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

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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.

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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

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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

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