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Quinine enhances the behavioral stimulant effect of cocaine in mice

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ABSTRACT

The Na^+-dependent dopamine transporter (DAT) is primarily responsible for regulating free dopamine (DA) concentrations in the brain by participating in the majority of DA uptake; however, other DA transporters may also participate, especially if cocaine or other drugs of abuse compromise DAT. Recently, such cocaine-insensitive low-affinity mono- and poly-amine OCT transporters were described in astrocytes which use DA as a substrate. These transporters are from a different transporter family and while insensitive to cocaine, they are specifically blocked by quinine and some steroids. Quinine is inexpensive and is often found in injected street drugs as an "adulterant". The present study was designed to determine the participation of OCTs in cocaine dependent behavioral and physiological changes in mice. Using FVB mice we showed, that daily single injections of quinine (10 mg/kg, i.p.) co-administered with cocaine (15 mg/kg, i.p.) for 10 days significantly enhanced cocaine-induced locomotor behavioral sensitization. Quinine had no significant effect on the time course of behavioral activation. In astrocytes from the ventral tegmental area of mice, transporter currents of quinine-sensitive monoamine transporters were also augmented after two weeks of cocaine administration. The importance of low-affinity high-capacity transporters for DA clearance is discussed, explaining the known ability of systemically administered DAT inhibitors to anomalously increase DA clearance.

1. Introduction

Neuropharmacological studies have established an important role for the dopaminergic system in the acute reinforcing effects of drugs of abuse. Dopamine (DA) is a neurobiological substrate mediating the reinforcing effects of alcohol, nicotine, opiates and psychostimulants, such as cocaine and amphetamines (Koob and Roberts, 1998; Volkow and Li, 2005). The effect of cocaine is the most direct — it has been established that the so-called "cocaine receptors" in the brain are mainly high-affinity neuronal-type dopamine transporters (DAT) (Ritz et al., 1987, 1990; Calligaro and Eldefrawi, 1988) and that cocaine acts to block the transporter, temporarily elevating extracellular DA by inhibiting its reuptake (Horn, 1990). The elevation of DA levels after cocaine administration was shown decades ago by in vivo microdialysis (Pettit and Justice, 1989) and cyclic voltammetry (Millar et al., 1985).

Elevation of extracellular DA is a temporary process as after some time its concentrations return to normal. The mechanism of this DA removal from extracellular space has been widely discussed in the literature, but still remains unclear. DA removal previously was mainly attributed to DAT (Ewing and Wightman, 1984; Jones et al., 1995; Wu et al., 2001). On the other hand, the same authors understand the role of extrasynaptic communication in DA transmission, in which DA is acting on spatially distinct, extracellular compartments. This implies that extrasynaptic uptake is mainly involved in rapid removal of extracellular DA (Garris et al., 1994).

Recently, low-affinity high-capacity monoamine transporters belonging to organic cation transporters family (OCT), or extracellular monoamine transporter (EMT) were characterized (Gründemann et al., 1998). Inazu et al. (2003) identified this type of transporter in astrocytes as OCT3, and others have found a splice variant for OCT1, with only partial sequence identity to OCT (Busch et al., 1998). OCTs belong to the SLC22A subfamily and are polyspecific transporting mono- and poly-amines of wide spectrum (Sala-Rabanal et al., 2013). OCT transporters saturate at 50–100 times higher concentration of monoamines, than DAT or norepinephrine transporter (NET) (Inazu et al., 2003) and have much higher capacity at high concentrations of substrates. At low concentrations (e.g., 100 nM) OCTs only contribute to about 20% of the DA uptake by astrocytes (Takeda et al., 2002) but their contribution increases for higher DA concentrations. Another low-affinity

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plasma membrane monoamine transporter (PMAT), belonging to the equilibrative nucleoside transporter family, was cloned from human brain and found in glial-like cells (Engel, et al., 2004). The multidrug and toxic compound extrusion (MATE) family of transporters can transport monoamines with low affinity and were also described in astrocyte-like cells as well (Hiasa et al., 2006). Therefore, we may conclude that low-affinity high-capacity glial transporters can play a key role in clearance of DA and other monoamines.

We previously showed (Iniouchine et al., 2008), that at high concentrations of DA, such as those usually used for in vitro slice electrophysiology (e.g., 40 μM), DA uptake depended mainly on low-affinity high-capacity transporters and was not affected by acute cocaine.

Our special interest in that study was the effect of OCT blockers on the level and the time scale of cocaine behavioral stimulant effect after acute cocaine–quinine co-administration. It is known, that quinine given at low concentrations is a blocker of OCT transporters (Busch et al., 1998; Arndt et al., 2001) and PMAT transporters (Engel et al., 2004). We, therefore, asked if quinine could interact with the extraneuronal monoamine transporters found on astrocytes (Iniouchine et al., 2008; Inyushin et al., 2010a).

This is relevant because quinine is a known "adulterant" frequently added to heroin, cocaine and some other drugs in the street, to "cut" them. Quinine had became so regularly used for this purpose, that in some of the US states the sale of large amounts of quinine are required to be reported to the State Board of Pharmacy (Pennsylvania Pharmacy Act, 63 PS §§ 390-1 to 390-13). Quinine is believed by some drug addicts to augment the rush associated with heroin (see Edwards, Augusta Chronicle, 2002). Interestingly, while quinine itself produces no addiction, the oral preference for quinine can be established in rats if for some time quinine was co-applied with cocaine (Falk et al., 1999).

Here we have shown, using cocaine/quinine co-administration in mice, that quinine facilitates the cocaine behavioral stimulant effect, while give no stimulation itself. Effects of quinine co-administration became more pronounced with prolonged used of cocaine for more than one week. Also, quinine sensitive monoamine transporter currents in astrocytes were augmented after 2 weeks of daily cocaine injections. Preliminary results were reported in abstract form (Inyushin et al., 2010a).

2. Materials and methods

2.1. Animals

Age-matched FVB male mice (The Jackson Laboratory, Bar Harbor, ME, USA) were used as the experimental subjects for behavioral studies. Adult animals were housed four per cage in the colony room and maintained at a constant temperature and humidity with a normal-phase 12-hour light/dark cycle. They were randomly assigned to the treatment groups before the study began. Experiments were carried out with IACUC approval and according to institutional animal care and use guidelines. Adequate measures were taken to minimize pain or discomfort to experimental animals.

It is known that the acute locomotor response to cocaine in FVB mice is smaller relative to other strains, except BALB mice. FVB mice also do not show prominent sensitization to repeated doses of cocaine during the first week (Eisener-Dorman et al., 2011). In other mice strains with similar sensitivity it was shown that unlike C57BL/6J, the C57BL/6N mice has a 45% lower acute and sensitized response to cocaine and methamphetamine due to mutations in Cyfip2 protein that generally affects the amount of excitatory synapses in animals' brain (Kumar et al., 2013). Others have found that low- or high-cocaine responding rat strains differ in striatal extracellular DA levels and DAT density (Nelson et al., 2009). This research shows the complexity and also the promise of studying cocaine locomotor behavioral sensitization in genetically different animals. On the other hand, the FVB strain has high reproductive success and large litters. The FVB are an inbred mouse strain, which is preferable for transgenic analyses, and is easily genetically manipulated due to prominent pronuclei in their fertilized eggs (Taketo et al., 1991). We used FVB mice in these experiments because of our future plans to use FVB/N based commercially available OCT transgenic animals (Taconic Hudson, NY, model 006622), and because FVB mice can be rapidly bred in our animal facility.

2.2. Drug concentrations

We used a 10 mg/kg concentration of quinine because we were aiming to mimic the ratio of cocaine–quinine found in "street drugs". The mean concentration of cocaine in street drug samples varies with years (Cunningham et al., 1984; Schneider and Meys, 2011) but stays between 43% and 64%. In our work we used 60% cocaine, and 40% quinine mix in our experiments. Also, we did additional experiments with intraperitoneal injections of 10 mg/kg quinine and found it has no clear behavioral effect (there was some limited inhibition of ambulatory behavior but without statistical significance). Also, from our previous experience we know that this concentration of quinine (10 mg/kg ≈ 30 μM) significantly reduces dopamine uptake by low affinity transporters in the brain, but only has limited or negligible effects on potassium currents (Iniouchine et al., 2008).

Peakman et al. (2003) and Zombeck et al. (2010) proved that 15 mg/kg i.p. cocaine is sufficient to produce a behavioral stimulation effect and sensitization in the FVB mouse strain used in our study. This lead as to use 15 mg/kg cocaine and 10 mg/kg quinine in our experiments

2.3. Behavioral testing

Behavioral experiments were conducted at the Behavioral Testing Facility of the Universidad Central del Caribe (http://www.uccaribe.edu/btf/). Measurements were made at room temperature (22–24 °C) in an appropriately lighted room during daylight hours. Test animals were placed inside a plastic test enclosure (each animal tested in a separate enclosure) within an acoustic chamber to mask external noises and other perturbations. Mice movements in the test enclosure were measured and evaluated using a video camera connected via a digital video board to the computer using Ethovision® software (version 3.0; Noldus Information Technology, Leesburg, VA, USA).

Mice were randomly assigned to two experimental groups (6 animals per group) that were treated daily for 10 days with either 15 mg/kg of cocaine, or 15-mg/kg cocaine plus 10-mg/kg quinine, as a single daily i.p. injection, to establish the development of cocaine behavioral sensitization. The third group was administered isovolumetric quinine injections over 10 days and served as a control. A fourth group, which served as a vehicle (saline) control group, was also tested. Each group was habituated to the behavioral testing procedures by administering a saline injection prior to being placed into the test enclosure and monitored by the video camera to measure locomotion for 5 days prior to beginning of the experiment. In addition, before each injection the animals were habituated to the test enclosure for 1 h. Mice were then injected with their respective drugs and returned to the testing chamber for 2 more hours during which their locomotor activity was analyzed. Locomotor activity was recorded as distance moved in cm during 1-min intervals following the daily injection. Cocaine hydrochloride and quinine hydrochloride dihydride were obtained from Sigma-Aldrich Co. (St. Louis, MO, USA) and were diluted in saline. Doses are expressed as the weight of the salts.

2.4. Preparation of brain slices

Adult mice were decapitated and the brains were removed from the skull in ice-cold (2 °C–4 °C) dissecting solution composed of (in mM): 126 NaCl; 2.5 KCl; 1.2 NaH_2PO_4; 7.0 $MgCl_2$; 0.5 $CaCl_2$; 25 Glucose; 25 $NaHCO_3$; saturated with 95% O_2 and 5% CO_2. Brain tissues were sectioned and 250 μm slices were cut using a vibroslicer (Leica VT 1000S,