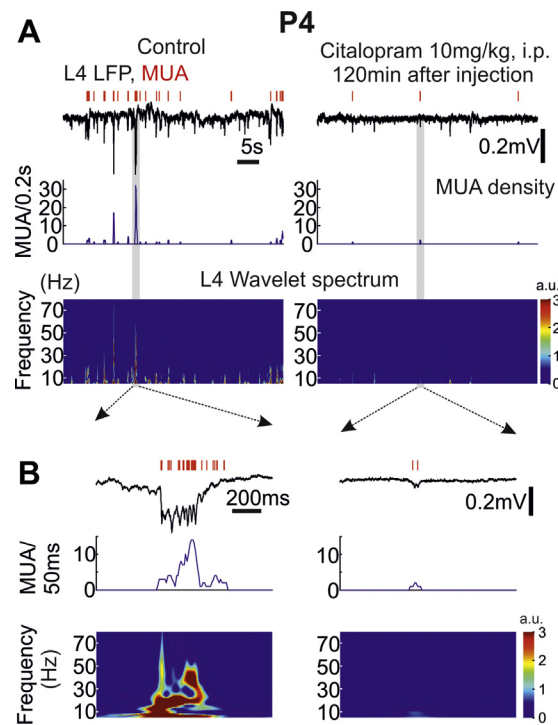
Fig. 3. Effects of citalopram on spontaneous activity in the barrel cortex of neonatal rats. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).
(A) Example traces of spontaneous electrical activity in L4 of the barrel cortex of a P4 rat (LFP-black traces; MUA-red bars above) in control conditions and 120 min after intraperitoneal injection of citalopram at 10 mg/kg. Shown below, are corresponding MUA frequency plots and wavelet spectrograms. Note that citalopram strongly suppresses ongoing LFP and MUA activity. (B) Individual oscillatory bursts in control conditions, and after administration of citalopram outlined by grey boxes on panel (A) are shown on an expanded time scale.

terminals. The inhibitory effects of citalopram on cortical activity were not observed in adolescent animals that is in keeping with the transient expression of serotonin receptors at thalamocortical terminals during the neonatal period and age-specific suppression of thalamocortical EPSCs in slices from neonatal but not adolescent animals (Rhoades et al., 1994; Laurent et al., 2002). The inhibitory effects of serotonin on thalamocortical transmission in slices from neonatal animals have been shown to involve activation of 5HT-1B type of serotonin receptors (Rhoades et al., 1994; Laurent et al., 2002). Moreover, knock-out of 5HT-1B receptors largely rescues barrel map formation in MAOA and SERT knock-out mice and complete rescue is achieved by further PCPA treatment (Salichon et al., 2001; Rebsam et al., 2002) suggesting potential co-involvement of 5HT-1D receptors which are also transiently expressed in by thalamic neurons soon after birth (Bonnin et al., 2006). In the future studies, it would be interesting to examine the receptors involved in excessive serotonin mediated suppression of the early activity in barrel cortex in vivo.

Several observations indicate that the actions of citalopram are not restricted to the level of thalamocortical transmission. Firstly, we observed not only a reduction in SEP amplitude, but also a strong increase in the SEP onset latency from the average value of 48 ms to 65 ms in the presence of citalopram. Yet, previous electrophysiological studies using thalamocortical slices in vitro have not reported any change in the onset latency of thalamocortical EPSCs during application of exogenous serotonin (Rhoades et al., 1994; Laurent et al., 2002). Secondly, exogenous serotonin has been shown to convert an activity-dependent depression of thalamocortical EPSCs, which develops during repetitive stimulation of thalamic inputs at gamma frequency (50 Hz), to facilitation (Laurent et al., 2002). Such a mechanism of action, providing facilitating gamma-rhythmic thalamic input would be supportive for cortical gamma oscillations. In addition, if the thalamocortical synapse is the only target of

citalopram action, one would expect little change in gamma oscillation frequency. However, we observed significant reduction both in EGO frequency and power, suggesting the effects of citalopram are not limited to thalamocortical transmission. Taken together, our findings of an increase in SEP onset latency and a reduction in EGO frequency and power indicate that in addition to its cortical actions, citalopram also affects transmission of excitation and rhythmogenesis at subcortical levels. These observations are in agreement with the decreased metabolic sensory evoked responses in the spinal and principal sensory trigeminal nuclei, the ventral posteromedial thalamic nucleus, and the barrel region of the somatosensory cortex in adult SERT-KO mice (Esaki et al., 2005). These potential subcortical targets in serotonin actions during the early developmental period would be interesting to examine in the future studies. Also, while present study focused on barrel cortex during the period from P2 to P5, it would be interesting to characterize serotoninergic modulation of sensory responses at earlier perinatal period, when the first thalamocortical synapses are established with the subplate neurons (Molnar et al., 2003; Higashi et al., 2005; Kanold and Luhmann 2010) and when the extracellular levels of endogenous serotonin are particularly high (Toda et al., 2013), and other cortical areas such as visual cortex, where serotonin controls the formation of the eye specific connections (Salichon et al., 2001) potentially through a modulation of the retinal wave driven spindle bursts (Hanganu et al., 2006; Colonnese and Khazipov 2010).

Because EGOs support synchronization of the topographically aligned thalamic and cortical neurons and provide conditions for the spike-time dependent plasticity at the thalamocortical synapses (Minlebaev et al., 2011; Yang et al., 2013), we suggest that the changes in activity patterns described in this study contribute to the adverse effects of SSRIs and other conditions resulting in elevated extracellular serotonin concentration on the development of barrel maps. While our results demonstrate acute actions
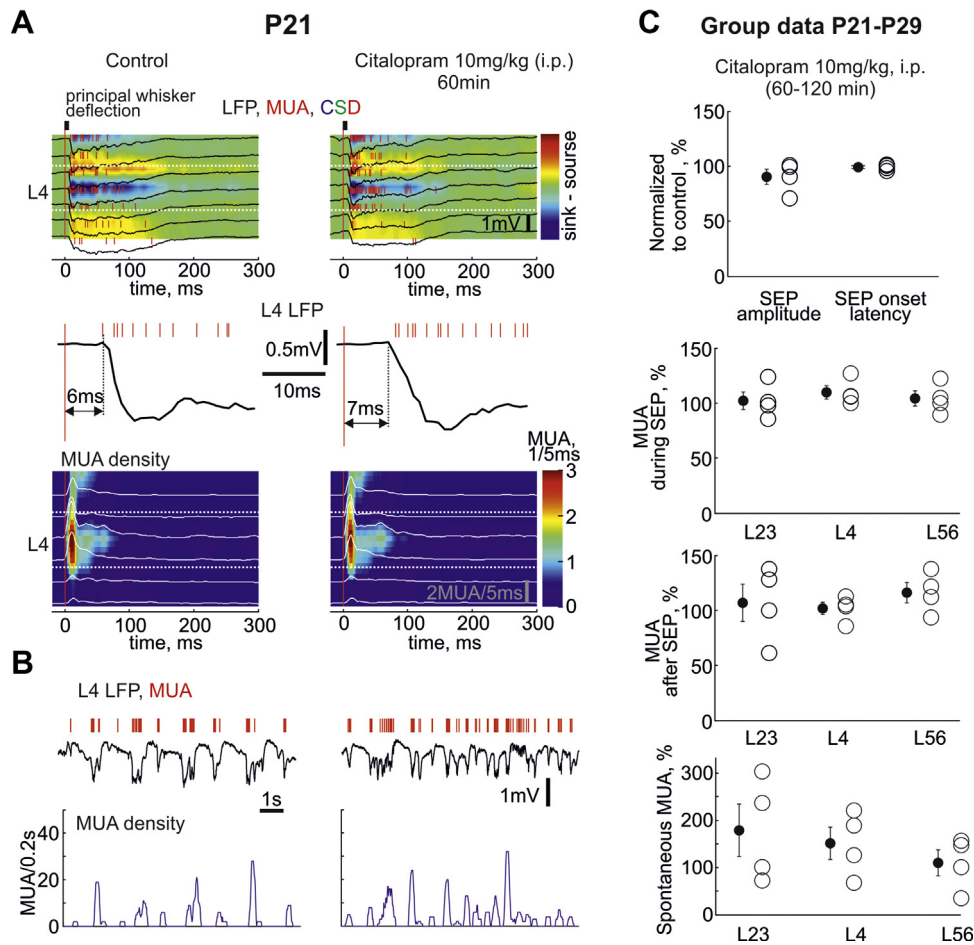
Fig. 4. Effects of citalopram on sensory evoked responses and spontaneous activity in the barrel cortex of adolescent rats.
(A) Sensory responses evoked by the principal whisker deflection at different cortical depths in the corresponding cortical column of a P21 rat barrel cortex (LFP-black traces; MUA-red bars overlaid on color coded current source density plot (CSD) in control conditions (left) and 60 min after citalopram injection (10 mg/kg, right). Stimulus onset is indicated by vertical red lines. Layer 4 borders are indicated by white dashed lines. Shown below, are corresponding LFP signals in L4 and SEPs on an expanded time scale (note little change in SEP amplitude and SEP onset delay) and corresponding stimulus-triggered average for MUA across layers (n = 120 responses). (B) Spontaneous activity in L4 before and after citalopram administration from the same animal. Corresponding MUA density plots are shown below. (C) Effects of citalopram on SEP amplitude and onset delay, MUA during and after SEP and overall spontaneous MUA across layers in the adolescent rat barrel cortex after administration of citalopram (10 mg/kg) normalized to the control values. Each open circle corresponds to an individual rat. Black circles show mean ± standard error. Pooled data from four P21-29 rats.

of SSRI inhibition in the neonatal barrel cortex, in the future studies it would be interesting to examine the long-term effects of elevated extracellular serotonin during the early developmental period on the functional organization of the barrel cortex including the alterations in thalamocortical signalling, topography of the thalamocortical maps and intracolumnar processing that are suggested by the anatomical and metabolic studies in adult SERT-KO animals (Esaki et al., 2005; Miceli et al., 2013).

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 potential conflicts of interest.

Acknowledgements

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