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REVIEW ARTICLE

Cocaine-induced Changes in the Expression of NMDA Receptor Subunits

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Abstract: Cocaine use disorder is manifested by repeated cycles of drug seeking and drug taking. Cocaine exposure causes synaptic transmission in the brain to exhibit persistent changes, which are poorly understood, while the pharmacotherapy of this disease has not been determined. Multiple potential mechanisms have been indicated to be involved in the etiology of cocaine use disorder. The glutamatergic system, especially N-methyl-D-aspartate (NMDA) receptors, may play a role in several physiological processes (synaptic plasticity, learning and memory) and in the pathogenesis of cocaine use disorder. The composition of the NMDA receptor subunits changes after contingent and noncontingent cocaine administration and after drug abstinence in a region-specific and time-dependent manner, as well as depending on the different protocols used for cocaine administration. Changes in the expression of NMDA receptor subunits may underlie the transition from cocaine abuse to dependence, as well as the transition from cocaine dependence to cocaine withdrawal. In this paper, we summarize the current knowledge regarding neuroadaptations within NMDA receptor subunits and scaffolding proteins observed following voluntary and passive cocaine intake, as well as the effects of NMDA receptor antagonists on cocaine-induced behavioral changes during cocaine seeking and relapse.

Keywords: Cocaine use disorder, contingent cocaine administration, noncontingent cocaine administration, NMDA receptor, NMDA receptor subunit, scaffolding protein.

1. INTRODUCTION

Glutamate is a primary excitatory neurotransmitter in the Central Nervous System (CNS) that can activate ionotropic receptors and/or metabotropic receptors. The glutamatergic system (glutamate levels, receptor and transporter expression) controls processes involved in learning, memory, habit forming, salience attribution and inhibitory control, which are disrupted during addiction [1]. N-methyl-D-aspartate (NMDA) receptors are glutamate-gated ion channels which, together with kainate and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, form a group of ionotropic glutamate receptors [2]. NMDA receptors play a significant role in several physiological processes, including synaptogenesis, synaptic plasticity, learning and memory. As such, these receptors are of major interest for their role in the pathogenesis of several CNS disorders, including substance use disorder (drug addiction) [3]. Substance use disorder is a serious and relapsing psychiatric disorder, consisting of the transition from episodic drug use to compulsive use and loss of control over drug intake.

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NMDA receptors are tetrameric (di- or tri-heteromeric) protein complexes composed of two obligatory GLUN1 subunits binding glycine and two GLUN2 (A-D) subunits binding glutamate. GLUN1 can also assemble with the third type of subunit, GLUN3 (A-B), but this type of complex only possesses a glycine binding site and does not functionally open NMDA channels [4]. The GLUN1 subunit is encoded by a single gene with eight distinct isoforms, with the GLUN2 subunit encoded by four separate genes and the GLUN3 subunit encoded by two different genes. NMDA receptor subunits are composed of four distinct domains: the N-terminal domain, the agonist-binding domain, the transmembrane domain (ion channel) and an intracellular C-terminal domain [5]. Under physiological conditions, NMDA receptors require the binding of both endogenous glutamate and the coagonist glycine, as well as depolarization of the cell membrane, which relieves the voltage-dependent block of the channel pore by magnesium (Mg^{2+}) [6]. NMDA receptor activation results in the opening of channel pores permeable to sodium (Na^{+}), potassium (K^{+}) and calcium (Ca^{2+}) (Fig. **1**). NMDA-mediated Ca^{2+} ion influx into dendritic spines drives synaptic plasticity phenomena, such as long-term potentiation (LTP) and long-term depression (LTD), as well as neuronal differentiation and excitotoxicity [7].

NMDA receptors show postsynaptic, perisynaptic, extrasynaptic and presynaptic localization in the CNS [8]. The

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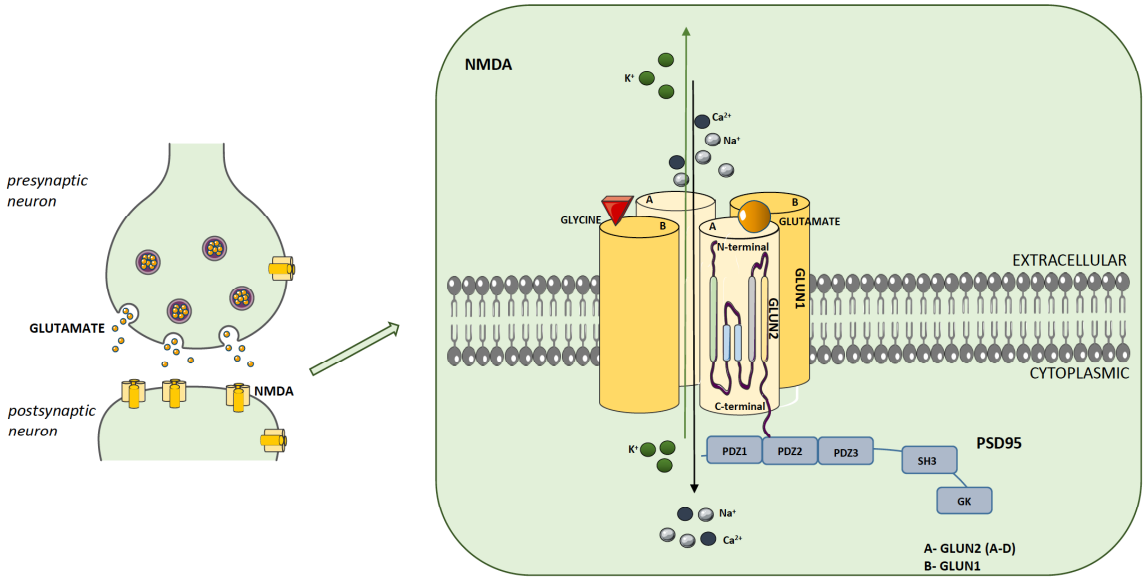

Fig. (1). Schematic illustration of NMDA receptors. Glutamate is released into extracellular and acts on NMDA receptors. NMDA receptors are found both pre- and postsynaptycally. Functional receptors in the CNS are formed mainly by tetrameric assemblies of two GLUN1 and two GLUN2 subunits which express the glycine and glutamate recognition sites, respectively. All NMDA receptors are permeant to Ca^{2+}, Na^{+} and K^{+}. In postsynaptic neuron NMDA receptors are stabilized by the scaffolding protein PSD95, composed by PDZ (PSD95, Drosophila discs large, and the adherens junction protein, Zonula occludens-1), SH3 (SRC Homology 3) and GK (guanylate kinase) domains. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

composition of the different receptor subtypes confers different biophysical and functional properties to NMDA receptors (*i.e.*, ion permeation, channel opening kinetics, localization to synaptic versus extrasynaptic membranes, protein–protein interactions, membrane trafficking and synaptic plasticity) [9]. NMDA receptors containing GLUN2A and GLUN2B differ in localization and function, namely, the former show synaptic localization and faster kinetics, and the latter show extrasynaptic localization and slower kinetics. In many brain regions, a phenotype of newborn excitatory synapses with an increased number of dendritic spines is characterized by the prevalence of GLUN2B-containing NMDA receptors. The GLUN2B subunit in such "immature" synapses is replaced by the GLUN2A subunit, which switches the maturation of excitatory synapses [10]. However, recent findings indicate that GLUN1/GLUN2A and GLUN1/GLUN2B complexes contribute to both synaptic and extrasynaptic pools of NMDA receptors, especially at later neurodevelopmental stages. The stoichiometric GLUN2B/2A NMDA receptor ratio seems to control the direction of synaptic plasticity (*i.e.*, potentiation or depression). Recent data suggest that an increase in the relative weight of GLUN2B subunits in synaptic NMDA receptors facilitates the induction of LTP at excitatory synapses *via* calmodulin-dependent protein kinase II (CamKII) or of LTD in hippocampal pyramidal neurons by Rac and p38 pathways. Conversely, GLUN2A-containing NMDA receptors induce Ras-GRF2-dependent LTP in hippocampal neurons [10, 11]. Furthermore, by using transgenic animals, it was found that the GLUN2A and GLUN2B subunits play a role in synaptic localization and clustering of NMDA receptors, while the GLUN1 receptor subunit plays an active role in controlling the delivery of NMDA receptors to synapses [11]. Interestingly, it was found that NMDA receptors composed of GLUN1/GLUN2B subunits form silent synapses (*i.e.*, NMDA-receptor-only synapses without AMPA receptors in which the activation of presynaptic fibers failed to trigger postsynaptic responses). In other words, GLUN1/GLUN2B subunits generate a form of metaplasticity, efficient to prime synapses to subsequent long-lasting plastic changes, such as LTP [10, 11]. The GLUN2 subunits modulate the electrophysiological properties of the NMDA receptors. GLUN2B has considerably slower deactivation kinetics than GLUN2A, while GLUN2D has even slower deactivation kinetics than GLUN2B [7]. Therefore, GLUN2D subunits remain open longer than GLUN2B and GLUN2A, which increases charge transfer and Ca^{2+} signaling [12]. GLUN2C-, GLUN2D- and GLUN3-containing NMDA receptor subunits are relatively less sensitive to Mg^{2+} blockade [13]. The GLUN2D subunits are largely expressed in cholinergic neurons of both dorsal and ventral striatum whereas GLUN2C is below detection level in the striatum [14].

In postsynaptic densities, NMDA receptors are structurally organized in a large macromolecular signaling complex consisting of scaffolding/adaptor proteins [8]. The membrane-associated guanylate kinase (MAGUK) family of proteins (*e.g.*, PSD95, PSD93, SAP102, and SAP97) link the receptors to the cellular cytoskeleton, where they are subject to dynamic processes for the regulation of synaptic function. The scaffolding protein primarily serves as a receptor anchor; however, recent studies have demonstrated its role in the regulation of intracellular signaling and internalization. Through many protein-interacting domains, the PSD proteins are able to regulate directly and/or indirectly the dynamics of postsynaptic receptors, thereby impacting neuroplasticity as glutamatergic neurotransmission takes place primarily at the postsynaptic densities.

Changes in NMDA receptor subunit composition may underline the transition from cocaine abuse to dependence, as well as the transition from cocaine dependence to cocaine withdrawal. The development of drug craving by enhancing the incentive motivational value of cocaine is accompanied by enduring different neuronal changes within glutamate signaling. In fact, the AMPA/NMDA receptor-mediated current ratio (an electrophysiological measure of LTP) was increased in the ventral tegmental area (VTA) of dopaminergic neurons [15] and in the nucleus accumbens [16] after contingent cocaine administration but not after passive cocaine administration. This persistent synaptic enhancement is resistant to behavioral extinction (even after 90 days of cocaine withdrawal) [7, 15, 16]. Therefore, changes in the NMDA receptor subunit composition may represent a potential cellular mechanism leading to pathological drug-seeking behavior.

The present review will summarize the current knowledge on the roles of the NMDA receptor subunit composition in contingent and noncontingent cocaine administration and in abstinence and will discuss new directions in studies of addiction based on a more comprehensive understanding of molecular determinants related to the glutamatergic system that participate in this brain disorder.

2. EFFECT OF COCAINE ON THE NMDA RECEPTOR SUBUNIT COMPOSITION

2.1. Noncontingent Cocaine Administration

2.1.1. Acute Cocaine Administration

In preclinical studies, it was shown that acute administration of cocaine increased the expression of NMDA subunits in the VTA, and cocaine induced an increase in tyrosine phosphorylation (activity of Fyn and Src kinases) of the GLUN2A subunit but not the GLUN2B subunit in juvenile Sabra rats [17]. Interestingly, other researchers showed that the expression of NMDA subunits did not change after acute cocaine administration in this structure [18, 19]. The differences in the NMDA receptor subunit expression may be connected with the different animal strains used in the study (Sabra rats [17] vs. Sprague Dawley rats [18, 19]), the age of rats (4-5 weeks [17] *vs*. 8-10 weeks old [18, 19]) or the time of measurement of the expression after a single cocaine injection (15 min [17] *vs*. 16 h [18] or 24 h [19]). In contrast, acute cocaine injection during the cocaine sensitization protocol reduced the GLUN1 mRNA level in the nucleus accumbens core, dorsolateral striatum and VTA [20], as well as the levels of mRNA for all NMDA receptor subunits examined in the prefrontal cortex [21]. The first exposure to cocaine may induce glutamate release in the prefrontal cortex-nucleus accumbens pathway followed by a depression of the activity of glutamate prefrontal cortex neurons [22]. Another study showed that acute cocaine (20 and 40 mg/kg) injection reduced the phosphorylation of the GLUN2B subunit in striatal neurons [23]. Conversely, the level of GLUN1 subunit mRNA was observed to increase in the hippocampal fields 1 h after a single cocaine injection, while other NMDA receptor subunits did not change in any examined structures [19, 24].

Inhibition of GLUN2A-containing NMDA receptors by **[**[[(1S)-1-(4-bromophenyl)ethyl]amino](1,2,3,4-tetrahydro-2,3-dioxo-5-quinoxalinyl)methyl] phosphonic acid tetrasodium hydrate (NVP-AAM077) or GLUN2B-containing NMDA receptors by (1R*,2S*)-erythro-2-(4-benzylpiperidino)-1-(4-hydroxyphenyl)-1-propanol hemi-(DL)-tartrate (ifenprodil) blocked the cocaine-induced increase in the AMPA/NMDA receptors current ratio and LTP in the VTA neurons following a single cocaine injection [25].

2.1.2. Repeated Cocaine Administration

A lack of changes in GLUN2A and 2B expression was observed in the VTA after repeated cocaine injections [18, 19]. At the same time, the level of the GLUN1 subunit was increased in the VTA but not in other regions of mesolimbic and nigrostriatal dopaminergic systems, which may contribute to an increased excitability of VTA dopaminergic neurons [18]. Another paper showed that one day after cocaine sensitization, a rise of the GLUN1 subunit levels in the VTA was reported [26]. Elevated levels of GLUN1 subunit expression were observed immediately (16 h or 24 h) after 7 days of cocaine administration; in contrast, repeated cocaine administration and then 21 days of resting, and the cocaine priming dose evoked a reduction in the GLUN1 mRNA level in the VTA and striatum [20]. Cocaine administered repeatedly evoked a long-term augmentation in the capacity of a single cocaine injection to increase the glutamate level in the VTA [27]. A decrease of the GLUN1 mRNA level in this structure may constitute a compensatory down-regulation in response to elevated synaptic concentrations of glutamate [20]. The same compensatory mechanism was most likely also observed in the nucleus accumbens [28], where the GLUN1 mRNA level was decreased after repeated cocaine treatment [29]. Cocaine treatment during conditioned place preference (CPP) paradigm reduced the accumbal GLUN2B subunit levels, which can impair NMDA receptor-dependent LTD (NMDA receptor postsynaptic hypofunction with reduced Ca^{2+} influx) in the nucleus accumbens of cocaine-treated rats [30]. In contrast, increased GLUN1 subunit levels were observed on the surface of the accumbal tissues after repeated cocaine treatment, which reflected the functional and active NMDA receptors [31]. Concomitantly, the surface and total levels, as well as the surface/total ratio, of GLUN2B subunits but not GLUN2A subunits were significantly increased in repeated cocaine-treated rats. The authors [31] proposed that (i) cocaine selectively shifted NMDA receptors containing GLUN2B subunit into the cell surface and that (ii) cocaine induced the synthesis of new GLUN2B subunits. These data seem to support the cocaine-induced generation of silent synapses in the nucleus accumbens shell and to provide support for its role in addiction-related learning and memory [31]. These data parallel observations of the new silent synapses in the nucleus accumbens shell of young (30 d old) rats, when GLUN2B levels were increased by induction of cAMP response element-binding protein (CREB)-dependent transcription of GLUN2B and synaptic incorporation of GLUN2B-containing receptors [32]. Furthermore, 2 weeks of resting in cocaine-sensitized rats induced an increase in GLUN2B expression in the nucleus accumbens shell after a priming dose of cocaine administration [33].

Additionally, phosphorylation of the Tyr1472 residue of the GLUN2B subunit was decreased in rats sensitized to cocaine in the nucleus accumbens core [33]. Tyrosine phosphorylation of the GLUN2B subunit plays a role in the regulation of channel activity and in the modulation of intracellular signaling through the interaction of the receptor with SH2 domain-containing molecules [34].

Mice repeatedly exposed to cocaine only displayed an increase in GLUN2C subunit expression in the prefrontal cortex. However, in cocaine-sensitized mice primed with cocaine, a decrease of GLUN2, observed after acute cocaine injection, was fully reversed [21]. In animals repeatedly treated with cocaine during adolescence, rats sensitized the glutamatergic synapses in the medial prefrontal cortex to stress and evoked different changes in glutamatergic signaling (glutamate release, fall of the glutamate transporters or rise in the GLUN1 subunit postsynaptic responsiveness) [35]. However, cocaine-induced glutamatergic rearrangements (increase in the number of dendritic spines and impaired postsynaptic glutamate signaling) occurred even after a single dose of cocaine in the adolescent medial prefrontal cortex, while they were not observed in adult rats [36].

Training by daily escalating doses of cocaine produced an increase in the hippocampal levels of GLUN2B (mRNA and protein) compared with training by a fixed daily dose of cocaine during CPP in mice 24 h after conditioning [37]. Increased hippocampal GLUN2B subunit levels may have the potential to carry greater Ca^{2+} current per unit charge, which may potentiate the influence on downstream signaling cascades that affect synaptic plasticity and learning and memory [38]. In rats, passively administered cocaine ("yoked" cocaine rats) associated with cocaine self-administration, the increased levels of the NMDA receptor subunits (GLUN1, GLUN2A and GLUN2B) and scaffolding proteins (SAP102 and SAP97) in the postsynaptic density fraction of the hippocampus were reported [39], while a decrease in GLUN1 subunit expression was observed in the dorsal striatum in "yoked" cocaine rats [3] (Table **1**).

In conclusion, these results indicate that repeated passive cocaine administration is associated with several region-specific changes within the NMDA receptor subunit composition, which may contribute to long-lasting neuroadaptation and behavioral sensitization, as well as difficulties encountered with the reversal of cocaine-induced behavioral changes.

2.1.3. Cocaine Abstinence

Three or 14 days of cocaine abstinence after repeated drug administration resulted in marked elevation in the GLUN1 subunit levels in the VTA [40]. Neuroanatomical changes in the VTA may persist even in the late stages of withdrawal from cocaine and may reflect a more permanent adaptation. The level of GLUN1 gene expression did not change on the last day of noncontingent cocaine administration, whereas the extinction induced an increase in GLUN1 mRNA level after 1 and 5 days of withdrawal and returned to control in the forebrain regions on day 10 in Lewis rats [41]. Early withdrawal (24 h) from repeated cocaine treatment provoked a reduction in the cortical and striatal levels of GLUN2B subunit mRNA and in the levels of GLUN1 subunit mRNA in the striatum, cortices, nucleus accumbens, globus pallidus, and subiculum, and these mRNA levels returned to the control level after 7 days of abstinence, while one week of withdrawal evoked a reduction in the GLUN2C subunit mRNA level in the cerebellum [24]. Two weeks of withdrawal from repeated cocaine injections did not change the level of GLUN2B in the dorsal striatum and nucleus accumbens, but an increasing trend was observed when both GLUN2A/B subunits were measured, suggesting that new GLUN2B-containing silent synapses were replaced by GLUN2A-containing synapses after longer withdrawal periods [42]. Repeated cocaine injections increased the accumbal subunits of NMDA receptors (in synaptosomal membranes and homogenate) 3 weeks but not 1 day after cocaine abstinence [43]. Therefore, changes in the nucleus accumbens seem to be often more persistent and evident after longer withdrawal times. However, 1 day after cocaine abstinence, NMDA receptor subunits internalized into nucleus accumbens neurons in a Ca^{2+}-dependent manner, which has been shown in decreased levels of NMDA receptor subunits in the synaptosomal membranes and in increased levels of these subunits in the light membrane fraction [43]. These internalization occurred after repeated cocaine exposure as a result of raised cocaine-induced glutamate levels [20, 43]. Similar changes were observed after 24 h, 72 h and 2 weeks of withdrawal from repeated cocaine injections in cortical areas, where a rise in GLUN2B expression was found, as well as in the neostriatum and nucleus accumbens, after 2 weeks of withdrawal [40]. Interestingly, acute withdrawal (24 h) from repeated cocaine administration evoked a fall of the GLUN2B subunit expression in the nucleus accumbens shell, which was replaced at 14 days of withdrawal by significant upregulation in the nucleus accumbens shell and core [40]. Acute withdrawal (30 h) from repeated cocaine did not alter the levels of NMDA subunit expression but reduced the GLUN2A/GLUN2B ratio in the ventral hippocampus, which led to the enhanced output to other structures, such as nucleus accumbens, basolateral amygdala or prefrontal cortex involved in the regulation of anxiety-like behaviors [44]. Moreover, 3 weeks after repeated cocaine injections, the levels of GLUN2B and GLUN2A protein expression were reduced in the nucleus accumbens shell in rats and did not change in B6 mice [45]. When comparing B6 mice and Sprague Dawley rats, increased GLUN2A expression was observed in the hippocampus and dorsal striatum in both species and in the prefrontal cortex in rats at 3 weeks of withdrawal from repeated cocaine administration [45].

Ten-day extinction training resulted in increased GLUN1 subunit expression in the hippocampus and nucleus accumbens in yoked cocaine rats, while GLUN2A protein expression was increased in the prefrontal cortex in those animals [3]. In addition, 10-day cocaine abstinence with extinction training decreased the hippocampal levels of SAP97 in rats not voluntarily taking cocaine [39] (Table **2**).

Taken together, these results indicate that changes in the NMDA receptor subunit after cocaine is administered non-voluntarily seem to be persistent and evident after lengthy withdrawal times. Increased accumbal GLUN2B subunit levels seem to be the most prevailing cocaine-induced effect after long-term withdrawal, suggesting a target for drug

Table 1. Changes in the NMDA receptor subunits and scaffolding proteins after noncontingent and contingent cocaine administration in rodents.

Behavioural Model and Neurochemical Measurement Time	Species	GLUN1	GLUN2A	GLUN2B	GLUN3	Refs.
NONCONTINGENT COCAINE ADMINISTRATION						
Acute						
acute cocaine injection (20 mg/kg; i.p.) measurement: 16 h after injection	Sprague Dawley rats	VTA- ϕ	VTA- ϕ	VTA- ϕ	No data.	[18]
acute cocaine injection (20 mg/kg; i.p.) measurement: 1 h or 24 h after injection	Sprague Dawley rats	**mRNA:** cingulate cortex- ϕ parietal cortex- ϕ temporal cortex- ϕ CA1- ϕ CA2-3- ↑ (1h) striatum- ϕ dentate gyrus- ↑ (1h) thalamus- n.d. cerebellum- ϕ nucleus accumbens- ϕ ventral pallidum- ϕ subiculum- ϕ entorhinal cortex- ϕ	**mRNA:** cingulate cortex- ϕ parietal cortex- ϕ temporal cortex- ϕ CA1- ϕ CA2-3- ϕ striatum- ϕ dentate gyrus- ϕ thalamus- n.d. cerebellum- ϕ nucleus accumbens- ϕ ventral pallidum- ϕ subiculum- ϕ entorhinal cortex- ϕ	**mRNA:** cingulate cortex- ϕ parietal cortex- ϕ temporal cortex- ϕ CA1- ϕ CA2-3- ϕ striatum- ϕ dentate gyrus- ϕ thalamus- ϕ cerebellum- n.d. nucleus accumbens- ϕ ventral pallidum- n.d. subiculum- ϕ entorhinal cortex- ϕ	No data.	[24]
acute cocaine injection (15 mg/kg; i.p.) measurement: 15 min after injection	Sabra rats	VTA- ↑	VTA- ↑	VTA- ↑	No data.	[17]
acute cocaine injection (10 mg/kg; i.p.) measurement: 40 min or 24 h after injection	Sprague Dawley rats	VTA- ϕ nucleus accumbens- ϕ dorsal striatum- ϕ	VTA- ϕ nucleus accumbens- ϕ dorsal striatum- ϕ	VTA- ϕ nucleus accumbens- ϕ dorsal striatum- ϕ	No data.	[19]
Repeated						
repeated cocaine injections (20 mg/kg; once a day; 7 days; i.p.) measurement: 16 h after last injection	Sprague Dawley rats	VTA- ↑	VTA- ϕ	VTA- ϕ	No data.	[18]
repeated cocaine injections (15 mg/kg; twice daily; 14 days; i.p.) measurement: 16 h after last injection	Sprague Dawley rats	VTA-↑ frontal-parietal cortex- ϕ medial prefrontal cortex- ϕ posterior cingulate cortex- ϕ striatum- ϕ nucleus accumbens- ϕ hippocampus- ϕ substantia nigra- ϕ	VTA- ϕ	VTA- ϕ	No data.	[18]

(Table 1) contd….

Behavioural Model and Neurochemical Measurement Time	Species	GLUN1	GLUN2A	GLUN2B	GLUN3	Refs.
NONCONTINGENT COCAINE ADMINISTRATION						
Repeated						
repeated cocaine injections (15 mg/kg; once a day; 5 days; i.p.) measurement: 24 h after last injection	Sprague Dawley rats	nucleus accumbens shell- ↑ (surface and surface:total ratio)	nucleus accumbens shell- ϕ	nucleus accumbens shell- ↑ (surface, total and surface:total ratio) (surface, total and surface:total ratio)	No data.	[31]
repeated cocaine injections (15 mg/kg; once a day; 5 days; i.p.) measurement: 24 h after last injection	Sprague Dawley rats	No data.	nucleus accumbens shell- ϕ	nucleus accumbens shell- ↑	No data.	[32]
repeated cocaine injection (10 mg/kg; 7 days; i.p.) measurement: 40 min after last injection	Sprague Dawley rats	VTA- ϕ nucleus accumbens- ϕ dorsal striatum- ϕ	VTA- ϕ nucleus accumbens- ϕ dorsal striatum- ϕ	VTA- ϕ nucleus accumbens- ϕ dorsal striatum- ϕ	No data.	[19]
Cocaine Sensitization						
cocaine sensitization (1 day- 15 mg/kg; 2-6 days- 30 mg/kg; 7 day- 15 mg/kg; 21 day of withdrawal) measurement: 24 h or 3 weeks after last injection	Sprague Dawley rats	VTA- ↑ (1 day but not at 3 weeks of withdrawal)	No data.	No data.	No data.	[26]
cocaine sensitization (**acute**- saline (1-8 days) – cocaine (15 mg/kg) (29 day) **repeated**- cocaine (15-30 mg/kg) (1-8 days) – saline (29 day); cocaine (15-30 mg/kg) (1-8 days) – cocaine (15 mg/kg) (29 day)) measurement: 24 h after last injection	Sprague Dawley rats	**mRNA:** VTA- ↓ (acute and repeated) nucleus accumbens shell- ϕ nucleus accumbens core- ↓ (acute) dorsolateral striatum- ↓ (acute and repeated) prefrontal cortex- ϕ	No data.	No data.	No data.	[20]
cocaine sensitization (1 day- 7.5 mg/kg, s.c.; 2-5 days- 40 mg/kg, s.c.; 18 days of withdrawal; 7.5 mg/kg, s.c.) measurement: 1 h after last injection	Sprague Dawley rats	No data.	No data.	prefrontal cortex- ϕ nucleus accumbens core- ϕ nucleus accumbens shell-↑ caudate- ϕ amygdala- ϕ	No data.	[33]
cocaine sensitization (1-2 days- handling; 3-7 days - 20 mg/kg; once a days; i.p.; 8-12 days- resting; 14 day- priming dose- 10 mg/kg) measurement: 1 h after last injection	C57BL/6J mice	prefrontal cortex- ↓ (vehicle-cocaine)	prefrontal cortex- ↓ (vehicle-cocaine); ↑ (cocaine-cocaine)	prefrontal cortex- ↓ (vehicle-cocaine) **GLUN2C:** prefrontal cortex- ↓ (vehicle-cocaine); ↑ (cocaine-vehicle; cocaine-cocaine)	No data.	[21]

(Table 1) contd….

Behavioural Model and Neurochemical Measurement Time	Species	GLUN1	GLUN2A	GLUN2B	GLUN3	Refs.
NONCONTINGENT COCAINE ADMINISTRATION						
Conditioned Place Preference (CPP)						
CPP (15 mg/kg; 7 days; i.p.; 14 days of withdrawal; cocaine 7.5 mg/kg) measurement: 1 h after last injection	Sprague Dawley rats	nucleus accumbens- ϕ	nucleus accumbens- ϕ	nucleus accumbens- ↓	No data.	[30]
CPP **Fix-C**- fixed daily dose of cocaine (4 days by 11.25 mg/kg) **Esc-C**- daily escalating doses of cocaine (3,6,12,24 mg/kg; 1 dose/day) measurement: 24 h after last injection	C57BL/6J mice	hippocampus- ϕ	hippocampus- ϕ	hippocampus- ↑ Fix-C; ↑ Esc-C (protein) hippocampus- ↑ Esc-C (mRNA)	No data.	[37]
CONTINGENT COCAINE ADMINISTRATION						
cocaine binge access (cocaine self-administration (0.5 mg/kg/infusion; 8-h/day; 14 days); cocaine binge- multiple 3h self-administration; 1h time outs; 6 days) measurement: 0 h after last session	Sprague Dawley rats	VTA- ϕ substantia nigra- ↑ nucleus accumbens- ϕ striatum- ↑ prefrontal cortex- ϕ	No data.	VTA- ϕ substantia nigra- ϕ nucleus accumbens- ϕ striatum- ↑ prefrontal cortex- ϕ	3A: nucleus accumbens- ϕ striatum- ↑ prefrontal cortex- ϕ 3B: nucleus accumbens- ϕ striatum- ↑ prefrontal cortex- ϕ	[49]
cocaine self-administration (0.5 mg/kg/infusion; 8-h/day; 15 days) measurement: 16 h after last session	Sprague Dawley rats	VTA- ↓SA nucleus accumbens- ϕ medial prefrontal cortex- ↑SA substantia nigra- ϕ dorsal caudate-putamen- ↑SA	VTA- ϕ nucleus accumbens- ϕ medial prefrontal cortex- ϕ substantia nigra- ϕ dorsal caudate-putamen- ↑SA	nucleus accumbens- ϕ medial prefrontal cortex- ϕ dorsal caudate-putamen- ↑SA	**GLUN3A and 3B:** nucleus accumbens- ϕ medial prefrontal cortex- ϕ dorsal caudate-putamen- ϕ	[48]
cocaine self-administration (0.5 mg/kg/infusion; 2-h/day; 14 days) measurement: 0 h after last session	Wistar rats	hippocampus- ϕ (homogenate); ↑YC, ↑SA (post-synaptic density)	hippocampus- ϕ (homogenate); ↑YC, ↑SA (post-synaptic density)	hippocampus- ϕ (homogenate); ↑YC, ↑SA (post-synaptic density)	No data.	[39]
				SCAFFOLDING PROTEINS: **SAP102:** hippocampus- ↑YC (homogenate); ↑YC, ↑SA (post-synaptic density) **SAP97:** hippocampus- ϕ (homogenate); ↑YC, ↑SA (post-synaptic density) **PSD95:** hippocampus- ϕ (homogenate); ϕ (post-synaptic density)	
cocaine self-administration (0.5 mg/kg/infusion; 2-h/day; 16 days) measurement: 0 h after last session	Wistar rats	prefrontal cortex- ϕ hippocampus- ↑SA dorsal striatum- ↓YC nucleus accumbens- ϕ	prefrontal cortex- ϕ hippocampus- ϕ dorsal striatum- ↑SA nucleus accumbens- ϕ	prefrontal cortex- ϕ hippocampus- ϕ dorsal striatum- ϕ nucleus accumbens- ϕ	No data.	[3]

Abbreviations: ϕ- no changes; ↑- increase; ↓- decrease; h- hour; i.p.- intraperitoneal; i.v.- intravenous; SA- self-administered group; s.c.- subcutaneous; YC- "yoked" cocaine group; VTA- ventral tegmental area.

Table 2. Changes in the NMDA receptor subunits and scaffolding proteins after withdrawal from noncontingent and contingent cocaine administration in rodents.

Behavioural Model	Species	GLUN1	GLUN2A	GLUN2B	GLUN3	Refs.
NONCONTINGENT COCAINE ADMINISTRATION						
24 h, 72 h and 14 days of withdrawal from repeated cocaine injections (15 mg/kg; once a day; 7 days; i.p.)	Sprague Dawley rats	VTA- ↑ (72 h and 14 days)	No data.	CA1, CA3, or dentate gyrus of hippocampus- ϕ dorsolateral neostriatum- ↑ (14 days) medial frontal cortex- ↑ (24 h, 72 h and 14 days) nucleus accumbens shell- ↓ (24 h), ↑ (14 days) nucleus accumbens core- ↑ (14 days) lateral frontal cortex- ↑ (72 h and 14 days) parietal cortex- ↑ (72 h and 14 days)	No data.	[34]
24 h, 7 days of withdrawal from repeated cocaine injections (20 mg/kg; once a day; 14 days; i.p.)	Sprague Dawley rats	**mRNA:** cingulate cortex- ↓(24 h) parietal cortex- ↓(24 h) temporal cortex- ϕ CA1- ϕ CA2-3- ϕ striatum- ↓(24 h) dentate gyrus- ↑(24 h) thalamus- ϕ cerebellum- ϕ nucleus accumbens- ↓(24 h) globus pallidus- ↓(24 h) subiculum- ϕ entorhinal cortex- ↓(24 h) substantia nigra- ϕ	**mRNA:** cingulate cortex- ϕ parietal cortex- ϕ temporal cortex- ϕ CA1- ϕ CA2-3- ϕ striatum- ϕ dentate gyrus- ϕ thalamus- ϕ cerebellum- ϕ nucleus accumbens- ϕ globus pallidus- ϕ subiculum- ϕ entorhinal cortex- ϕ substantia nigra- ϕ	**mRNA:** cingulate cortex- ϕ parietal cortex- ↓(24 h) temporal cortex- ϕ CA1- ϕ CA2-3- ϕ striatum- ↓(24 h) dentate gyrus- ϕ thalamus- ϕ cerebellum- ϕ nucleus accumbens- ϕ globus pallidus- ϕ subiculum- ϕ entorhinal cortex- ϕ substantia nigra- ϕ **GLUN2C:** cerebellum- ↓(7d) No changes in other structures.	No data.	[24]
3 weeks of withdrawal from repeated cocaine injections (30 mg/kg; once a day; 7 days; i.p.)	Sprague Dawley rats	No data.	prefrontal cortex- ↑ hippocampus- ↑ nucleus accumbens shell- ↓ nucleus accumbens core- ϕ dorsal striatum- ↑	prefrontal cortex- ↑ hippocampus- ϕ nucleus accumbens shell- ↓ nucleus accumbens core- ϕ dorsal striatum- ϕ	No data.	[45]
3 weeks of withdrawal from repeated cocaine injections (30 mg/kg; once a day; 7 days; i.p.)	B6 mice	No data.	prefrontal cortex- ϕ hippocampus- ↑ nucleus accumbens shell- ϕ nucleus accumbens core- ϕ dorsal striatum- ↑	prefrontal cortex- ϕ hippocampus- ϕ nucleus accumbens shell- ϕ nucleus accumbens core- ϕ dorsal striatum- ϕ	No data.	[45]
15 days of withdrawal from repeated cocaine injections (15 mg/kg; once a day; 8 days; i.p.)	Sprague Dawley rats	No data.	No data.	nucleus accumbens- ϕ dorsal striatum- ϕ	No data.	[42]

(Table 2) contd….

Behavioural Model	Species	GLUN1	GLUN2A	GLUN2B	GLUN3	Refs.
NONCONTINGENT COCAINE ADMINISTRATION						
1 day or 21 days after cocaine sensitization (15 mg/kg; 5 days; i.p.))	Sabra rats	nucleus accumbens- ↓ (1 d- synaptosomal membranes); ↑ (1 d -light membrane fraction) nucleus accumbens- ↑ (21 d- synaptosomal membranes and homogenate) hippocampus- ϕ	nucleus accumbens- ↓ (1 d- synaptosomal membranes); ↑ (1 d -light membrane fraction) nucleus accumbens- ↑ (21 d- synaptosomal membranes and homogenate) hippocampus- ϕ	nucleus accumbens- ↓ (1 d- synaptosomal membranes); ↑ (1 d -light membrane fraction) nucleus accumbens- ↑ (21 d- synaptosomal membranes and homogenate) hippocampus- ϕ	No data.	[43]
30 h of withdrawal from repeated cocaine injections (20 mg/kg; once a day; 7 days; i.p.)	Sprague Dawley rats	ventral hippocampus- ϕ	ventral hippocampus- ϕ	ventral hippocampus- ϕ	No data.	[44]
0, 1, 5, 10 days of withdrawal from non-contingent cocaine injections (1 mg/kg/inf.; 3 weeks; i.v..)	Lewis rats	**mRNA:** medial prefrontal cortex- ↑ (1 d, 5 d) caudate putamen- ↑ (1 d, 5 d) nucleus accumbens- ↑ (5 d) olfactory tubercle- ↑ (1 d, 5 d) piriform cortex- ↑ (1 d, 5 d, 10 d)	No data.	No data.	No data.	[41]
CONTINGENT COCAINE ADMINISTRATION						
0, 1, 5, 10 days of extinction from contingent cocaine self‑administration (1 mg/kg/inf.; 3 weeks; i.v.)	Lewis rats	**mRNA:** medial prefrontal cortex- ↑ (0 d, 1 d); ↓ (10 d) caudate putamen- ↑ (0 d, 1 d- cont); ↓ (5 d, 10 d- cont) nucleus accumbens- ↑ (0 d- cont); ↓ (5 d, 10 d- cont) olfactory tubercle- ↑ (0 d, 1 d- cont) piriform cortex- ↑ (0 d, 1 d- cont)	No data.	No data.	No data.	[41]
1, 30, 90 days of withdrawal from cocaine self‑administration (1 mg/kg/inf.; 10 days; i.v.)	Long-Evans rats	VTA- ↑ (1 d, 30 d, 90 d) nucleus accumbens- ↑ (1 d, 90 d)	No data.	No data.	No data.	[54]
7 days of withdrawal from cocaine self‑administration (1 mg/kg/inf.; 14 days; i.v.)	Sprague Dawley rats	nucleus accumbens core- ↓ nucleus accumbens shell- ϕ	No data.	No data.	No data.	[58]
14 days of withdrawal from cocaine binge access - cocaine self-administration (0.5 mg/kg/infusion; 8-h/day; 14 days) - cocaine binge-multiple 3h self-administration; 1h time outs; 6 days)	Sprague Dawley rats	VTA- ϕ substantia nigra- ϕ nucleus accumbens- ϕ striatum- ↑ prefrontal cortex- ϕ	No data.	VTA- ϕ substantia nigra- ϕ nucleus accumbens- ϕ striatum- ↑ prefrontal cortex- ↑	**3A:** nucleus accumbens- ϕ striatum- ϕ prefrontal cortex- ↓ **3B:** nucleus accumbens- ϕ striatum- ↑ prefrontal cortex- ϕ	[49]

(Table 2) contd….

Behavioural Model	Species	GLUN1	GLUN2A	GLUN2B	GLUN3	Refs.
CONTINGENT COCAINE ADMINISTRATION						
10-14 days of abstinence from cocaine self-administration (1 mg/kg/infusion; 6-h session; 14 days) Home cage SA box Extinction	Sprague-Dawley rats	**Home cage:** nucleus accumbens shell- ϕ nucleus accumbens core- ϕ dorsolateral striatum- ↓ (total) **SA box:** nucleus accumbens shell- ϕ nucleus accumbens core- ϕ dorsolateral striatum- ↓ (total) **Extinction:** nucleus accumbens shell- ↓ (synaptosomal) nucleus accumbens core- ϕ dorsolateral striatum- ↑ (total and synaptosomal)	No data.	No data. **SCAFFOLDING PROTEIN:** **PSD95:** **Home cage:** nucleus accumbens shell- ϕ nucleus accumbens core- ϕ dorsolateral striatum- ϕ **SA box:** nucleus accumbens shell- ϕ nucleus accumbens core- ϕ dorsolateral striatum- ϕ **Extinction:** nucleus accumbens shell- ↓ (synaptosomal) nucleus accumbens core- ↑ (total) dorsolateral striatum- ϕ	No data.	[57]
1, 14, 60 days of withdrawal from cocaine self-administration (0.25 mg/kg/infusion; 1-h session; 7 days) and - brief access (1h; 10 days) -extended access (6h; 10 days)	Sprague-Dawley rats	No data.	medial prefrontal cortex- ↑ (extended; 60 d) nucleus accumbens core- ϕ nucleus accumbens shell- ϕ VTA- ϕ	medial prefrontal cortex- ↑ (extended; 14 d) nucleus accumbens core- ϕ nucleus accumbens shell- ϕ VTA- ϕ	No data.	[60]
45 days of withdrawal from cocaine self-administration (0.5 mg/kg/infusion; 6-h/day; 10 days)	Sprague Dawley rats	nucleus accumbens- ϕ	nucleus accumbens- ϕ	nucleus accumbens- ϕ	No data.	[53]
1 day of withdrawal from cocaine self-administration (0.25 mg/kg/infusion; 2-h/day; 14 days)	Sprague Dawley rats	nucleus accumbens shell- ϕ	nucleus accumbens shell- ↑	nucleus accumbens shell- ↑	No data.	[56]
1 day of extinction from cocaine self-administration (0.5 mg/kg/infusion; 2-h/day; 14 days)	Wistar rats	hippocampus- ϕ (homogenate); ϕ (post-synaptic density)	hippocampus- ϕ (homogenate); ϕ (post-synaptic density)	hippocampus- ϕ (homogenate); ϕ (post-synaptic density) **SCAFFOLDING PROTEINS:** **SAP102:** hippocampus- ϕ (homogenate); ϕ (post-synaptic density) **SAP97:** hippocampus- ϕ (homogenate); ϕ (post-synaptic density) **PSD95:** hippocampus- ϕ (homogenate); ϕ (post-synaptic density)	No data.	[39]
10 days of extinction from cocaine self-administration (0.5 mg/kg/infusion; 2-h/day; 14 days)	Wistar rats	hippocampus- ϕ (homogenate); ϕ (post-synaptic density)	hippocampus- ϕ (homogenate); ϕ (post-synaptic density)	hippocampus- ϕ (homogenate); ϕ (post-synaptic density) **SCAFFOLDING PROTEINS:** **SAP102:** hippocampus- ϕ (homogenate); ϕ (post-synaptic density) **SAP97:** hippocampus- ↓YC (homogenate); ↓YC (post-synaptic density) **PSD95:** hippocampus- ϕ (homogenate); ϕ (post-synaptic density)	No data.	[39]

(Table 2) contd….

Behavioural Model	Species	GLUN1	GLUN2A	GLUN2B	GLUN3	Refs.
CONTINGENT COCAINE ADMINISTRATION						
13 days of abstinence from cocaine self-administration (0.25 mg/kg/infusion; 1.5 h/day; 4 days) Home cage Extinction	Long-Evans rats	No data.	ventromedial prefrontal cortex- ϕ nucleus accumbens- ↑ home cage; ↑ extinction	ventromedial prefrontal cortex- ϕ nucleus accumbens- ↑ home cage	No data.	[55]
10 days of extinction from cocaine self-administration (0.5 mg/kg/infusion; 2-h/day; 14 days)	Wistar rats	prefrontal cortex- ϕ hippocampus- ↑SA; ↑YC dorsal striatum- ϕ nucleus accumbens- ↑SA; ↑YC	prefrontal cortex- ↑SA; ↑YC hippocampus- ↑SA dorsal striatum- ϕ nucleus accumbens- ϕ	prefrontal cortex- ϕ hippocampus- ↑SA dorsal striatum- ϕ nucleus accumbens- ϕ	No data.	[3]
3, 30 days of withdrawal from cocaine self-administration (0.25 mg/kg/infusion; 6-h/day; 10 days)	Sprague Dawley rats	No data.	dorsomedial prefrontal cortex- ϕ ventromedial prefrontal cortex- ϕ	dorsomedial prefrontal cortex- ↑ (3, 30 d) ventromedial prefrontal cortex- ϕ	No data.	[59]

Abbreviations: ϕ- no changes; ↑- increase; ↓- decrease; h- hour; i.p.- intraperitoneal; i.v.- intravenous; SA- self-administered group; YC- "yoked" cocaine group; VTA- ventral tegmental area.

design. In fact, ifenprodil, a GLUN2B-containing NMDA receptor antagonist, reversed the higher amplitude and decay kinetics of NMDA receptor currents in infralimbic prefrontal pyramidal neurons of male rats. Infralimbic infusions of ifenprodil disrupted consolidation of extinction of the CPP and prevented the enhanced extinction induced by tropomyosin-related kinase B (TrkB) receptor activation [46].

2.2. Contingent Cocaine Administration

2.2.1. Cocaine Self-administration

Voluntary cocaine administration induced different changes within the composition of NMDA receptor subunits. Cocaine self-administration decreased GLUN1 subunit expression in the VTA, which may represent a compensatory mechanism to offset the elevated responsivity of NMDA receptor stimulation to cocaine [47], thereby reducing the excitability of dopamine neurons in the VTA [48]. Furthermore, the increased levels of GLUN2A and 2B whereas no changes in GLUN3A and 3B subunit expression were observed in the dorsal caudate putamen in rats self-administering cocaine, whereas no significant changes in NMDA subunit expression were observed in the mesolimbic pathways [48]. Cocaine self-administration increased GLUN1 subunit expression in the medial prefrontal cortex and dorsal caudate-putamen in rats [48]. Increased levels of the GLUN1 subunit in the prefrontal cortex lead to increased Ca^{2+} permeability in neurons and initiated the long-term synaptic changes associated with cocaine [48]. Binge access to cocaine evoked an increase in the expression of GLUN1, GLUN2B, GLUN3A and GLUN3B in the striatum, and an increase in the GLUN1 subunit expression was observed in the substantia nigra [49], which is part of the nigrostriatal dopamine pathway that does not appear to be involved in the reinforcing effects of cocaine. The increased levels of the NMDA receptor subunits (GLUN1, GLUN2A and GLUN2B) and scaffolding proteins (SAP102 and SAP97) in the postsynaptic density fraction but not in the whole homogenate of the hippocampus were reported in rats self-administering cocaine [39]. It should be emphasized that authors focused on the postsynaptic density, which is a specialized region of the postsynaptic membrane where most glutamate transmission occurs. The NMDA receptor level in the homogenate represents only steady, not dynamic (receptor trafficking), changes. In fact, these data indicated increased cocaine-induced trafficking toward the membrane of NMDA receptors without changing the receptor synthesis [39]. These findings are supported by the study with another cocaine self-administration procedure in which increased GLUN1 and GLUN2A subunit levels were reported in the rat hippocampus and dorsal striatum, respectively, in rats [3] (Table **1**). In cocaine-naïve animals, removal of serotonin transporter (SERT-/-) reduced the mRNA levels of NMDA receptor subunit genes (*GRIN1*, *GRIN2A* and *GRIN2B*) in the habenula, which is the structure involved in motivational and emotional states, such as drug abuse. After short-access (1 h daily, 14 days) or long-access (6 h daily, 14 days) cocaine self-administration, *GRIN1* mRNA levels decreased in SERT+/+ rats to levels equal to those of SERT-/- rats, which supports the role of the increased levels of serotonin in the modulation of glutamate neurotransmission in the habenula [50].

In human postmortem studies, it was shown that the hippocampal expression of *GRIN2B* (encoding GLUN2B) was upregulated in cocaine addicts, while the expression of *GRIN2D* (encoding GLUN2D) was reduced in the hippocampus, of cocaine addicts compared to controls [12]. These data highlighted the role of the GLUN2B subunits in a principal pathway leading to cocaine use disorder [12]. In cocaine overdose victims, the increased expression of the GLUN1 subunit was shown in the VTA but not in the lateral substantia nigra [51] and in the nucleus accumbens but not in the putamen [52]. Parallel changes were also observed in rhesus monkeys self-administering cocaine [52]. The latter changes may indicate the increased excitability due to in-

creased Ca^{2+} flux through NMDA receptors in these structures which, in turn, may induce long-term biochemical and behavioral effects of cocaine in humans.

In conclusion, cocaine administered voluntary may potentiate the NMDA receptor-dependent signaling in the limbic structures involved in the reinforcing and motivational aspects of cocaine, which may be a potential mechanism for contingent cocaine administration.

2.2.2. Cocaine Abstinence

Long drug abstinence (45 days) did not change NMDA receptor subunits in the nucleus accumbens in rats previously administered cocaine [53], while 90-day abstinence provoked a long-lasting increase in the level of GLUN1 subunit expression in the VTA and nucleus accumbens [54]. Thus, the duration of cocaine withdrawal seems to be important for the interpretation of results. In contrast, different forced abstinence conditions may generate several alterations in NMDA receptor subunit composition. In fact, rats housed in isolated conditions during cocaine abstinence had increased accumbal levels of the NMDA receptor subunits (2A and 2B) [55, 56], while in rats subjected to extinction procedures, a decrease in GLUN1 expression in the nucleus accumbens shell [57] and core [58] and a rise in GLUN2A were observed [55], which have a critical role in motor learning, especially for the slow acquisition phase [11]. A synaptosomal decrease in the GLUN1 subunit level was accompanied by a reduction in PSD95 protein expression in the nucleus accumbens shell after extinction training [57]. This decrease reflects the reduced availability of functional NMDA receptors, which suggests that reduced NMDA receptor activity in the nucleus accumbens shell may contribute to extinction [57]. In contrast, 10-day cocaine abstinence with extinction training resulted in increased GLUN1 subunit expression in the homogenate of the nucleus accumbens, which probably did not reflect the functional significance of NMDA receptor alteration in rats with a history of cocaine self-administration [3]. Withdrawal from cocaine binge (3-h sessions with 1-h timeouts for 6 days) access did not change the increased striatal levels of the GLUN1, GLUN2B and GLUN3B subunit protein expression, while the level of GLUN3A subunit returned to the levels of control group [49]. The level of GLUN1 subunit expression was either decreased in the dorsolateral striatum in animals remaining in the home cage and exposed to a self-administration box or increased in rats that underwent extinction training, which is associated with the control of motor learning [57].

Coincidentally, withdrawal from cocaine induced either a rise in GLUN2B expression or a fall in GLUN3A expression in the prefrontal cortex [49]. Cocaine self-administration evoked an increase in GLUN1 gene expression in all forebrain areas, which decreased progressively in the absence of cocaine, except for the olfactory tubercle [41]. Additionally, GLUN2A protein expression was increased in the prefrontal cortex of cocaine self-administered rats after 10 days of abstinence [3]. In contrast, 13 days of cocaine abstinence did not change GLUN2A and GLUN2B protein expression in the ventromedial prefrontal cortex [55], and elevated GLUN2B subunit protein expression was observed in the dorsomedial prefrontal cortex in early and late withdrawal [59]. Extended access to cocaine induced long-lasting increases in the GLUN2A (60 days) and GLUN2B (14 days) subunit expression within the medial prefrontal cortex [60], while in previous research conducted by this group, it was shown that following 20 min of withdrawal from brief access but not extended access to cocaine self-administration induced an increase in the NMDA receptor expression in the ventromedial prefrontal cortex [61]. Taken together, these results indicate that the increased excitability of the prefrontal cortex during withdrawal is likely mediated by the upregulation of different NMDA receptor subunits, which provide similar functional goals.

One-day and 10-day cocaine abstinence with extinction training abolished the cocaine-induced increase in the hippocampal levels of GLUN1, GLUN2A and GLUN2B subunits in the postsynaptic density fraction, which suggests that the trafficking of NMDA receptors toward the membrane was dependent on previous cocaine presence [39]. Increased hippocampal levels of GLUN2A and GLUN2B subunits were observed in rats with a history of cocaine self-administration, which may reflect compensatory mechanisms of cocaine-mediated disturbed neurogenesis and memory-seeking processes in hippocampal cells [3, 62].

In summary, the duration of cocaine withdrawal and abstinence conditions seem to be important factors to trigger changes in NMDA receptor subunit composition.

3. NMDA RECEPTORS AS TARGETS FOR THE TREATMENT OF COCAINE USE DISORDER

3.1. Preclinical Studies

Preclinical behavioral and molecular studies have demonstrated that NMDA receptors are involved in the neuroplasticity associated with drug addiction [10, 56]. NMDA receptors play a significant role in the development of cocaine-induced locomotor activation [63] and cocaine self-administration [63, 64]. However, NMDA receptor antagonists act bidirectionally. In fact, reduction [63, 65] or facilitation [66] of cocaine-induced hyperlocomotion; reduction [67] or induction [68] of sensitization to locomotor effects of cocaine; and attenuation [69] or increase [70] of cocaine self-administration were reported. Pharmacological blockade of NMDA receptors in the nucleus accumbens core or shell promoted the reinstatement of cocaine seeking [71, 72], while NMDA receptor blockade in dopaminergic cells prevented cocaine reinstatement and reduced cocaine preference [73]. Systemic injections of NMDA receptor antagonists attenuated the consolidation of cocaine-cue memories during cocaine CPP or their intra-basolateral amygdala infusions following cocaine-cue associative learning blocked the consolidation of cocaine-cue memories [74]. Other studies indicated disruption of the reconsolidation of drug-cue memories after systemic administration of NMDA receptor antagonists to rodents [75, 76] or administration into the rodents' infralimbic medial prefrontal cortex [77]. In contrast to the latter observation, it was shown that blockade of NMDA receptors impaired extinction learning [55]. Facilitation of extinction learning in animals was shown in rats receiving systemic [78-80] or intra-basolateral amygdala infusions [79] of the partial NMDA receptor agonist, D-cycloserine. D-cycloserine

treatment in the CPP paradigm did not change cocaine-primed reinstatement [81], but it was shown either to reduce spontaneous recovery [82, 83] or increase spontaneous recovery in rodents. However, in cocaine, self-administration of D-cycloserine reduced the reacquisition of cocaine self-administration [84] and cue-induced reinstatement [85].

3.1.1. Preclinical Studies with NMDAR Subtype-selective Compounds

Based on the assumption that NMDA receptors are essential for the development of cocaine-induced locomotor sensitization, NMDA antagonists should alter this process. In fact, intra-accumbal inhibition of GLUN2B-containing NMDA receptors by selective antagonist (α*R*,β*S*)-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol maleate (Ro 25-6981) prevented cocaine-induced locomotor sensitization, probably by inhibition of cocaine-induced silent synapses [32]. Furthermore, inhibition of the GLUN2A subunit during the development of psychomotor sensitization attenuated the enhanced locomotor activity following repeated cocaine injections [25]. Inhibition of GLUN2B-containing NMDA receptors by ifenprodil attenuated the development of cocaine psychomotor sensitization [43]. The GLUN2B-subunit antagonists ifenprodil and CP-101,606 blocked cocaine-induced habits in adult mice with a history of subchronic cocaine exposure in adolescence [86].

At the same time, blockade of the GLUN2B-containing NMDA receptors by ifenprodil reduced the acquisition and reconsolidation of cocaine memory after a fixed daily dose or escalating daily doses of cocaine [37]. Systemic inhibition of GLUN2B-containing NMDA receptors by the selective antagonist Ro 25-6981 prevented cocaine-induced locomotor sensitization and cocaine-induced CPP [87], while eliprodil attenuated expression of cocaine-conditioned motor activity at doses that did not significantly affect spontaneous motor activity [88].

Several lines of evidence have demonstrated changes in NMDA receptors and their subunit expression in cocaine addiction. NMDA receptor-dependent mechanisms are critical for the disturbances in synaptic plasticity and occur during cocaine abstinence; thus, they may serve as new critical biomarkers of drive to cocaine seeking and relapse; however, the published evidence is equivocal. Administration of Ro 25-6981, a GLUN2B subunit antagonist, into the prelimbic cortex of rats blocked the suppressive effect of brain-derived neurotrophic factor (BDNF) on cocaine seeking, as well as blocking BDNF-induced elevation of phosphorylated GLUN2B subunits [89]. Conversely, infusion of Ro 25-6981 into the infralimbic medial prefrontal cortex or nucleus accumbens shell did not alter lever pressing during the extinction retention tests [77]. Although extrasynaptic GLUN2B subunit expression was increased after 1 day of abstinence from cocaine self-administration, GLUN2B subunit blockade by Ro 25-6981 did not change NMDA receptor-mediated currents (functional expression of GLUN2B did not change) [56]. Administration of Ro 25-6981 into the dorsal hippocampus dose-dependently impaired drug context-induced reinstatement of cocaine-seeking behavior without altering instrumental behavior in the extinction context or food-reinforced instrumental responding [90]. In cocaine self-administered rats, it was shown that NMDA-dependent LTD was impaired in the oval bed nucleus of the stria terminalis synapses. This effect could be rescued by Ro 25-6981 or ifenprodil [91]. Blockade of GLUN2B-containing NMDA receptors reduced the correlation between synaptic strength and reinstatement of cocaine-seeking behavior after 30 days of withdrawal from cocaine [91].

Infusion of the GLUN2A-containing NMDA receptor antagonist 3-chloro-4-fluoro-N-[4-[[2-(phenylcarbonyl)hydrazino]carbonyl]benzyl]benzenesulfonamide (TCN-201) into the prelimbic cortex inhibited the BDNF-mediated increase in phospho-GLUN2A [89]. Blocking GLUN2A-containing NMDA receptors by NVP-AAM077 infused into the infralimbic medial prefrontal cortex resulted in reduced lever pressing during the retention test, suggesting that GLUN2A-containing NMDA receptors modulate reconsolidation [77]. The intra-dorsal hippocampus injection of NVP-AAM077 following or in the absence of cocaine-memory reactivation attenuated subsequent drug context-induced cocaine-seeking behavior in a memory reactivation-dependent manner [92]. The same results were observed for the GLUN2B subunit antagonist ifenprodil, which mitigated cue-induced reinstatement of cocaine seeking in mice self-administering cocaine [86]. Ifenprodil administered into the dorsomedial prefrontal cortex lowered cue-elicited cocaine-seeking while potentiating cue-elicited sucrose-seeking [59].

3.2. Clinical Studies

Despite strong preclinical support for the beneficial effects of glutamatergic NMDA receptor ligands, in clinical trials, D-cycloserine failed to significantly attenuate cocaine cue reactivity based on subjective craving and physiological reactivity [93] and did not facilitate extinction [94] or treatment retention goals of cognitive behavioral therapy [95]. Furthermore, memantine was not effective as the treatment for cocaine dependence [96] but was not reinforcing and did not have abuse potential in cocaine-dependent individuals [97].

CONCLUSION

Based on preclinical research, noncontingent and contingent cocaine administration provokes modulation of NMDA receptor subunit expression in rodents as a cellular mechanism that may contribute to cocaine-induced behavioral alterations. Experimenter-delivered cocaine administration is associated with several region-specific changes within the NMDA receptor subunit composition, which may contribute to difficulties encountered with the reversal of cocaine-induced behavioral neuroadaptation. Cocaine self-administration may potentiate NMDA receptor-dependent signaling in the limbic structures involved in the reinforcing and motivational aspects of cocaine; these changes are long-lasting and may suggest a target for drug design. Withdrawal from noncontingent and contingent cocaine administration alters the expression of NMDA subunits in a region-specific and abstinence duration-dependent manner. Overall, cocaine use disorder seems to be related to significant adaptations in NMDA receptors, which may be involved in several neural processes, such as synaptic plasticity, promotion of LTP or formation of aversive memory. Changes in the brain envi-

ronment, either from endogenous factors (kinases, phosphatases, and other regulatory enzymes) or external variables, may induce alterations in the expression, distribution, and consequently function of the NMDA receptor subunits. Moreover, synaptic NMDA receptors are additionally regulated by the activity-dependent redistribution of receptors into and away from the synapse, and these processes should be investigated in future studies. The blockade of NMDA receptor subunits during abstinence may be an important step for developing targeted pharmacotherapies for cocaine use disorder; however, further studies will be required to understand the relevance of these multitargeted interactions.

LIST OF ABBREVIATIONS

AMPA	=	α-Amino-3-hydroxy-5-Methyl-4-isoxazole Propionic Acid
BDNF	=	Brain-Derived Neurotrophic Factor
CamKII	=	Calmodulin-Dependent Protein Kinase II
CNS	=	Central Nervous System
CPP	=	Conditioned Place Preference
CREB	=	cAMP, Response Element-Binding Protein
LTD	=	Long-Term Depression
LTP	=	Long-Term Potentiation
MAGUK	=	Membrane-Associated Guanylate Kinase
NMDA	=	N-Methyl-D-Aspartate
VTA	=	Ventral Tegmental Area

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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