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Mefloquine in the nucleus accumbens promotes social avoidance and anxiety-like behavior in mice

Mitra Heshmati, Sam A. Golden, Madeline L. Pfau, Daniel J. Christoffel, Elena L. Seeley, Michael E. Cahill, Lena A. Khibnik, Scott J. Russo*

Fishberg Department of Neuroscience and Friedman Brain Institute, Graduate School of Biomedical Sciences at the Icahn School of Medicine at Mount Sinai, New York, NY, USA

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ABSTRACT

Mefloquine continues to be a key drug used for malaria chemoprophylaxis and treatment, despite reports of adverse events like depression and anxiety. It is unknown how mefloquine acts within the central nervous system to cause depression and anxiety or why some individuals are more vulnerable. We show that intraperitoneal injection of mefloquine in mice, when coupled to subthreshold social defeat stress, is sufficient to produce depression-like social avoidance behavior. Direct infusion of mefloquine into the nucleus accumbens (NAc), a key brain reward region, increased stress-induced social avoidance and anxiety behavior. In contrast, infusion into the ventral hippocampus had no effect. Whole cell recordings from NAc medium spiny neurons indicated that mefloquine application increases the frequency of spontaneous excitatory postsynaptic currents, a synaptic adaptation that we have previously shown to be associated with increased susceptibility to social defeat stress. Together, these data demonstrate a role for the NAc in mefloquine-induced depression and anxiety-like behaviors.

1. Introduction

Neuropsychiatric adverse events such as depression, anxiety, psychosis, and suicidality have been reported in patients taking mefloquine for malaria treatment and prophylaxis (Caillon et al., 1992; Croft and World, 1996; Whitworth and Aichhorn, 2005). Such cases compelled the U.S. Food and Drug Administration to issue a warning for the drug, cautioning physicians to use mefloquine only with appropriate monitoring for adverse events like depression (FDA, 2004). Mefloquine continues to be widely prescribed and remains one of a handful of key drugs available for treating chloroquine-resistant malaria (Chen et al., 2007; Jacquerioz and Croft, 2009). The U.S. military widely prescribed mefloquine for malaria prophylaxis during the 2007 war in Afghanistan, and there is evidence of severe neuropsychiatric reactions in soldiers with a prior history of depression (Nevin, 2010; Peterson et al., 2011). Reviews of the clinical data conclude that there is also increased risk of depression side effects following long-term prophylactic use in tourists traveling to malaria endemic regions (Ringqvist et al., 2015).

However, it is currently unknown why mefloquine causes depression or anxiety. A better understanding of the drug actions in the brain might aid in identifying susceptibility traits and developing new therapies for depression and stress disorders. Here we use the preclinical model of social defeat stress to investigate mefloquine-induced depression and anxiety-related behavioral changes. In addition, because our previous studies have identified increased frequency of excitatory postsynaptic currents (EPSCs) on NAc MSNs to be associated with susceptibility to chronic social defeat stress (Christoffel et al., 2011, 2015), we performed whole cell electrophysiology recordings from NAc medium spiny neurons following bath application of mefloquine. Together, these findings highlight a novel, clinically relevant connection between the NAc and depression- and anxiety-like behaviors resulting from mefloquine exposure.

2. Experimental procedures

2.1. Animals

Seven to eight week-old C57BL/6J male mice (Jackson

* Corresponding author. Icahn School of Medicine at Mount Sinai, 1425 Madison Avenue, Box 1065, New York, NY 10029, USA.
E-mail address: scott.russo@mssm.edu (S.J. Russo).

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Laboratories, Bar Harbor, Maine) were used for all behavioral experiments. Mice were group housed before the start of all experiments and maintained on a 12 h light/dark cycle with ad libitum access to food and water. 4 month-old retired male CD-1 breeders (Charles River Laboratories, Wilmington, Massachusetts) were singly housed and used as aggressors in the subthreshold social defeat stress paradigm. Behavioral assessments and tissue collection were performed during the animals' light phase (0700–1900 h). Mouse procedures were performed in accordance with the Institutional Animal Care and Use Committee guidelines of the Icahn School of Medicine at Mount Sinai.

2.2. Drug

Mefloquine hydrochloride, Lot #111M4707V, (Sigma–Aldrich, St. Louis, Missouri) was dissolved in dimethyl sulfoxide (DMSO) for a 38 mg/mL stock solution. Intraperitoneal injections (drug: 20 mg/kg mefloquine or 5 mg/kg mefloquine in 0.9% saline, or vehicle: 5% DMSO in 0.9% saline) were administered 20 min prior to stress. Direct cannula microinfusions (150 μM mefloquine or 1% DMSO in artificial cerebrospinal fluid; see Electrophysiology methods) were performed using a minipump (Harvard Apparatus, Holliston, Massachusetts) and internal cannula (Plastics One, Roanoke, Virginia) at a rate of 0.1 mL/min for 5 min followed by a 5 min rest period with the cannula still in place. Drug dosing was based on the doses used for malaria treatment (20 mg/kg) and prophylaxis (5 mg/kg) in humans, as well as previous literature using mefloquine to block gap junctions in mice (Schoenfeld et al., 2014; Bissiere et al., 2011). Since mefloquine has a long elimination half-life of approximately two to three weeks (Karbwang and White, 1990), the drug was given only once as a pretreatment prior to subthreshold social defeat stress. Subsequent behavioral tests were performed without additional drug administrations.

2.3. Cannula surgery

Eight-week old C57BL/6J male mice were anesthetized with a mixture of ketamine (100 mg/kg) and xylazine (10 mg/kg) in 0.9% saline. Mice were positioned in a small animal stereotaxic instrument (David Kopf Instruments, Tujunga, California), and the skull surface was exposed. Bilateral guide cannulas from Plastics One were implanted so the tip of the cannulas reached the nucleus accumbens (bregma coordinates: anterior, 1.5 mm; mediolateral, 0.8 mm; dorsoventral, 3.6 mm) or ventral hippocampus (bregma coordinates: posterior, 3.2 mm; mediolateral, 3.0 mm; dorsoventral, 4.2 mm). Ventral hippocampal coordinates were based on these published studies (Schoenfeld et al., 2014; Adhikari et al., 2010).

2.4. Behavioral testing

Mice underwent a single pairing of mefloquine administration with stress, followed by behavioral testing.

2.4.1. Subthreshold social defeat stress

Subthreshold social defeat stress is a well-validated model for studying vulnerability factors in mice (Christoffel et al., 2012; Dias et al., 2014; Golden et al., 2013; Wilkinson et al., 2011). Control animals do not develop social interaction deficits after subthreshold defeat, but manipulations that promote susceptibility will result in social avoidance. We used a subthreshold social defeat stress to measure increased susceptibility to stress as previously described (Krishnan et al., 2007; Berton et al., 2006). Mice were single-housed one day prior to beginning stress experiments. Mice were then exposed to a novel CD-1 aggressor for 5 min followed by 10 min rest in the home cage. Exposure to the CD-1 aggressor was repeated for a total of 3 physical interactions. All aggressors were screened for aggressive behavior prior to use according to published protocols (Golden et al., 2011).

2.4.2. Social interaction

Twenty-four hours following subthreshold social defeat stress, mice underwent the social interaction test as previously described (Berton et al., 2006; Golden et al., 2011). Mice were placed into a novel open field arena with a small animal cage at one end. Their movement was recorded for 2.5 min in the absence of a social target (target absent trial), followed by 2.5 min in the presence of a novel CD-1 mouse (target present trial). Duration spent in the interaction zone (in seconds) as well as distance traveled (in centimeters) was measured using Ethovision software (Noldus Information Technology, Leesburg, Virginia). Heat maps were generated using the "heat map" function on the Ethovision software to create a representative image of the animals' movements during the target present trial. Heat map scale bar represents the normalized time spent at each XY coordinate during the trial. Social interaction ratio was calculated as duration in the interaction zone during the target present trial divided by duration in the interaction zone during the target absent trial. A ratio less than 1 indicates social avoidance.

2.4.3. Elevated plus maze

The elevated plus maze consisted of two, straight intersecting runways positioned 60 cm above the floor and divided into two open and two closed arms. Mice were placed into the center of the maze and allowed to explore for a period of 5 min. Duration spent and entrances in the open arms and the closed arms were recorded using Ethovision software under red-light conditions. Heat map scale bar represents the normalized duration at each XY coordinate during the trial.

2.5. Perfusion and tissue processing

Following behavioral studies, mice were anesthetized with 15% chloral hydrate. Transcardial perfusion was performed with cold phosphate-buffered saline (pH 7.4) followed by 4% paraformaldehyde in phosphate-buffered saline. Brains were dissected and post fixed overnight in 4% paraformaldehyde. Each brain was cut on a vibratome (Leica) into 50 μm coronal slices to validate cannula placement site.

2.6. Electrophysiology

Seven week-old C57BL/6J male mice were anesthetized using isoflurane and perfused for 1 min with ice-cold artificial cerebrospinal fluid (aCSF) containing in mM: 128 NaCl, 10 D-Glucose, 1.25 NaH_2PO_4, 25 $NaHCO_3$, 2 $MgSO_4 \cdot 7H20$, 3 KCl, 2 $CaCl_2 \cdot 2H_2O$ (pH 7.35, 295–305 mOsm, oxygenated with 95% O_2 and 5% CO_2). 250 μm acute brain slices containing the NAc were cut in sucrose-aCSF containing 254 mM sucrose instead of NaCl. Slices were incubated in the holding chamber for 1 h at 32 °C. 25 μM mefloquine, or vehicle, was added to the holding chamber and incubated for 1 h at room temperature. The dose and protocol for mefloquine application was based on previously published slice electrophysiology studies (Cruikshank et al., 2004; Allison et al., 2011). Slices were then transferred to a recording chamber with a constant flow rate (2 mL/min) of carbogenated aCSF at room temperature, containing either 25 μM mefloquine or vehicle. NAc shell MSNs were identified by their location and size using infrared differential interference contrast microscopy, and confirmed by the presence of inward rectification. Patch clamp recordings were made in whole-cell configuration using glass microelectrodes (3–5 MΩ) filled with an

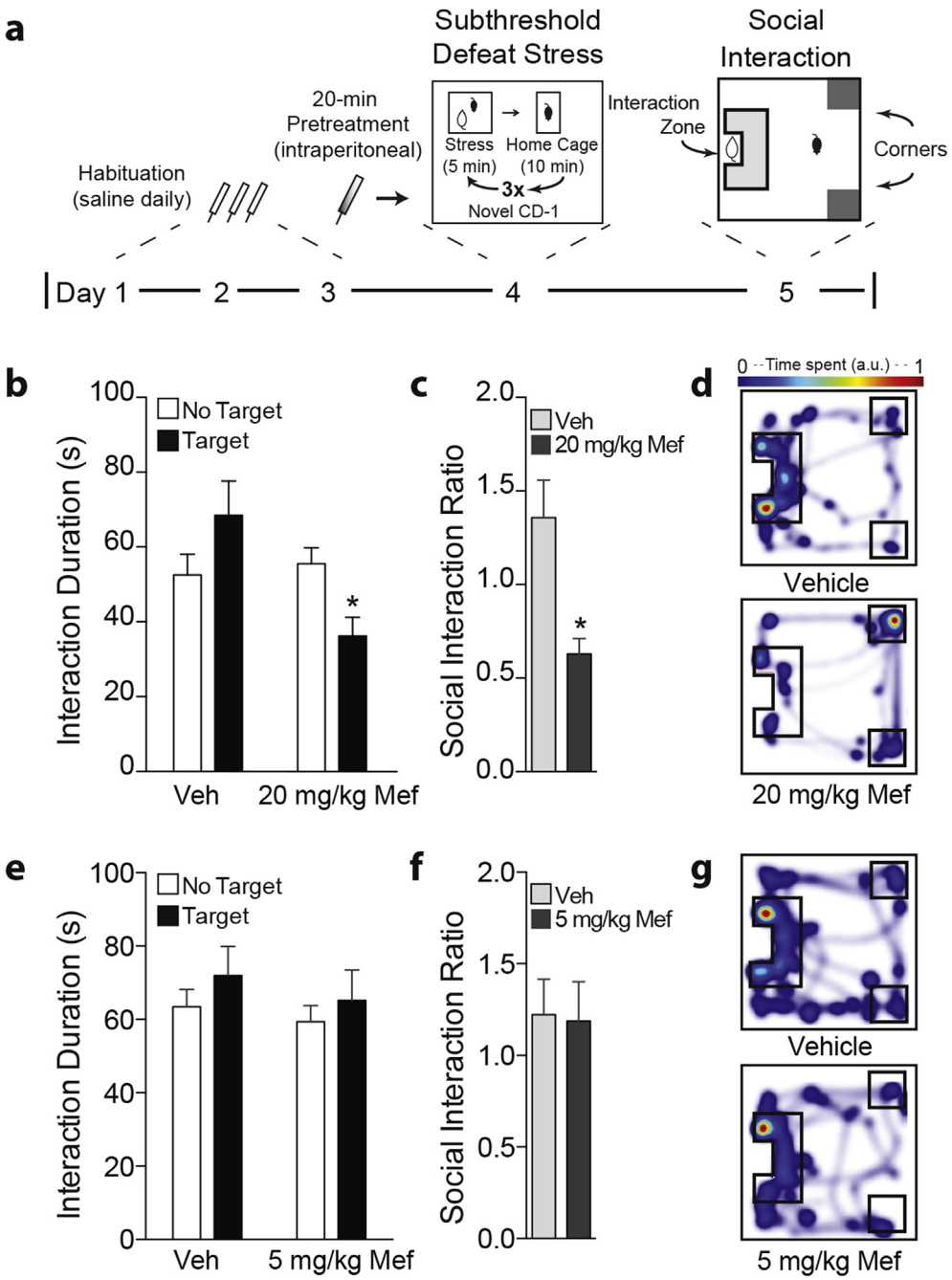

Fig. 1. Single intraperitoneal injection of mefloquine promotes social avoidance behavior following subthreshold social defeat stress. (a) Experimental timeline. (b) Animals that received 20 mg/kg mefloquine prior to stress display decreased time in the interaction zone with a target animal present (*$p < 0.01$, two-way repeated measures ANOVA, $n = 9$ mice/group). (c) Mice that received 20 mg/kg mefloquine also showed a decrease in social interaction ratio (*$p < 0.01$, Student's t-test). (d) Representative heat maps from the target present trial. (e) Animals that received 5 mg/kg mefloquine prior to stress did not display reduced social interaction ($p < 0.05$, two-way repeated measures ANOVA, $n = 9–10$ mice/group). (f) 5 mg/kg mefloquine did not affect social interaction ratio ($p < 0.05$, Student's t-test). (g) Representative heat maps from the target present trial. Data are represented as group means. Error bars represent SEM.

internal solution containing (mM): 115 potassium gluconate, 20 KCl, 1.5 $MgCl_2$, 10 phosphocreatine, 10 HEPES, 2 magnesium ATP, and 0.5 GTP (pH 7.2, 285 mOsm). 50 μM picrotoxin was added to the bath to isolate spontaneous excitatory postsynaptic currents (sEPSCs). Recordings were made with a computer-controlled amplifier (MultiClamp 700B), digitized (Digidata 1440), and acquired with Axoscope 10.1 (Molecular Devices) at a sampling rate of 10 kHz. The frequency and amplitude of sEPSCs were analyzed using MiniAnalysis software (Synaptosoft). Analysis was performed on 18 cells from 3 mice ($n = 3$ animals, 9 cells per group).

2.7. Statistics

All data are expressed as the mean ± SEM. Mean differences between groups were determined using Student's t-test, two-way analysis of variance (ANOVA) or repeated measures two-way ANOVA when appropriate, followed by Bonferroni post-tests if the main effect or interaction was significant at $p < 0.05$. Statistical analyses were performed using Prism 5.0 (GraphPad Software).

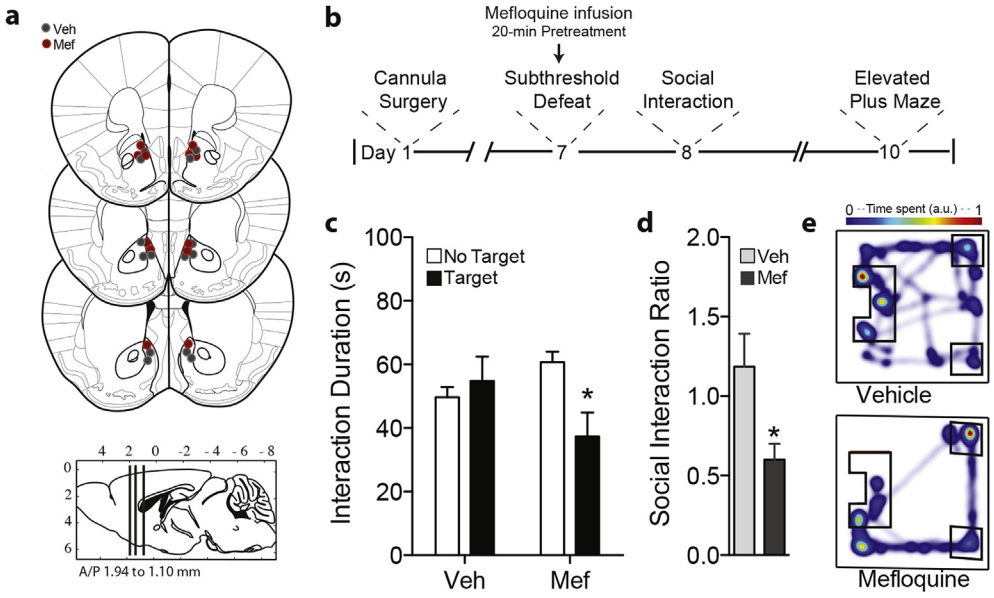

Fig. 2. Direct infusion of mefloquine into nucleus accumbens promotes social avoidance behavior following subthreshold social defeat stress. (a) Schematic depicting bilateral cannula placements for all animals included in analysis (n = 6–7 mice/group). Images are modified from Paxinos and Franklin, 2001. (b) Experimental timeline. (c) Mefloquine administration decreased interaction duration in the social interaction test one day following stress and drug infusion (*p < 0.01, two-way repeated measures ANOVA, n = 6–7 mice/group). (d) Animals that received mefloquine had a lower social interaction ratio (*p < 0.01, Student's t-test). (e) Representative heat maps from the target present trial. Data are represented as group means. Error bars represent SEM.

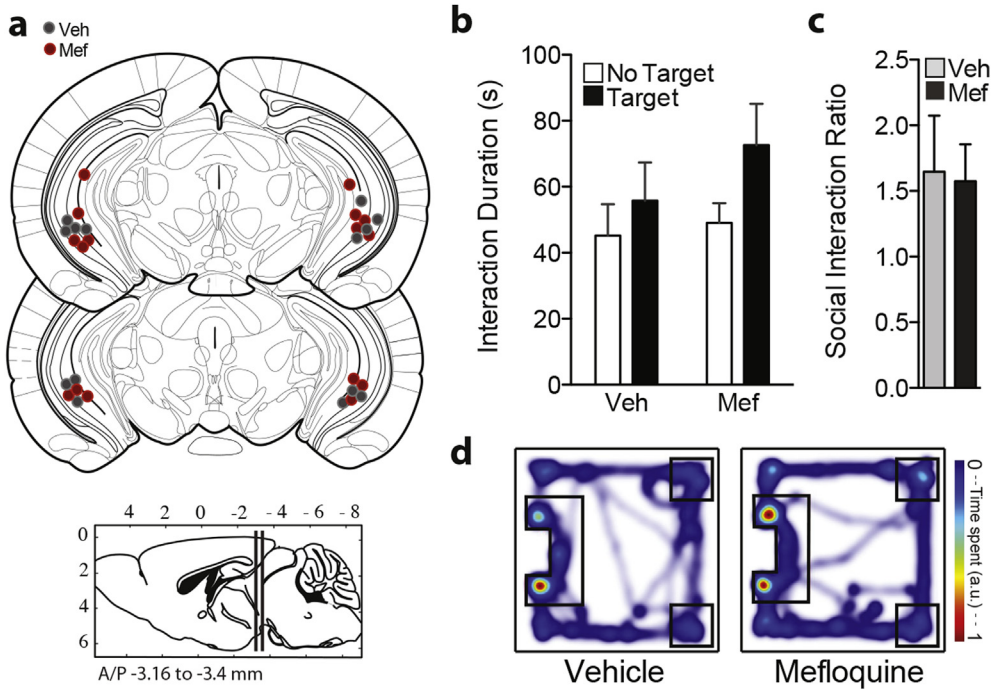

Fig. 3. Direct infusion of mefloquine into ventral hippocampus has no effect on social avoidance behavior following subthreshold social defeat stress. (a) Schematic depicting bilateral cannula placements in the ventral hippocampus (n = 7–8 mice/group). Images are modified from Paxinos and Franklin, 2001. (b) There was no effect of mefloquine on time spent in the interaction zone during the social interaction test (p > 0.05, two-way repeated measures ANOVA, n = 8–9 mice/group). (c) Vehicle and mefloquine-infused mice had similar social interaction ratios (p > 0.05, Student's t-test). (d) Representative heat maps from the target present trial. Data are represented as group means. Error bars represent SEM.

3. Results

In order to examine pro-depressant effects of mefloquine in mice, we first delivered an intraperitoneal injection of either mefloquine or vehicle and exposed mice to subthreshold social defeat stress (Fig. 1). We assayed doses that in humans reflect a malaria treatment dose of 20 mg/kg and a prophylactic dose of 5 mg/kg (Schlagenhauf et al., 2011; Dow et al., 2006). One day following social defeat, mice were tested for social interaction behavior (Fig. 1a). Mice that received intraperitoneal injection of 20 mg/kg

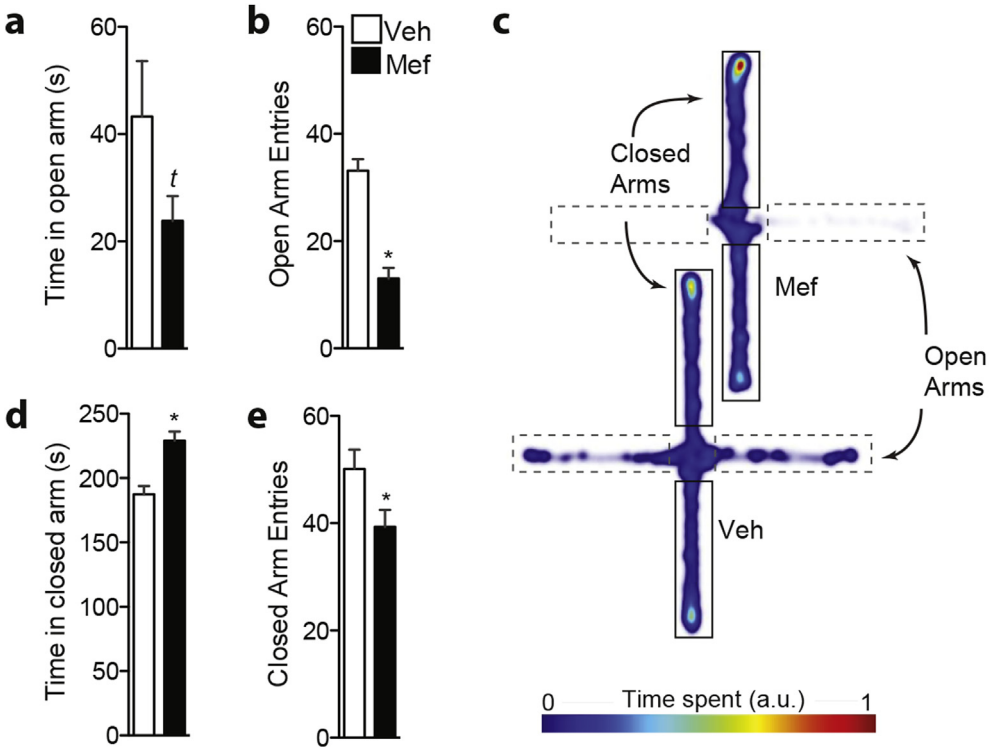

Fig. 4. Direct infusion of mefloquine into nucleus accumbens coupled to stress is anxiogenic. (a) Stressed mice that received direct infusion of mefloquine into nucleus accumbens trend towards less time in the open arms ($^{t}p = 0.13$, Student's t-test, n = 6–7 mice/group). (b) Drug-treated animals display decreased frequency of open arm entries (*p < 0.01, Student's t-test, n = 6–7 mice/group). (c) Drug-treated animals spend greater time in the closed arms of the elevated plus maze (*p < 0.01, Student's t-test, n = 6–7 mice/group) and (d) have a lower number of closed arm entries (*p < 0.05, Student's t-test, n = 6–7mice/group). (e) Representative heat maps. Data are shown as means. Error bars represent SEM.

mefloquine, compared to vehicle, displayed social avoidance behavior after the subthreshold stress. We found a main effect of drug for time spent in the interaction zone with a novel animal present (two-way repeated measures ANOVA: $F_{(1,16)} = 15.09$, $p < 0.01$; Fig. 1b). Post hoc analysis revealed that mefloquine reduced time in interaction zone with a target mouse present ($p < 0.05$). Mice receiving mefloquine also displayed social avoidance behavior as measured by a significant reduction in social interaction ratio (Student's t-test, $p < 0.01$; Fig. 1c). When animals were administered the lower 5 mg/kg dose of mefloquine prior to stress, there was no effect on either interaction time (two-way repeated measures ANOVA, $p < 0.05$; Fig. 1e) or social interaction ratio (Student's t-test, $p<0.05$; Fig. 1f). In addition, we observed no difference in total distance traveled or mean velocity between groups during the "no target" trial, demonstrating that the drug does not affect basal locomotor activity (Supplemental Fig. 1a–d).

Since the nucleus accumbens (NAc) is a brain region that has been implicated in depression as well as social defeat stress (Christoffel et al., 2011; Golden et al., 2013; Bewernick et al., 2010; Schlaepfer et al., 2008) we examined the effects of direct mefloquine infusion into the NAc on stress-induced social avoidance. Bilateral guide cannulas were implanted in the NAc and appropriate placement was assessed by post-hoc histology following all behavioral studies (Fig. 2a, b). Direct infusion of mefloquine into the NAc, coupled to subthreshold social defeat stress, resulted in decreased time spent in the interaction zone with a social target present (two-way repeated measures ANOVA: $F_{(1,11)} = 13.12$, $p < 0.01$; Fig. 2c, e). Bonferroni posttests revealed a significant effect of mefloquine. In addition, mefloquine-infused animals had a lower social interaction ratio compared to the vehicle group (Student's t-test, $p < 0.01$; Fig. 2d, e).

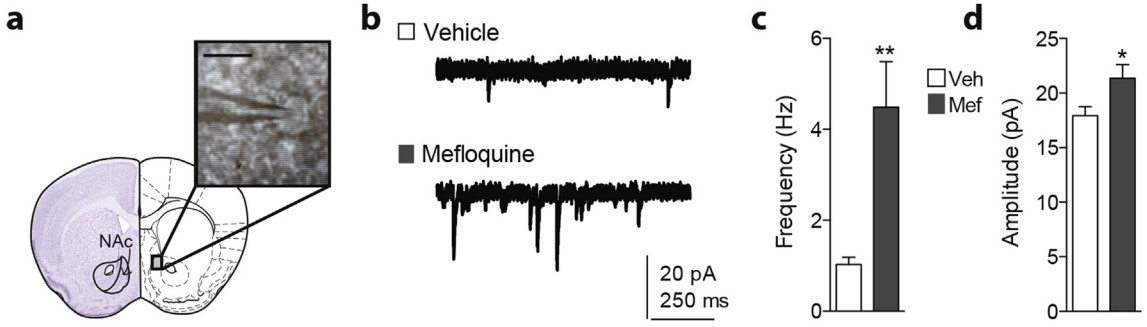

Fig. 5. (a) Schematic depicting whole cell recordings from NAc shell medium spiny neurons. Scale bar: 20 μm. (b) Representative traces. Scale: 20 pA, 250 ms. (c) Cells from slices incubated in 25 μM mefloquine display increased sEPSC frequency compared to DMSO-vehicle (**p < 0.01, Student's t-test, n = 9 cells per group). (d) An additional increase in sEPSC amplitude was observed (*p > 0.05, Student's t-test, n = 9 cells per group). Data are represented as means. Error bars represent SEM. Atlas image modified from Paxinos and Franklin, 2001.

In a parallel study, direct infusion of mefloquine into the ventral hippocampus prior to subthreshold social defeat stress did not result in social interaction deficits when assayed in the social interaction test the following day (Fig. 3). Both vehicle and drug-infused groups spent similar time in the interaction zone with a social target present (two-way repeated measures ANOVA: $p > 0.05$; Fig. 3b), and we observed no differences in social interaction ratios (Student's t-test, $p > 0.05$; Fig. 3c). When exploring the arena without a target present, all animals that received cannula infusions of vehicle or drug in either NAc or ventral hippocampus showed equivalent locomotor activity, supporting the conclusion that these changes in social interaction behavior are not due to differences in basal locomotor activity (Supplemental Fig. 1e–h). Together, these data support a selective role for the NAc in mediating the effects of mefloquine on social avoidance behavior.

Direct infusion of mefloquine into the NAc also increased anxiety behavior as measured by the elevated plus maze test (Fig. 4). Mice that had previously received mefloquine coupled to subthreshold social defeat stress trended towards less time in the open arms (Student's t-test, $p = 0.13$; Fig. 4a) and entered the open arms less frequently than vehicle-infused mice (Student's t-test, $p < 0.01$; Fig. 4b). Mefloquine-infused mice also spent more time in the closed arms (Student's t-test, $p < 0.01$; Fig. 4c). Overall, these data show that a single infusion of mefloquine into the NAc produces both depression- and anxiety-like behaviors.

To assess whether mefloquine alters synaptic plasticity in the NAc, which we have shown previously to regulate stress-induced depression-like behavior (Christoffel et al., 2011; Christoffel et al., 2015), we performed whole cell electrophysiological recordings from NAc MSNs following bath application of mefloquine (Fig. 5). Mefloquine or DMSO as vehicle was added to the bath solution for 1 h prior and perfused throughout recordings, using a protocol based on studies using mefloquine in slice electrophysiology (Cruikshank et al., 2004; Caridha et al., 2008). We observed a significant increase in sEPSC frequency on NAc MSNs in the mefloquine-treated cells (Student's t-test, $p < 0.01$; Fig. 5c). There was an additional increase in sEPSC amplitude compared to vehicle cells (Student's t-test, $p < 0.05$; Fig. 5d), suggesting an increase in the strength and number of presynaptic excitatory events following mefloquine exposure.

4. Discussion

Mefloquine remains a widely prescribed treatment for malaria despite adverse psychiatric outcomes (Jacquerioz and Croft, 2009). It is also one of the antimalarial drugs approved for use by pregnant women and infants (Radeva-Petrova et al., 2014; Gosling et al., 2009). However, there is controversy regarding mefloquine's safety and the prevalence of adverse effects (Chen et al., 2007; Schneider et al., 2013; Toovey, 2009). Using a preclinical model of psychiatric illness, we show that a single intraperitoneal injection of mefloquine is sufficient to produce social avoidance behavior induced by social defeat stress. This effect was only observed at the higher dose used for malaria treatment and not at a prophylactic dose. Since long-term prophylaxis is associated with psychiatric episodes, it is possible repeated exposure to the lower dose is needed to promote social avoidance. In addition, we show that the NAc is an important site of action for the pro-depressant and anxiogenic effects of mefloquine, since direct NAc infusion promoted these behaviors while ventral hippocampal infusion had no effect. Whole cell electrophysiological recordings suggest that mefloquine exposure induces functional alterations in synaptic transmission on NAc MSNs.

Changes in excitatory synaptic transmission in the NAc have been shown to underlie stress susceptibility and the manifestation of depression-like social avoidance and anxiety-like behaviors (Christoffel et al., 2011, 2012, 2015; Golden et al., 2013). These previous studies showed that mice displaying social avoidance behavior exhibited an increase in the number of excitatory synapses in the NAc and pruning of these newly formed synapses was sufficient to reverse social avoidance. Here we observe that mefloquine increases sEPSC frequency and amplitude on NAc MSNs, pointing either to an increase in presynaptic glutamate release or the strength of excitatory synapses on NAc MSNs. In line with this hypothesis, previous electrophysiological studies have found that bath application of mefloquine increases spontaneously occurring activity in cortical cells (Cruikshank et al., 2004). One likely mechanism of action may involve altered calcium homeostasis, since mefloquine has been shown to increase intracellular calcium (Caridha et al., 2008; Dow et al., 2003). Increased calcium could lead to an increase in sEPSC frequency by promoting synaptic vesicle release. Future studies will expand upon these correlative findings to determine whether altered excitatory synaptic transmission in the NAc as a result of mefloquine exposure promotes depression- and anxiety-like behavior.

Interestingly, recurring depression was observed years after taking mefloquine for malaria prophylaxis (Whitworth and Aichhorn, 2005). Together with our data, this suggests that mefloquine might induce an alteration of neurocircuitry, potentially involving dysregulation of the NAc and mesolimbic reward circuits (Russo and Nestler, 2013). Alternatively, patients with a history of major depressive disorder may be at higher risk of developing psychiatric side effects of mefloquine (Peterson et al., 2011) because the drug exacerbates preexisting neurocircuitry deficits in reward processing. Further studies are needed to investigate the mechanism and time course underlying mefloquine-induced depression effects in the NAc.

Currently, mefloquine is still used for the treatment and prophylaxis of malaria (Schlagenhauf et al., 2010). Thus, it is important that we gain a greater understanding of the drug's mechanism at a preclinical level, which will better inform clinical practice and potentially identify new strategies to prevent or reduce psychiatric side effects. In addition, a greater understanding of the mechanisms and brain regions involved in mefloquine-induced depression and anxiety will provide insights into depression pathophysiology in general, leading to identification of novel targets for therapeutic development.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Funding and disclosure

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.neuropharm.2015.10.013.

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