Cocaine fails to elevate pallidal glutamate in rats sensitized to cocaine

Imran A. Khaliq[1], Sharifeh Farasat[1], Larry C. Ackerson[1] and

Kabirullah Lutfy[2]*

Running Title: Cocaine sensitization & pallidal glutamate and dopamine

[1]Dept. of Psychiatry and Biobehavioral Sciences, Neuropsychiatric Institute

University of California, Los Angeles, 760 Westwood Plaza

Los Angeles, CA 90024

[2]Dept. of Pharmaceutical Sciences, College of Pharmacy

Western University of Health Sciences, 309 East Second Street

Pomona, CA 91766

Phone (909) 469-5327

Fax (909) 469-5600

E-mail: klutfy@westernu.edu

*To whom proofs and reprint requests should be addressed

Abstract

Systemic cocaine administration is shown to elevate extracellular pallidal dopamine and glutamate. However, it is unclear whether sensitization would develop to this action of cocaine after repeated cocaine administration. Thus, using microdialysis in freely behaving rats, we determined whether the ability of cocaine to elevate pallidal dopamine and glutamate will be enhanced in rats sensitized to cocaine. First, the effect of cocaine on pallidal dopamine and glutamate was determined in naïve rats. Next, the effect of cocaine on pallidal glutamate and dopamine was determined in sensitized rats in which separate groups of rats were treated with either saline or cocaine (20 mg/kg, i.p.) once daily for 3 days. On day 7, a microdialysis probe was lowered into the pallidum and, 18 h later, samples were collected 1 h prior to and 2 h after cocaine (20 mg/kg, i.p.) administration. Our results demonstrate that single cocaine administration significantly increased pallidal dopamine and glutamate. Despite the fact that repeated cocaine administration increased the motor stimulatory action of cocaine, the same treatment failed to enhance the ability of cocaine to elevate pallidal dopamine or glutamte. Taken together, the present results suggest that sensitization does not develop to cocaine-induced elevation of pallidal dopamine or glutamate.

Key Words: Cocaine; Sensitization; Ventral Pallidum; Dopamine; Glutamate; Microdialysis

Introduction

The ventral pallidum (VP) has been implicated in motor stimulation and reward induced by cocaine, opioids and other drugs of abuse. Indeed, the VP projects to and receives information from numerous brain regions related to motor behavior and reward. It has reciprocal connections with both the nucleus accumbens (Nuc Acc) and ventral tegmental area (VTA) (Groenewegen et al. 1993; Kalivas et al. 1993). Dopamine neurons from the VTA project to the VP (Klitenick et al. 1992; Napier and Potter 1989). Approximately, 30-60% of VTA-pallidal fibers are stained positive for tyrosine hydroxylase (Klitenick et al. 1992), and a moderate density of dopamine D_1 and D_2 receptors have been identified in the VP (Beckstead 1988; Boyson and Adams 1997). Behavioral studies have also revealed the importance of pallidal dopamine in the motor stimulatory and rewarding action of cocaine. Thus, pallidal dopamine depletion by 6-hydroxydopamine infusion has been shown to attenuate the motor stimulatory action of systemically administered cocaine (Gong et al. 1997). Additionally, intra-pallidal cocaine administration has shown to increase locomotion and induce conditioned place preference (Gong et al. 1996).

The VP also receives glutamatergic projections from prefrontal cortex, amygdala and subthalamic nucleus (Fuller et al. 1987; Groenewegen and Berendse 1990; Kita and Kitai 1987). The involvement of pallidal glutamate receptors in motor activation has likewise been shown. Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), Kainate and N-methyl-D-aspartate (NMDA) injections into the VP stimulate motor activity (Churchill and Kalivas 1999;

Wallace and Uretsky 1991). Additionally, activation of NMDA and AMPA receptors in the VTA elevates pallidal dopamine and glutamate and increases motor activity (Fuchs and Hauber 2003; Kretschmer et al. 2000).

Behavioral sensitization is referred to as a progressive increase in motor activity after repeated intermittent administration of cocaine and other drugs of abuse (Post and Rose 1976; Shuster et al 1977; Kalivas and Duffy 1993; Stewart and Badiani 1993). This phenomenon is thought to play an important role in the development and maintenance of drug dependency (Robinson and Berridge 2000). Indeed, the phenomenon of sensitization has revealed a host of adaptive changes that may underlie the neurochemical and cellular substrates of drug dependency (reviewed by Robinson and Berridge 1993; Robinson and Berridge 2000; Vanderschuren and Kalivas 2000; Woolverton and Johnson 1992). Thus, behavioral sensitization is considered an animal model of drug addiction, particularly craving (reviewed by Robinson and Berridge 1993; Robinson and Berridge 2000).

Behavioral sensitization is thought to involve neuroadaptations in circuits involving dopaminergic and glutamatergic neurons along the mesocorticolimbic structures (for review, see Vanderschuren and Kalivas 2000). Most neurochemical studies have demonstrated changes in dopamine and glutamate in the VTA or Nuc Acc, because these brain regions are thought to be substrates for the development and expression of sensitization, respectively (Hooks et al. 1992; Kalivas and Weber 1988; Paulson and Robinson 1991; Vanderschuren and Kalivas 2000; Vezina and Stewart 1990). However, neuroadaptations could

also occur in other brain regions. Given the importance of pallidal dopamine and glutamate in motor activity and reward, the present study was designed to determine whether cocaine would produce a greater elevation in pallidal dopamine or glutamate in rats sensitized to cocaine than in non-sensitized control rats.

Methods

Subjects Male Sprague Dawley rats (weighing 180-200g) obtained from Harlan (San Diego, CA), were used in this study. Rats were housed 2-3 per cage with free access to food and water under an alternating 12-h light/12-h dark cycle one week prior to any experimentation. All experiments were conducted during the light cycle according to the guidelines set forth by the National Institute of Health (NIH) and approved by the Institutional Animal Care and Use Committee.

Drugs Cocaine, obtained from the National Institute on Drug Abuse Drug Supply Program (Research Triangle Park, NC), was dissolved in normal saline (0.9% NaCl in double-distilled water) immediately prior to intraperitoneal (i.p.) administration.

Experimental paradigms The effect of single and repeated intermittent cocaine administration on pallidal dopamine and glutamate was determined using microdialysis in freely behaving rats.

Effects of single cocaine administration on pallidal dopamine and glutamate Rats were anesthetized with halothane in a mixture of nitrous oxide and oxygen (1:1) and placed on a stereotaxic frame. A small incision was made to expose the skull. A 2-mm microdialysis probe (concentric design, PAN AN69), perfused continuously at 2 µl/min with artificial cerebrospinal fluid (aCSF), containing 125mM NaCL, 2.5mM KCL, 0.9 mM NaH2PO4, 5mM Na2HPO4, 1.2mM CaCl2, 1mM MgCl2, and 2.5mM d-Glucose (pH = 7.4), was lowered into the VP (DV=-8.6mm). The coordinates (AP=-0.3mm and ML=+2.6mm) were

according to the atlas of Paxinos and Watson (1986) with Bregma as the point of reference. The probe was secured in place with 3 metallic skull screws and dental cement. Animals were returned to microdialysis chambers and, 18 h later, samples were collected 1 h prior to and 2 h after saline or cocaine (20 mg/kg, i.p.) administration. At the end of each experiment, samples were divided into separate vials and frozen at -80°C until the day of the assay for independent analysis of dopamine and glutamate by HPLC with electrochemical and fluorometric detection, respectively (for details, see Murphy and Maidment 1999).

Effects of repeated cocaine administration on pallidal dopamine and glutamate A 3-day cocaine regimen shown to induce behavioral sensitization (Lutfy et al. 2002; Lutfy and Maidment 2002) was used to test whether cocaine would produce a greater elevation of pallidal dopamine and glutamate in rats sensitized to cocaine than in non-sensitized control rats. Rats were habituated to the testing chambers for 1 h, treated with either saline or cocaine (20 mg/kg, i.p.) and motor activity was recorded for a further 1-h period. The same treatment was given once daily for 3 consecutive days. On day 7, a 2-mm microdialysis probe was lowered into the VP, as described above, and 18 h later, samples were collected for measurement of pallidal dopamine and glutamate 1 h prior to and 2 h after cocaine (20 mg/kg, i.p.) administration. Our results of single dose studies showed that cocaine-induced elevation of pallidal glutamate returned to basal level by approximately 75 min. Therefore, only 10 samples (4 prior to and 6 after cocaine administration) were run through the HPLC for glutamate measurement.

Effects of repeated cocaine administration on cocaine-induced motor stimulation In order to verify that such a paradigm indeed produces sensitization, different groups of rats were habituated to the testing chambers for 1 h, treated with saline or cocaine (20 mg/kg, i.p.) once daily for 3 days, as described above, and tested on day 8. On the test day, rats were habituated to the testing chambers for 1 h, injected with cocaine (20 mg/kg, i.p.) and motor activity was recorded for a further 1-h period.

Histological analysis of probe placement At the end of each experiment, rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and transcardially infused with 50 ml potassium phosphate buffer followed by 50 ml phosphate buffered formalin (10%). Brains were removed, cryoprotected, sectioned (40 µm), stained with cresyl violet and viewed under the microscope.

Data Analysis A repeated-measure analysis of variance (ANOVA) was used to analyze the data. Saline or cocaine treatment and time with regards to treatment were used as the between and within factors, respectively. Whereever appropriate, the Newman-Keuls post-hoc test was used to reveal significant differences between different groups. A $p<0.05$ was considered significant.

Results

Effects of single cocaine administration on pallidal dopamine and glutamate Cocaine administration increased pallidal dopamine in naïve rats (Fig. 1A). A repeated-measure ANOVA revealed a main effect of treatment ($F(1,6) = 9.34$; $p<0.02$), a main effect of time ($F(11,66) = 9.49$; $p<0.01$) and a main interaction between treatment and time ($F(11,66) = 8.47$; $p<0.01$). Similarly, a significant increase in pallidal glutamate was observed after cocaine administration in naïve rats (Fig. 1B). As basal glutamate levels varied within each group, data were normalized as percent change from baseline (the average of 4 samples before cocaine administration) and analyzed. A repeated-measure ANOVA showed a main effect of treatment ($F(1,6) = 19.20$; $p<0.005$), a main effect of time ($F(8,48) = 6.45$; $p<0.005$) and a main interaction between treatment and time ($F(8,48) = 4.66$; $p<0.02$). There were two rats (belong to the saline group) with misplaced probe placement. This was not included in data analysis.

Effects of repeated cocaine administration on pallidal dopamine and glutamate Repeated cocaine administration did not significantly alter basal levels of pallidal dopamine (0.74 ± 0.13 and 0.53 ± 0.09 nM for saline- and cocaine-treated rats, respectively) or glutamate (6.17 ± 2.47 and 8.99 ± 2.59 pM for saline- and cocaine-treated rats, respectively).

Figure 1A

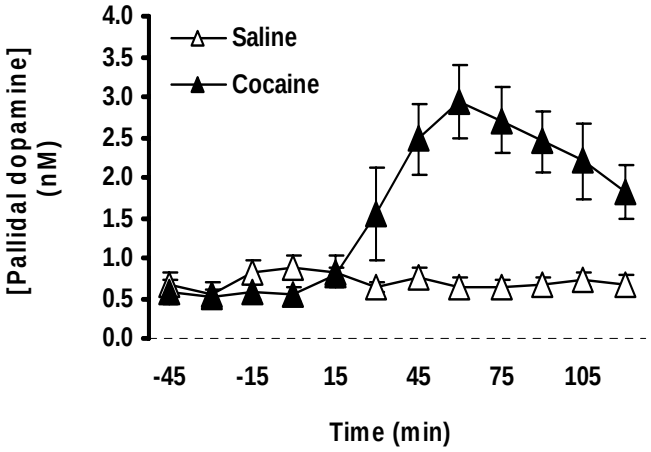

Figure 1B

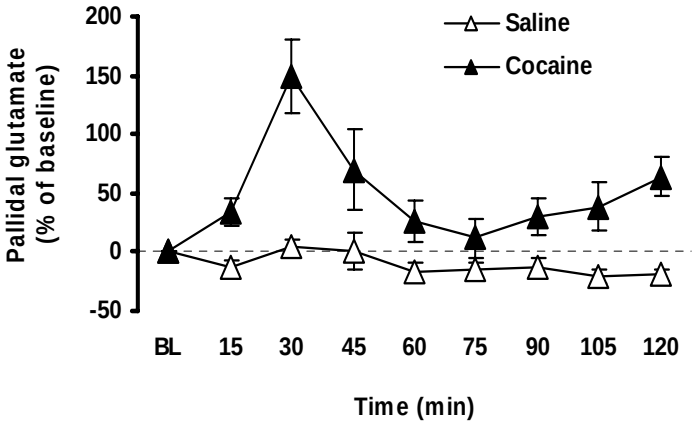

Figure 1 Effects of cocaine administration on pallidal dopamine (1A) and glutamate (1B) in naïve rats. A 2-mm microdialysis probe was lowered into the VP and, 18 h later, samples were collected for measurement of extracellular dopamine 1 h prior to and 2 h after cocaine (20 mg/kg, i.p.) administration. Data are mean ± s.e.m. of 4 rats per group.

As expected, cocaine increased extracellular dopamine in saline-treated control rats and this response was not altered in sensitized rats (Fig. 2A). A two-way repeated-measure ANOVA revealed a main effect of time ($F(8,80) = 27.53$, $p<0.05$), but no main effect of pretreatment ($F(1,10) = 0.14$, $p>0.05$) or interaction between pretreatment and time ($F(8,80) = .28$, $p>0.05$), showing that cocaine similarly elevated extracellular dopamine in control and sensitized rats. The effect of cocaine on pallidal glutamate in control and sensitized rats is shown in Figure 2B. A two-way repeated measure ANOVA revealed a main effect of pretreatment ($F(1,10)= 8.38$, $p<0.05$), a main effect of time ($F(6,60) = 7.02$, $p<0.05$) and a trend toward main interaction between pretreatment and time ($F(6,60) = 1.87$, $p=0.05$; one-tailed), showing that the ability of cocaine to increase pallidal glutamate was significantly reduced in rats treated with cocaine on days 1-3 ($p<0.05$).

Effects of repeated cocaine administration on cocaine-induced motor stimulation In order to verify whether behavioral sensitization develops after repeated cocaine administration, different groups of rats were treated with saline or cocaine on days 1-3 and tested for cocaine-induced motor stimulation on day 8. Behavioral sensitization developed to the motor stimulatory action of cocaine (Fig. 3). A repeated-measure ANOVA revealed a main effect of pretreatment (saline or cocaine on days 1-3) ($F(1,9) = 9.63$; $p<0.01$), a main effect of time with respect to cocaine administration on the test day ($F(7,63) = 28.21$; $p<0.001$) and a main interaction between pretreatment and time ($F(7,63) = 3.71$; $p<0.005$),

indicating that cocaine produced motor stimulation, the magnitude of which was greater in rats that received cocaine, as compared to saline, on days 1-3.

Figure 2A

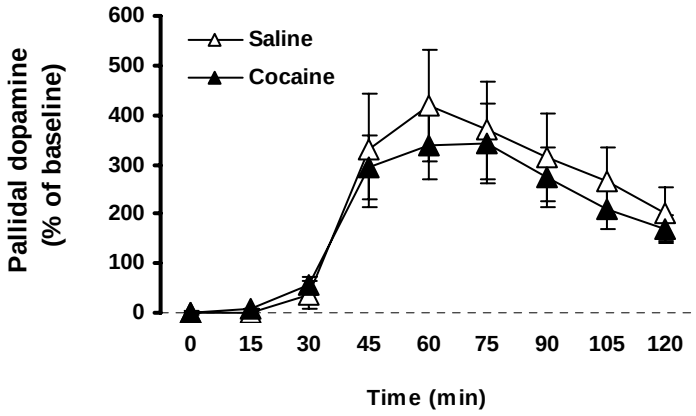

Figure 2B

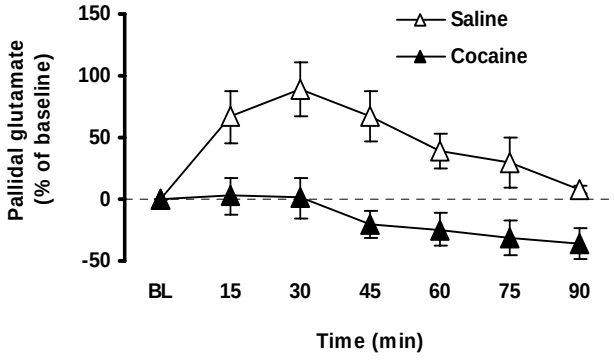

Figure 2 Effects of cocaine administration on pallidal dopamine (2A) and glutamate (2B) in saline-treated control and cocaine-sensitized rats. Rats were treated with saline or cocaine (20 mg/kg, i.p.) once daily for 3 days. On day 7, a 2-mm microdialysis probe was lowered into the VP and, 18 h later, samples were collected for measurement of extracellular dopamine 1 h prior to and 2 h after cocaine (20 mg/kg, i.p.) administration. Values are expressed as percentage of baseline dopamine (0.74 ± 0.13 and 0.53 ± 0.09 nM for saline- and cocaine-treated rats) and glutamate (6.17 ± 2.47 and 8.99 ± 2.59 pM for saline- and cocaine-treated rats). Data are mean ± s.e.m. of 5-6 rats per group.

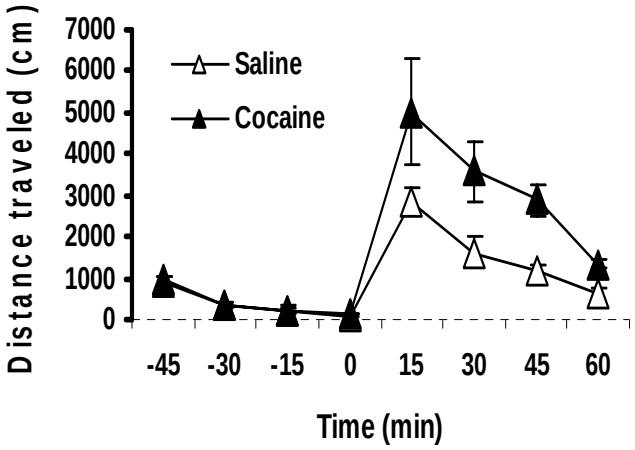

Figure 3 Effects of repeated cocaine administration on the motor stimulatory action of cocaine. Rats were habituated to the testing chamber for 1 h and then injected with saline or cocaine (20 mg/kg, i.p.). Rats were treated with the respective treatment for 3 days and tested on day 8 after a challenge dose of cocaine (20 mg/kg, i.p.). Data are mean ± s.e.m. of 5-6 rats/group.

Discussion

Cocaine elevates extracellular dopamine by blocking the dopamine transporter located on the terminal fields of dopaminergic neurons (Ritz et al. 1987), a response thought to be critical for motor stimulatory action of cocaine (Giros et al., 1996). Indeed, there is a significant correlation between the ability of cocaine to increase accumbal dopamine and basal motor activity (Hurd et al., 1988). Cocaine also evokes an increase in glutamate in the VTA as well as in other

brain regions, such as the Nuc Acc and pre-frontal cortex (Kalivas and Duffy 1995; Reid and Berger 1996; Reid et al. 1997; Smith et al. 1995), which may contribute to cocaine-induced motor stimulation and behavioral sensitization (reviewed by Vanderschuren and Kalivas 2000).

Most neurochemical studies have aimed at quantifying alterations in dopamine and glutamate in the VTA or Nuc Acc, because these brain regions are thought to be substrates for the development and expression of sensitization, respectively (Hooks et al. 1992; Kalivas and Weber 1988; Paulson and Robinson 1991; Vanderschuren and Kalivas 2000; Vezina and Stewart 1990). While increases in dopaminergic neurotransmission are thought to play a functional role in the development of sensitization, such changes in accumbal doapmine are not consistently reported in cocaine-sensitized rats. In fact, there are reports showing that extracellular dopamine levels decrease in the Nuc Acc in cocaine-sensitized rats (Cadoni et al. 2000). Thus, dopaminergic pathways other than mesoaccumbal axis may become sensitized after repeated cocaine administration.

As VP receives dopaminergic inputs from the VTA and cocaine can increase extracellular levels of dopamine in the VP (Gong et al., 1997; Sizemore et al., 2000), we tested the possibility that the ability of cocaine to elevate pallidal dopamine might be enhanced (neurochemical sensitization) after repeated cocaine administration. Consistent with the results of previous studies (Gong et al., 1997; Sizemore et al., 2000), we found that extracellular level of pallidal dopamine was enhanced after systemic cocaine administration (Fig. 1A).

However, sensitization did not develop to this action of coccaine (Fig. 2A), indicating that the mesopallidal dopamine does not show neurochemical sensitization. Gong and colleagues (1997) have demonstrated that elevation of pallidal dopamine by cocaine plays a critical role in cocaine-induced motor stimulation and reward (Gong et al. 1996, 1997). However, in the present study, the rise in pallidal dopamine did not appear to correlate well with the time-course of cocaine-induced motor stimulation. As can be observed, there is an immediate increase in motor activity after cocaine administration (Fig. 3) but the level of dopamine peaks at a later time point (Fig. 1A) and remains elevated at the time when the motor stimulatory action of cocaine declined to almost basal levels (1 h after cocaine administration).

The lack of neurochemical sensitization of mesopallidal dopamine neurons could be due to the fact that neurotransmitters other than dopamine may be involved in this process (see below). An overwhelming body of evidence indicates that behavioral sensitization is a consequence of adaptive changes involving not only the dopamine but also other neurotransmitter and/or neuropeptide systems (for reviews, see Shippenberg and Rea 1997; Vanderschuren and Kalivas 2000). For example, administration of NMDA receptor antagonists blocks the development of cocaine-induced behavioral sensitization (Karler et al. 1989). Moreover, previous studies have shown that extracellular glutamate increases in the Nuc Acc (Reid and Berger 1996) or VTA (Kalivas and Duffy 1995) in cocaine-sensitized rats. Additionally, evidence exists to demonstrate that expression of cocaine sensitization is context-dependent and that cortical glutamatergic

afferents are involved in this phenomenon (for review, see Vanderschuren and Kalivas 2000). Since VP receives glutamatergic inputs from various brain regions (Fuller et al. 1987; Groenewegen and Berendse 1990; Kita and Kitai 1987), we determined whether pallidal glutamate level would be increased after cocaine administration and whether sensitization develops to this action of cocaine. Although an earlier study has determined the effect of cocaine on pallidal glutamate in rats trained to self-administer cocaine (Sizemore et al. 2000), this is the first study to show that acute cocaine administration significantly elevates pallidal glutamate levels in naïve rats (Fig 1B), which correlated well with the motor stimulatory action of cocaine (Fig. 3). Furthermore, our results are in accordance with previous findings demonstrating that intra-pallidal injection of glutamate agonists (AMPA, Kainate and NMDA) stimulate motor activity (Churchill and Kalivas 1999; Wallace and Uretsky 1991). However, despite the fact that repeated cocaine administration caused behavioral sensitization, the same treatment failed to increase the ability of cocaine to elevate extracellular glutamate in cocaine-sensitized rats. In fact, cocaine failed to increase pallidal glutamate in rats sensitized to cocaine (Fig. 2B). Even though, it is unclear how repeated cocaine will reduce the ability of cocaine to increase pallidal glutamate, the lack of an action of cocaine on pallidal glutamate in sensitized rats could be due to decreased glutamatergic inputs to the pallidum and/or reduced intra-pallidal glutamatergic neurotransmission per se. Previous studies have shown that withdrawal from cocaine can lead to a decrease in accumbal glutamate levels due to a reduction in cystine/glutamate exchange in the Nuc Acc (Baker et

al., 2003). However, our results showed no significant differences in basal pallidal glutamate levels between control (6.17 ± 2.47 pM) and cocaine-sensitized (8.99 ± 2.59 pM) rats. Although it is unclear at the present time how repeated cocaine administration leads to a decrease in the ability of cocaine to elevate pallidal glutamate, we speculate that the increase in pallidal glutamate induced by each cocaine administration during induction of sensitization (days 1-3) may also facilitate a pallidal inhibitory, possibly GABA-ergic, output to the VTA and other brain regions. However, after repeated cocaine administration the drug fails to elevate pallidal glutamate, which could possibly lead to decreased pallidal GABA-ergic output to these motoric regions and, therefore, an enhanced motor activity (behavioral sensitization).

In summary, acute cocaine administration elevated extracellular levels of dopamine and glutamate in the VP in naïve rats. However, the ability of cocaine to increase pallidal dopamine and glutamate was not enhanced in rats sensitized to the motor stimulatory action of cocaine.

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