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Short communication

Intravenous administration of Tat-NR2B9c peptide, a PSD95 inhibitor, attenuates reinstatement of cocaine-seeking behavior in rats

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ABSTRACT

Cocaine use disorder is a serious, chronic and relapsing disease of the nervous system, for which effective treatments do not yet exist. Recently, the role of the *N*-methyl-D-aspartate (NMDA) receptor subunit GluN2B has been highlighted in cocaine abstinence followed by extinction training. Since the GluN2B subunit is stabilized at synaptic level by the interaction with its scaffolding protein PSD95, in this study we aimed at investigating efficacy of Tat-NR2B9c peptide, a PSD95 inhibitor, which disrupts the interaction of PSD95 with GluN2B, in the attenuation of cocaine seeking-behavior or cue-induced reinstatement. We found that Tat-NR2B9c, administered intravenously, attenuated the reinstatement of active lever presses induced by a priming dose of cocaine or by drug-associated conditioned stimuli. At the same time, the GluN2B/PSD95 complex levels were decreased in the ventral hippocampus of rats that previously self-administered cocaine injected with Tat-NR2B9c during cocaine- or cue-induced reinstatement. In conclusion, we here provide the first evidence showing that the disruption of the GluN2B/PSD95 complexes during cocaine abstinence followed by extinction training may represent a useful strategy to reduce reinstatement of cocaine-seeking behavior.

1. Introduction

Several preclinical and clinical studies showed that glutamatergic dysregulation within prefrontal cortical-hippocampal-striatal circuits has been implicated in cocaine use disorder [1–6]. Moreover, the long-lasting adaptation within the *N*-methyl-D-aspartate (NMDA) receptor subunits has been shown following cocaine abstinence under different condition [7–10]. The NMDA is anchored to the postsynaptic membrane by means of several scaffolding proteins, primarily postsynaptic density protein 95 (PSD95) [7]. Previously, we have shown that 10-day cocaine abstinence followed by extinction training up-regulated the GluN2B subunit levels (both at gene and protein level) as well as the GluN2B/PSD95 complex in the ventral hippocampus (vHIP), while a GluN2B subunit antagonist (CP 101,606) attenuated cocaine-seeking behavior [9]. Based on the assumption that alterations in NMDA receptor subunit localization and its interaction with intracellular scaffolding protein in animal models lead to higher cocaine-seeking and/or higher rates of cocaine reinstatement, we decided to apply during cocaine abstinence the new cell-permeable peptide Tat-NR2B9c, specifically targeted to the disruption of GluN2B/PSD95 complex, in an attempt to attenuate the subsequent drug-seeking and relapse behaviors.

Tat-NR2B9c is a 9-mer peptide corresponding to the C-terminus of the GluN2B subunit (NR2B9c) covalently conjugated to TAT to facilitate permeation across the blood-brain barrier [11]. Tat-NR2B9c acts as a PSD95 inhibitor, which disrupts the interaction of PSD95 with GluN2B. Since the initial application of Tat-NR2B9c in stroke [12], the same approach has also been employed in other neurological diseases including Alzheimer disease [13], epilepsy [14], and neuropathic pain [15,16]; however, the potential effect on cocaine-seeking behavior has not been examined yet.

In the present study, the Tat-NR2B9c has been administered intravenously with cocaine (*Experiment 1*) or with a cocaine-associated

Abbreviations: NMDA, *N*-methyl-D-aspartate; PSD95, postsynaptic density protein 95; vHIP, ventral hippocampus.

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conditional stimulus (cue) (*Experiment 2*) to evaluate its influence on drug seeking behavior in rats. Next, we assessed the formation of the GluN2B/PSD95 complex after Tat-NR2B9c administration in the vHIP, whose formation is promoted following 10-day cocaine abstinence after cocaine self-administration in rats [9].

2. Methods

2.1. Animals

Male Wistar rats (Charles River Laboratories, Germany; initial weight: 225−250 g; age: 7–8 weeks; at the outset of experiments (before surgery, after 7 days of quarantine): 250−280 g; age: 8–9 weeks) were kept individually in standard plastic rodent cages at room temperature of 22 ± 1 °C and 55 ± 10 % humidity with a 12-h light-dark cycle with the lights on at 06:00 am (the experiments were performed in the light period of the rats). All experiments were carried out in accordance with EU directive 2010/63/EU and with the approval of the local ethics commission (169/2020, 14/2021). There were 5–6 animals per group.

2.2. Drugs

Cocaine hydrochloride [Toronto Research Chemicals (TRC), Canada] was dissolved in 0.9 % saline and administered *i.v.* (0.1 mL per infusion) or *i.p.* (1 mL/kg). Tat-NR2B9c (MedChemExpress, USA), a synthetic peptide consisting of the C-terminal 9 amino acids of the GluN2B subunit (Lys-Leu-Ser-Ser-Ile-Glu-Ser-Asp-Val) fused to the cell membrane protein transduction domain of the HIV-1-Tat protein was dissolved in sterile 0.9 % saline and given *i.v.* (1 mL/kg).

2.3. Behavioral procedures

2.3.1. Intravenous catheter implantation and initial training to lever presses

The rats were anesthetized with a mixture of ketamine hydrochloride (75 mg/kg, i.m.; Biowet, Poland) and xylazine (5 mg/kg, i.m; Biowet, Poland) and a silastic catheter was implanted into the external right jugular vein as described previously (Bystrowska et al., 2019). The animals were trained for 2–3 days to press a lever ("active") for 2 h daily in standard operant chambers (Med-Associates, St. Albans, USA) with a response schedule with a fixed ratio (FR) from 1 to 5 that was reinforced with food (sweetened milk). A day before lever-press training and during the three initial days of training, each rat had food limited to 25 g per day (ca. 80 % daily food intake).

2.3.2. Cocaine self-administration

Self-administration (2-h daily sessions performed 6 days/week, 14 sessions) occurred on an FR 5 schedule with a 20 s timeout, where presses on the "active" lever resulted in delivery of a single cocaine infusion (0.5 mg/kg/infusion in 0.1 mL) and the simultaneous presentation of a stimulus light over the "active" lever and a tone (2000 Hz; 15 dB, 5 s). After 14 days of cocaine self-administration sessions, animals exhibited a stable number of lever presses during the last 6 sessions, with a less than 10 % difference in their daily intake of cocaine [6].

2.3.3. Cocaine abstinence with extinction training

After 14 days of cocaine self-administration, animals underwent a 10-day extinction training period in the experimental cage, where cocaine was replaced with saline (0.1 mL/infusion) and no conditioned stimuli were presented. On the 10th day of extinction, animals met the extinction criterion (i.e., responses regarding the "active" lever fell to <10 % of the responses regarding the "active" lever reached during maintenance).

2.3.4. Reinstatement training and peripheral administration of Tat-NR2B9c

Following extinction training, four separate groups of rats (N = 5–6/group) were tested for response reinstatement (2 h) induced by a noncontingent presentation of self-administered reinforcements (10 mg/kg cocaine *i.p.*) or cue-induced reinstatement (light and tone, previously associated with cocaine self-administration).

During cue-induced reinstatement, an active lever response was reinforced by a 5 s presentation of the light and tone paired with an infusion of saline, and an "inactive" lever response again had no programmed consequence. During cocaine-induced reinstatement, an active lever response resulted in an intravenous injection of saline only. During reinforcements, an FR5 schedule meant that an *i.v.* saline delivery occurred after every 5 correct responses. The cumulative number of lever presses was recorded after a 120-min session.

Rats were pretreated with Tat-NR2B9c peptide (7.8 mg/kg/day; *i.v.*) 48 h, 24 h and 1 h before the reinstatement sessions before the cocaine- or cue-induced reinstatement sessions (Fig. 1).

2.4. Brain structure isolation

Rats were decapitated immediately after the last reinstatement session (test) and their brains were rapidly removed on ice-chilled surfaces. vHIP was isolated between coordinates from the bregma (AP ~ -5.2 to -6.04 mm, ML ~ 4 ± 6 mm, DV ~ 4.5−9 mm) according to The Rat Brain Atlas [17], immediately frozen on dry ice and stored at −80 °C for biochemical analysis.

2.5. Biochemical analyses

2.5.1. Coimmunoprecipitation

Frozen brain structures (from *experiments 1* and *2*) were homogenized in a cold 0.32 M sucrose buffer pH 7.4 in the presence of a cocktail of protease and phosphatase (Sigma-Aldrich, USA) inhibitors. For protein determination, a bicinchoninic acid assay protein assay kit (Serva, Germany) was used. Coimmunoprecipitation was performed according the procedure described previously [9]. Briefly, aliquots of total homogenate were incubated with rabbit anti-PSD95 monoclonal antibody (ab76115; Abcam, UK) overnight at 4 °C. Protein A-Sepharose beads (Sigma-Aldrich; USA) were added to each sample and incubated, then samples were centrifuged, and the immunocomplexes with protein A beads were collected and washed. Protein A beads were pelleted, while the immunocomplexes were eluted with 30 μL of SDS-PAGE sample buffer and subjected to immunoblotting as described previously [6]. The membranes with immunoprecipitated PSD95 protein were probed with rabbit anti-GluN2B polyclonal antibody (1:1000; ab65783; Abcam, UK). The blots were washed and incubated with goat anti-rabbit secondary antibody (1:6000; 926- 68071; Li-cor, USA). Negative controls included Sepharose-linked secondary antibodies or Sepharose beads only. PSD95 was also immunoprobed in the bead-unbound fraction. All membranes visualized with a fluorescence detection Odyssey Clx (Li-cor, USA). The results are presented as a % of the control of the normalized OD (GluN2B/PSD95).

2.6. Statistical analyses

In behavioral experiments, the number of active and "inactive" lever responses were analyzed using analyses of variance (ANOVAs) for repeated measurements, and a factorial ANOVA was used to analyze the reinstatement test followed by a post hoc *Newman-Keuls* test. In neurochemical studies, statistical analyses were performed with *t*-Student test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Cocaine self-administration and cocaine abstinence with extinction training

The mean number of cocaine infusions per day during the last 3 self-

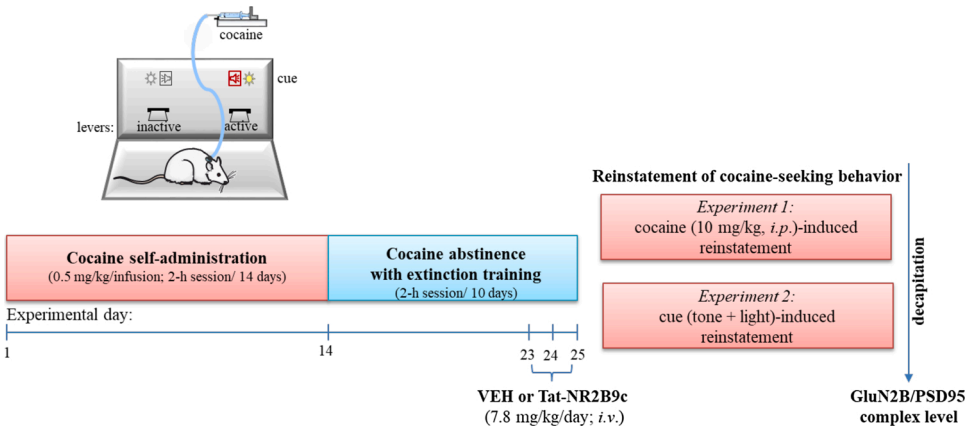

Fig. 1. Diagram illustrating the experimental procedure.

administration days varied from 27 to 32. The average total cocaine intake for all groups of rats was between 161–182 mg after 14 days of cocaine self-administration (Table 1). The mean daily cocaine intake for rats was 11−14 mg/day.

Experiment 1: During the extinction training, the rats self-administering cocaine pressed the "active" lever more frequently than the "inactive" lever from the 4th session of self-administration to the 1 st extinction day (lever $F(1, 18) = 136$, $p < 0.0001$, day ($F(18, 324) = 19.08$, $p < 0.0001$; interaction lever × day ($F(18, 324) = 19.933$, $p < 0.0001$).

Experiment 2: During the extinction training, the rats self-administering cocaine pressed the "active" lever more frequently than the "inactive" lever from the 4th session of self-administration to the 1 st extinction day (lever $F(1, 22) = 60$, $p < 0.0001$, day ($F(18, 396) = 6.35$, $p < 0.0001$; interaction lever × day ($F(18, 396) = 6.87$, $p < 0.0001$).

3.2. Cocaine-induced reinstatement of cocaine-seeking behavior and Tat-NR2B9c peptide administration

3.2.1. Cocaine-induced reinstatement of cocaine-seeking behavior

After 10 days of extinction trials, two separate groups of rats (N = 5/group) were tested for the response reinstatement induced by cocaine (10 mg/kg, *i.p.;* Fig. 2a).

A factorial ANOVA indicated a significant main effect for cocaine (treatment × lever interaction ($F(1, 16) = 26.33$, $p < 0.0001$) and lever ($F(1, 16) = 41.29$, $p < 0.00001$), as well as treatment ($F(1, 16) = 24.14$, $p < 0.0001$). The post hoc *Newman-Keuls* test confirmed that cocaine (10 mg/kg) significantly increased the active lever responses ($p < 0.0001$), but no changes were observed in the number of "inactive" lever presses.

3.2.2. Effect of Tat-NR2B9c

A factorial ANOVA indicated significant main effect of repeated administered Tat-NR2B9c (7.8 mg/kg) on cocaine (10 mg/kg)-induced reinstatement (treatment × lever interaction ($F(1, 16) = 4.56$, $p = 0.04$) and lever ($F(1, 16) = 54.43$, $p < 0.0001$), as well as treatment ($F(1, 16) = 7.59$, $p = 0.01$) (Fig. 2a).

3.3. Cue-induced reinstatement of cocaine-seeking behavior and Tat-NR2B9c peptide administration

3.3.1. Cue-induced reinstatement of cocaine-seeking behavior

After 10 days of extinction trials, two separate groups of rats (N = 6/group) were tested for the response reinstatement induced by the cue paired earlier with cocaine infusions.

A factorial ANOVA indicated a significant main effect for cue (treatment × lever interaction ($F(1, 20) = 7.42$, $p < 0.01$) and lever ($F(1, 20) = 14.36$, $p < 0.001$), as well as treatment ($F(1, 20) = 9.82$, $p < 0.005$) on cocaine-seeking behavior (Fig. 2b). The post hoc *Newman-Keuls* test confirmed that cocaine (10 mg/kg) and the conditioned cue significantly increased the active lever responses ($p < 0.01$), but no changes were observed in the number of "inactive" lever presses.

3.3.2. Effect of Tat-NR2B9c

A factorial ANOVA indicated a significant main effect of repeated administered Tat-NR2B9c on cue-induced reinstatement (treatment × -lever interaction ($F(1, 20 = 4.57$; $p < 0.04$) and lever ($F(1, 20) = 17.85$, $p < 0.001$), as well as treatment ($F(1, 20) = 7.49$, $p < 0.01$). The post hoc *Newman-Keuls* test confirmed that Tat-NR2B9c significantly ($p < 0.01$) reduced the number of "active" lever presses without affecting the number of "inactive" lever presses (Fig. 2b).

3.4. Coimmunoprecipitation of GluN2B with PSD95

The Tat-NR2B9c administration provoked a reduction (ca. 15.68 %) in the GluN2B/PSD95 complex association in the vHIP in the rats during cocaine-induced ($t(8) = 2.515$, $p = 0.0361$) (Fig. 3a) reinstatement of cocaine-seeking behavior, and a decreased GluN2B/PSD95 complex (ca. 8.2 %) cue-induced ($t(10) = 3.266$, $p = 0.0085$) (Fig. 3b) reinstatement of cocaine-seeking behavior.

4. Discussion

In the present study, we examined the effect of Tat-NR2B9c on cocaine-seeking behavior in rats with a previous history of cocaine self-

Table 1
Cocaine (0.5 mg/kg/infusion) self-administration. Average of presses on the levers, cocaine infusion, and total cocaine intake per group.

Experiment	Group	Active lever (last 3 days)	Inactive lever (last 3 days)	Cocaine infusion (last 3 days)	Total cocaine intake (14 SA days)	Rats
1	*VEH*	197 ± 21	17 ± 13	30 ± 3.7	161 ± 19	N = 5
	Tat-NR2B9c	158 ± 11	20 ± 11	29 ± 2.0	171 ± 9	N = 5
2	*VEH*	242 ± 90	5 ± 1.6	32 ± 4.1	181 ± 18	N = 6
	Tat-NR2B9c	158 ± 35	7 ± 1.6	27 ± 4.6	182 ± 23	N = 6

Data are presented as mean ± SEM. SA- self-administration; VEH- vehicle.

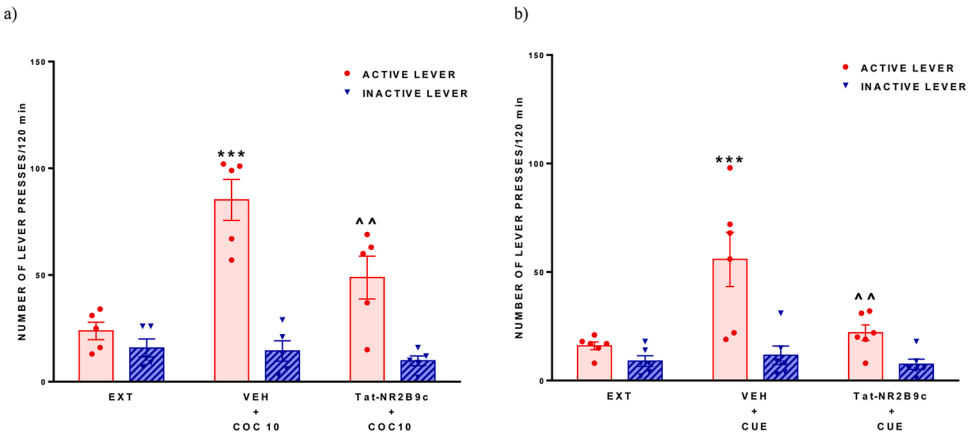

Fig. 2. Effects of repeated administration of Tat-NR2B9c (7.8 mg/kg/day, 3 times, *i.v.*) or vehicle (VEH; *i.v.*) on **a)** cocaine (COC; 10 mg/kg, *i.p.*)- or **b)** CUE (lights + tone)-induced seeking-behaviour in rats. The numbers of „active" and „inactive" lever presses are expressed as the means (± SEM) of the data from 5-6 rats/group. EXT – mean of last three extinction training sessions. ***p < 0.001 vs EXT; ^^p < 0.01 vs VEH + COC 10 or VEH + CUE.

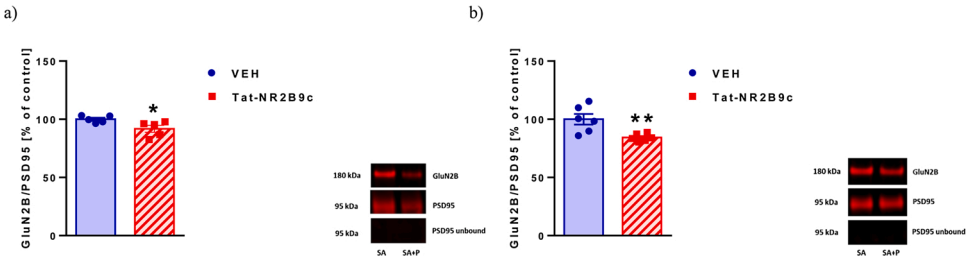

Fig. 3. The interaction between PSD95 and GluN2B subunit in the vHIP after Tat-NR2B9c (7.8 mg/kg/day, 3 times, *i.v.*) administration during **a)** cocaine-induced and **b)** cue-induced reinstatement in rats previously self-administered cocaine following cocaine abstinence with extinction training. Representative membranes are presented. All data are expressed as the mean ± the SEM. N = 5-6 rats/group. vHIP- ventral hippocampus. *p < 0.05, **p < 0.01 vs. vehicle (VEH).

administration that underwent cocaine abstinence followed by extinction training. We found that Tat-NR2B9c attenuated the reinstatement of active lever presses induced by either a priming dose of cocaine or drug-associated conditioned stimuli. Since we had previously shown that the GluN2B/PSD95 complex was increased in the vHIP of rats that previously self-administered cocaine following cocaine abstinence with extinction training [9], we decided to use Tat-NR2B-9c peptide, a PSD95 inhibitor that disrupts the interaction of PSD95 with GluN2B specifically designed to disrupt protein interactions between PSD95 and GluN2B without interfering with the function of the NMDA receptor ion channel [18] to evaluate its potential role in cocaine-induced reinstatement. In line with our hypothesis, we found that the peptide reduced the formation of the GluN2B/PSD95 complex in the vHIP in rats that previously self-administered cocaine.

The possibility that this mechanism could be critical for the attenuation of the reinstatement of cocaine-seeking behavior in these rats is corroborated by our previous data showing that administration of a GluN2B subunit antagonist, CP 101,606 either systemically or directly into the vHIP, attenuated the reinstatement of active lever presses induced by a priming dose of cocaine and by the drug-associated combined conditioned stimuli [9]. Previously, we have shown that the levels of the GluN2B subunit (gene and protein) in the whole homogenate and PSD fraction and GluN2B/PSD95 complex were increased in the vHIP suggesting increased synthesis of this subunit and a cocaine-induced modification in intracellular glutamate receptor trafficking in this structure in rats previously self-administered cocaine following cocaine abstinence with extinction training [9]. Moreover, CP 101,606, a GluN2B subunit antagonist, administered peripherally or into the vHIP attenuated the reinstatement of active lever presses induced by a priming dose of cocaine and by the drug-associated combined conditioned stimuli presumably as a consequence of the reduction of the GluN2B/PSD95 complex in the vHip [9]. Ten-day extinction training increased insertion of the GluN2B subunits to the cellular cytoskeleton via interaction with cytoskeletal protein PSD95, while Tat-NR2B9c disrupts this altered interaction and attenuates the cocaine-seeking behavior in rats. The interaction of GluN2B subunit with PSD95 is involved in dynamic processes for the regulation of synaptic function and signal transduction. However, Tat-NR2B9c was designed to disrupt protein interactions involving PSD95 in the NMDA receptor signaling complex while not interfering with the function of the NMDA receptor ion channel [18].

Blocking the interactions of the NMDA receptor with downstream signaling molecules may be an alternative approach to classical NMDA antagonists for the neurotoxicity induced by excitotoxic NMDA receptor signaling via calcium-dependent cascade and the production of nitric oxide. In fact, Tat-Nr2B9c also inhibits the interaction of PSD95 with the neuronal nitric oxide synthase (nNOS) [19]. Additionally, Tat-NR2B9c may promote the formation of a neurexin-1-neuroligin-1-PSD95 complex [19], reduce neuronal death and degeneration, as well as decrease the matrix metalloproteinase 9 activity and inflammatory processes improving the cognitive and learning ability in rats [19]. So, the beneficial effect of Tat-NR2B9c o the cocaine-seeking behavior may be also associated with the effect of this peptide on several mechanism in rat brain.

5. Conclusions

In conclusion, this is the first study in which a potential application of Tat-Nr2B9c during cocaine abstinence was tested in rats. Our findings indicate that blocking the interaction of the GluN2B/PSD95 complex in the vHIP may be instrumental to attenuate the reinstatement of cocaine seeking behavior, thus representing a potential therapeutic approach to

reduce relapse rates. These data are strengthened by the evidence that the effect of Tat-Nr2B9c has been investigated on reinstatement induced by a priming dose of cocaine or by drug-associated conditioned stimuli, i.e. two procedures that closely mimic the conditions that precipitate relapse in humans. In addition, these findings further support the critical role of specific glutamate dynamics in the regulation of cocaine reinstatement.

Author contributions

I.S.- Data curation; Formal analysis; Methodology; Validation; Visualization; Writing - original draft; Writing - review & editing. K. Wydra- Formal analysis; Methodology; Validation; Visualization; Writing - review & editing; K.Witek, P.S., A.S., and R.P.- Formal analysis. L.C., F.F., and M.S.- Conceptualization; Data curation; Investigation; Methodology; Writing - review & editing. M.F.- Conceptualization; Data curation; Funding acquisition; Investigation; Supervision; Writing - review & editing.

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Declaration of Competing Interest

The authors report no declarations of interest.

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