Can cocaine-induced neuroinflammation explain maladaptive cocaine-associated memories?

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Abstract

Persistent and intrusive memories define a number of psychiatric disorders, including posttraumatic stress disorder and substance use disorder. In the latter, memory for drug-paired cues plays a critical role in sustaining compulsive drug use as these are potent triggers of relapse. As with many drugs, cocaine-cue associated memory is strengthened across presentations as cues become reliable predictors of drug availability. Recently, the targeting of cocaine-associated memory through disruption of the reconsolidation process has emerged as a potential therapeutic strategy; reconsolidation reflects the active process by which memory is re-stabilized after retrieval. In addition, a separate line of work reveals that neuroinflammatory markers, regulated by cocaine intake, play a role in memory processes. Our review brings these two literatures together by summarizing recent findings on cocaine-associated reconsolidation and cocaine-induced neuroinflammation. We discuss the interactions between reconsolidation processes and neuroinflammation following cocaine use, concluding with a new perspective on treatment to decrease risk of relapse to cocaine use.
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Abbreviations

ADAMs: a disintegrin and metalloproteinase
AMPAR: AMPA receptor
BLA: basolateral amygdala
CaMKII: calcium/calmodulin-dependent protein kinase II
CB2R: cannabinoid 2 receptor
Cdk5: cyclin dependent kinase 5
CNS: central nervous system
CPP: conditioned place preference
CPu: caudate putamen
CS: conditioned stimulus
DA: dopamine
DAMPS: danger-associated molecular patterns
DH: dorsal hippocampus
eIF2α: eukaryotic initiation factor 2α
ERK: extracellular signal-regulated kinases
GPCRs: G protein coupled receptor
HAT: histone acetyltransferase
IFNγ: interferon γ
IL-1: interleukin-1
IL-1ra: IL-1 receptor antagonist
IL-1β: interleukin 1β
IL-6: interleukin 6
iNOS: inducible nitric oxide synthase
IRAK1: IL-1R-associated kinase 1
IRF3: interferon regulatory factor 3
JNK: c-Jun N-terminal kinases
LPS: lipopolysaccharide
LTD: long-term depression
LTM: long-term memory
LTP: long-term potentiation
MAPK: mitogen-associated protein kinase
MCSF: macrophage colony-stimulating factor
MD2: myeloid differentiation protein 2
MMPs: matrix metalloproteinases
mPFC: medial prefrontal cortex
mTOR: mammalian target of rapamycin
MyD88: myeloid differentiation primary response 88
NAc: nucleus accumbens
NCAM: Neural cell adhesion molecule
NFκB: nuclear factor-kappa B
NMDARs: NMDA receptor
PAMPs: pathogen-associated molecular patterns
PDGFs: platelet-derived growth factor
PET: positron emission tomography
PKA: protein kinase A
PRR: pattern recognition receptor
PSD95: postsynaptic density protein 95
PTSD: posttraumatic stress disorder
SA: self-administration
STM: short-term memory

TLRs: Toll-like receptor

TNFR: TNF receptor

TNFα: tumor necrosis factor α

TRAM: TRIF-related adaptor molecule

TRIF: Toll interleukin receptor-domain-containing adapter-inducing interferon-β

US: unconditioned stimulus

VTA: ventral tegmental area

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1. Introduction

Drug addiction is a worldwide health problem and a primary risk factor for a variety of medical conditions. For example, cocaine use increases the risk of myocardial infarction by 24 times, and induces convulsions in 1 to 10% of users. Cocaine abuse is comorbid with other psychiatric disorders, with 24% of cocaine users reporting an anxiety disorder (OFDT, 2012). Among addictive drugs, cocaine is the most commonly consumed illicit psychostimulant in the world: 18 million people worldwide have used cocaine, among which approximately 400 000 have a cocaine use disorder (World Drug Report, 2018). The powerful reinforcing properties of cocaine lead to escalation of intake and loss of control over consumption, producing compulsive drug seeking and drug taking despite obvious negative consequences. Importantly, cocaine abuse is characterized by a high vulnerability to chronic relapse (Koob and Volkow, 2016), which explains its resistance to treatment and perpetuation of maladaptive behavior.

Cocaine, like others drugs of abuse, directly or indirectly impacts the mesocorticolimbic pathway, leading to enhancement of dopamine (DA) neurotransmission from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) (Di Chiara and Imperato, 1988). This “reward pathway” mediates the reinforcing effects of natural reinforcers that have evolutionary significance (e.g., food, mating). The critical role of DA in this pathway may involve one or more processes, such as associative learning (Corbit and Balleine, 2016), error prediction (i.e., relationship between expected and actual outcomes) (Schultz, 2016), and motivation (Salamone et al., 2016). Regardless of the precise process, there is general agreement that drugs of abuse, such as cocaine, hijack this system, increasing
DA neurotransmission that results in strengthened reinforcement (Chen et al., 2008; Bamford et al., 2018).

The reinforcing effect of cocaine depends on both instrumental and classical conditioning. The former occurs as individuals learn the relationship between drug intake and drug effects, including the consequences of drug administration on alleviating withdrawal (for a discussion on the relative contributions of positive versus negative reinforcement in addiction, see review Wise & Koob, 2014); the latter when environmental cues become associated with drug intake (Wikler & Pescor, 1967; Tiffany, 1990). With classical conditioning, drug-paired cues acquire characteristics predicting drug availability, including DA release in the striatum (Ito et al., 2002). In rodents, these conditioned cues, previously associated with cocaine consumption, can then become conditioned reinforcers and induce drug-seeking behavior, even after a long period of abstinence (Grimm et al., 2001). Enhanced drug-seeking can be observed even when animals have to override aversive stimuli such as electric shock (Saunders et al., 2013). Unfortunately, no effective treatments have been found to efficiently reduce rates of relapse, and it has been hypothesized that an association between environmental cues and pharmacological effects of cocaine, strongly anchored in memory, is part of the problem (Hyman et al., 2006). This has stimulated a new direction in addiction research, targeting memory processes, particularly when they are reactivated, in order to weaken memories associated with cocaine and, thereby, decrease the risk of relapse (Torregrossa & Taylor, 2016).

In that respect, neuroinflammation may be an interesting target as numerous studies have linked neuroinflammatory markers to memory processes (see review Bader and Winklhofer, 2019). In addition, both human and animal studies reveal an association
between chronic cocaine consumption and the upregulation of several neuroinflammatory markers (see review Clark et al., 2013). The present review aims to discuss the hypothesis that cocaine addiction results, at least in part, from an involvement of traditional neuroinflammatory pathways in memory processes. We summarize evidence that neuroinflammatory cytokines have a dual function in memory, and that cocaine intake can increase release of these cytokines. Finally, we propose that altered memory processes observed in cocaine addiction may result from neuroinflammatory mechanisms.

2. Memory

2.1. Memory: general process

Memory is the mental process of acquiring, retaining and retrieving information. It is critical for cognitive processes, such as language, decision making, and spatial navigation. Memory is a time-dependent process with three phases: encoding, storage, and retrieval. Gold and McGaugh’s (1975) single-trace theory hypothesized that each new event triggers a short-term memory (STM), which either fades or is encoded and stored in long-term memory (LTM) through an active process. Whether a memory moves into LTM or not depends on factors such as repetition and the attentional state of the individual. The idea that memory storage is an active process was established by several pioneering studies demonstrating that memory retention could be disrupted after post-learning manipulations (e.g., electroconvulsion or protein synthesis inhibition) (Grecksch and Matthies, 1980). This active process allows a labile memory trace to transition to a stable and fixed form. Following this initial work, Misain and co-workers (1968) showed that old memories that are retrieved could also be disrupted by a post-reactivation manipulation (e.g., electroconvulsion). This study introduced the idea that memory may always be in
one of two forms: active memory describes newly acquired memories as well as older, reactivated memories, whereas inactive memory corresponds to stored memories (Lewis, 1979). In other words, the process by which memory is retained in LTM indefinitely is not passive; rather, this is a flexible process within which memory can be modified and updated over time.

2.2. Consolidation and reconsolidation

The consolidation/reconsolidation theory emerged to describe the two processes in which memory switches from active to inactive forms (Lewis, 1979). Consolidation corresponds to the storage of a new memory whereas reconsolidation corresponds to the storage of a reactivated memory (i.e., previously-acquired memories that are retrieved). Some of the earliest studies on memory consolidation highlighted a time and protein synthesis dependent mechanism. Indeed, increasing the delay between memory formation and a subsequent manipulation produced a predictable degradation of amnesia: memory was impaired when a disruption was induced up to 6 hours after learning (Kopp et al., 1966). A protein synthesis dependent mechanism of consolidation was revealed in 1968, with evidence that cycloheximide (a protein synthesis inhibitor) induces memory impairment when administered 3 hours after learning (Barondes and Cohen, 1968), suggesting that the manipulation did not impact STM, but altered memory retention through LTM. In another study, protein synthesis inhibition disturbed avoidance conditioning when it was administered 10 min prior to or 80, 240 and 360 min after training, but not when administered 45 and 165 min after training (Grecksch and Matthies, 1980). This suggested that there are two phases of memory that are dependent on protein synthesis. Taken together, these
results support the consolidation theory by showing that memory can be modified during a period following its formation and is then sustained by de novo protein synthesis.

In addition to consolidation processes, memory reactivation by retrieval also leads to a period of instability (a few hours) in which memory is labile (Misain et al., 1968). Reconsolidation is necessary to restabilize the memory into an inactive form so that it may be stored and maintained across time. Reconsolidation provides a mechanism for updating memories over time, a process that provides an evolutionary advantage to organisms by facilitating behavioural flexibility.

After a twenty-year hiatus, Nader and co-workers (2000) revived research on consolidation and reconsolidation using a fear conditioning paradigm. In simple consolidation experiments, rats experience a tone (conditioned stimulus, CS) followed by a shock (unconditioned stimulus, US); the next day, they freeze in response to the tone. Administration of a protein synthesis inhibitor (anisomycin) up to 3 hours following the CS-US pairing, prevents the freezing response to the CS on the next day. Nader and colleagues extended this principle to reconsolidation showing that protein synthesis inhibition also disrupts post-retrieval modification of the CS-US association; administration of anisomycin following CS-induced freezing eliminates conditioned responses on a subsequent test day. In other words, memory of the CS-US association is altered following its retrieval, verifying that reconsolidation is an active process during which previously-acquired memories are labile. This process appears to be shared by many species (Nader and Hardt, 2009) and is associated with specific neural sites in the mammalian brain, such as the
amygdala or nucleus accumbens (Nader et al., 2000; Fuchs et al., 2009; Torregrossa et al., 2010; Théberge et al., 2010; Arguello et al., 2014). A consolidation/reconsolidation description of memory is supported by evidence that both processes involve molecular and cellular mechanisms that underlie synaptic plasticity, such as long-term potentiation (LTP) (Lynch, 2004). LTP is a cellular mechanism characterized by an increase in post-synaptic neuronal responses after brief high-frequency stimulation (Nicoll, 2017). It is considered one of the cellular bases underlying learning and memory, particularly as it matches Hebbian learning rules. LTP is described as a two-phase process, i.e., early-LTP and late-LTP, corresponding to induction and maintenance in which synaptic modifications occur through de novo protein synthesis (see review Baltaci et al., 2019). Importantly, a two-phase process is also found in consolidation research (Grecksch and Matthies, 1980).

2.3. Integration and state-dependency

Despite the fact that the consolidation hypothesis is accepted by a large part of the scientific community, some authors have proposed that state-dependency and integration, at least to some degree, could explain the findings of consolidation experiments (Gisquet-Verrier and Riccio, 2019). This alternative hypothesis developed from studies using a passive avoidance paradigm, in which memory impairments induced by cycloheximide were reversed if subjects were presented with a reminder of the original memory (Quartermain et al., 1970). In further work (Gisquet-Verrier et al., 2015), administration of cycloheximide (i.e., protein synthesis inhibitor) following a single session of an inhibitory avoidance task
induced amnesia in a later retention test. Importantly, this amnesia was reversed by another cycloheximide injection 30 min prior to the retention test. The same effect was observed with manipulations following memory retrieval, confirming that the original memory was not erased, but still accessible when appropriate cues were provided on the retention test. According to the authors, these effects confirm that an amnesic effect induced by protein synthesis inhibition was induced by a retrieval impairment rather than disruption of memory storage. State-dependency and integration theories consider that the animal’s internal state acts as a CS during memory formation. As such, memory recall is inhibited when the internal state of the animal does not match the internal state during memory acquisition. This theory argues that memory is active for a short period of time, during which both internal and external cues will be integrated into this memory in a protein synthesis independent manner (Gisquet-Verrier and Riccio, 2019). Despite the appeal, state dependence and integration theories of memories can not explain all instances of memory consolidation. This includes rare instances of enhanced memory (Lee et al., 2009; Stringfield et al., 2017) and memory impairments when treatments are given beyond the “integration period” (Grecksch and Matthies, 1980; Monsey et al., 2017).

In sum, researchers generally agree on the involvement of an active mechanism underlying memory storage, but this phenomenon is explained by different theories. This review does not address the validity of either proposal, but supports the idea that both phenomena could account for memory formation. The remainder of the review will focus on consolidation and reconsolidation as these are more plausible accounts for memory formation of drug-associated environmental cues.
3. Cocaine and reconsolidation

3.1. Theory of reconsolidation for cocaine addiction

Some psychiatric disorders, such as posttraumatic stress (PTSD) and addiction, are characterized by aberrant and persistent memories. In both cases, strong memories are closely linked to the development of these disorders and to the continuation of associated maladaptive behaviors (Dunbar and Taylor, 2017; Monfils and Holms, 2018). CS-US associations become abnormally strong and result in chronic anxiety and fear (e.g., PTSD) or in the persistence of drug intake despite negative consequences (e.g., addiction). As with other drugs of abuse, cocaine addiction is characterized by a high vulnerability to relapse, even after prolonged periods of abstinence.

One of the triggers of relapse in humans is exposure to conditioned cues previously associated with cocaine consumption, a phenomenon that can be modeled in rodents using a reinstatement paradigm (Shaham et al., 2003). In this paradigm, animals acquire drug self-administration (SA) or learn to associate a specific location with drug effects (conditioned place preference, CPP). Responses are then extinguished during a withdrawal period. Reinstatement of the drug-seeking response (lever pressing or time spent in the drug-paired compartment) is traditionally induced by exposure to an acute priming injection of drug, drug-associated cues, or environmental stressors. In the early 2000s, the reinstatement paradigm was incorporated into reconsolidation studies to highlight the relationship between specific memory processes and relapse-like behavior (i.e., reinstatement) (Lee et al.,
2006; see review Sorg, 2012). These studies were designed to decipher mechanisms involved in the memory of drug-cue associations. Behavioral protocols of these studies are based on the same sequence of phases as reconsolidation studies using fear conditioning: learning, extinction, reactivation (induced by cues, context, or cocaine) followed by a memory manipulation assay, and reinstatement. Drug reinstatement studies suggested that manipulating reconsolidation of cocaine-associated memories is a potential therapeutic strategy to reduce relapse (Rich and Torregrossa, 2018). The next section will summarize the main findings from this work, highlighting the role of several signaling molecules in mediating reconsolidation of cocaine-associated memories, using CPP and SA paradigms (see Table 1). The main goal of these studies was to reduce cocaine-associated reconsolidation and/or to enhance cocaine-associated extinction.

### 3.2. Target molecules uncovered in cocaine-associated reconsolidation

A premise of this work is that reconsolidation of cocaine-associated memories follows the same principles as reconsolidation of fear-associated memories, and depends on *de novo* protein synthesis. Indeed, several studies have disrupted cocaine-associated reconsolidation (Fuchs *et al.*, 2009; Wells *et al.*, 2011; Dunbar and Taylor, 2016; Zhu *et al.*, 2018) using inhibitors of protein synthesis, administered either systemically or *in situ* in the basolateral amygdala (BLA). In contrast, no impact on reconsolidation was observed after dorsal hippocampus (DH) or dorsal striatum (caudate putamen; CPu) inhibition (Ramirez *et al.*, 2009; Fuchs *et al.*, 2009). Further dissociation of protein synthesis effects were revealed with evidence that inhibition of protein synthesis in the medial prefrontal cortex (mPFC) alters reconsolidation of
memory triggered by cocaine combined with cocaine-paired cues (Sorg et al., 2015), but not by a context associated with cocaine (Ramirez et al., 2009). This differential outcome suggests that memories triggered by cocaine-associated context versus cocaine combined with discrete cues might be supported by different neural substrates, pathways, and/or mechanisms. Altogether, these results indicate that protein synthesis is a necessary step in cocaine-associated reconsolidation and the effect is mediated in specific brain structures. This site-specific process argues against a general effect of protein synthesis inhibition, as proposed in the state-dependency theory (Gisquet-Verrier and Riccio, 2019).

Studies examining mechanisms of cocaine addiction within a reconsolidation framework have revealed several molecular targets, receptor subtypes, and intracellular pathways that contribute to this process (see table 1). Given their critical role in learning, memory, and synaptic plasticity (Baudry et al., 2015), it is not surprising that glutamatergic NMDA receptors (NMDARs) are heavily involved in cocaine reconsolidation. Indeed, inhibition of NMDARs, either systemically (Li et al., 2016) or directly in NAc shell (Alaghband and Marshall, 2013) or DH (Wells et al., 2016), affected cocaine-associated reconsolidation. In contrast, NMDARs activation produces inconsistent effects, enhancing both cocaine-associated extinction (Torregrossa et al., 2010) and reconsolidation (Lee et al., 2009), resulting in opposing effects on drug-seeking behavior (i.e., decreases and increases respectively). This could represent a major limitation for therapeutic intervention as it would be difficult to limit effects to an interval that would result in the decrease of cocaine-seeking behavior.
Other molecular targets involved in learning and memory have been investigated in reconsolidation processes, such as calcium/calmodulin-dependent protein kinase II (CaMKII) and protein kinase A (PKA). CaMKII inhibition in the BLA weakens cocaine-associated reconsolidation and enhances extinction (Rich et al., 2016), although another study failed to produce the same effect (Arguello et al., 2014). PKA inhibition in the BLA (Shanchez et al., 2010; Arguello et al., 2014), but not in the dorsal striatum (Arguello et al., 2014), disrupts cocaine-associated reconsolidation. Altogether, these results highlight the complexity of molecular mechanisms underlying reconsolidation and extinction of cocaine-associated memories, as both involve learning processes.

Several G protein coupled receptors (GPCRs) have been targeted for modulating reconsolidation in order to reduce cocaine-seeking behaviors. For example, blocking dopaminergic D1 (Li et al., 2016) or D3 (Yan et al., 2013) receptors reduces cocaine-seeking behavior, whereas D2 receptor blockade has no effect (Li et al., 2016). Inhibiting adrenergic receptors produced inconsistent results: no effect (Dunbar and Taylor, 2016) or an inhibition of cocaine-seeking behavior (Fricks-Gleason and Marshall, 2008; Zhu et al., 2018). These discrepancies could be explained by different ‘reconsolidation’ paradigms, with single or repeated memory manipulations (i.e., one versus multiple retrieval sessions and treatments) producing different effects (Fricks-Gleason and Marshall, 2008). Moreover, reactivation by context versus cocaine also has different effects on the modulation of seeking behavior (Dunbar and Taylor, 2016; Zhu et al., 2018). This work has been applied to clinical populations of drug addicts with a study examining the efficacy of propranolol, a β-adrenergic antagonist, as a therapeutic strategy targeting
reconsolidation (Lonergan et al., 2016). When administered immediately prior to participants reading a personalized script detailing a drug-use experience, the antagonist decreased self-reported drug-craving (Lonergan et al., 2016), suggesting that it interfered with reconsolidation of the drug-associated memory that was reactivated during the script reading. Unfortunately, this study lacked follow-up measures on the percentage of patients who relapsed following study participation. Recently, cannabidiol, a phytocannabinoid agonist, known to have many beneficial effects on several health conditions (Crippa et al., 2018), has been shown to disrupt reconsolidation of cocaine-associated context memory in rats (de Carvalho and Takahashi, 2016). These pharmacological agents could represent promising candidates for treating relapse to cocaine use.

In addition to GPCRs, a number of intracellular signaling mechanisms have been investigated in reconsolidation processes related to cocaine administration in rodents. Systemic or in situ (e.g., NAc or amygdala) disruption of specific pathways, including mTOR, Cdk5, eIF2α, decreases cocaine-associated reconsolidation, leading to a reduction of cocaine-seeking behavior. Some studies have examined the effect of stress on relapse-like behavior and/or cocaine-associated memories but whether this directly impacts reconsolidation is still not fully understood (see Table 1). Interestingly, cellular stress-like NOS signalling pathways disrupt reconsolidation and reduce cocaine-seeking behavior (Itzhak et al., 2008). Cocaine induces transcriptional adaptations in brain structures (Piechota et al., 2010) and some of these modifications are under the control of epigenetic factors (De Sa Nogueira et al., 2018), which themselves are involved in cocaine-associated reconsolidation. For example, intra-amygdala inhibition of DNA-methyltransferase (Shi et al., 2015) or
systemic inhibition of histone acetyltransferase (HAT) (Monsey et al., 2017; Dunbar and Taylor, 2017) disrupt reconsolidation of cocaine memories.

In conclusion, the process of reconsolidation in cocaine addiction has been demonstrated, although limitations for therapeutic interventions remain. The wide diversity of experimental paradigms, the brain areas under study, and the specificity of the pharmacological tools may explain the diverse findings on reconsolidation related to cocaine-seeking behavior. Noteably, a reactivation phase appears to be critical in this process, as reduction of seeking behavior may result from an action on either extinction or reconsolidation. Furthermore, cues, context, or cocaine reactivation involve distinct memory pathways that may be differentially altered by candidate molecules. Therapeutic approaches, even if promising, require further investigation to selectively target the reconsolidation process in cocaine addiction.

4. Neuroinflammation and memory

It is interesting to note that some of the pharmacological agents tested in the framework of the reconsolidation theory of cocaine addiction display anti-inflammatory properties. The resulting effects on cocaine seeking behavior, therefore, could also be explained, at least partially, by an inhibition of neuroinflammation. For example, garcinol (Monsey et al. 2017; Dunbar and Taylor 2017) is considered a HAT inhibitor, and cannabidiol (de Carvalho and Takahashi, 2016) is a “multi-target” compound which affects several channels and/or receptors, including the cannabinoid 2 receptor (CB2R) (Devinsky et al., 2016). Noticeably, both pharmacological tools also display anti-inflammatory (e.g., direct and indirect
inhibiton of NFκB activation) and antioxidant (e.g., inhibition of iNOS) properties (see reviews Padhye et al., 2009 and Kozela et al., 2017). Moreover, among the molecular targets highlighted in reconsolidation of cocaine memories, some are also involved in inflammatory mechanism. For example, the β-adrenergic receptor pathway, which is currently targeted in human trials, displays cross-talk with immune and inflammatory pathways (see review, Scanzano and Cosentino, 2015). The β-adrenergic receptors are considered to be immunomodulators. Opposite results have been described following stimulation of β-adrenergic receptors, with either an anti-inflammatory action or an enhancement of a pro-inflammatory state (see review, Kolmus et al., 2015). In addition, other downstream signaling molecules, also studied in cocaine-associated reconsolidation, have been linked to inflammatory pathways, such as PKA (Tao et al., 2016; Ghosh et al., 2016) and CaMKII (Tsakiri et al., 2008). The former appears to be necessary for microglial transition from pro-inflammatory to anti-inflammatory states, whereas CaMKII mediates interleukine synthesis in neuronal cultures challenged for immune responses. Based on these observations, neuroinflammatory processes during cocaine reconsolidation represent an important line of further investigation.

4.1. Neuroinflammation: general process

For many years, the brain was thought to be an “immune-privileged” organ, protected by the blood brain barrier that isolates the central nervous system (CNS) from the peripheral immune system. Lately, a significant body of evidence has revealed the existence of a specific innate immune system inside the CNS which, when activated, results in neuroinflammation (see review Rivest, 2009). Microglia
plays an important role in this process as they are CNS resident macrophage-derived cells and have a major role in immune surveillance (Subramaniam and Federoff, 2017). Besides microglia, all brain cell types (e.g., astrocytes, oligodendrocytes, and neurons) are also involved in the neuroinflammatory process.

The main pathway involved in neuroinflammatory processes is triggered by pattern recognition receptors (PRR), including pathogen- or danger-associated patterns (i.e., PAMPs and DAMPs), which address pathogen invasion or tissue damage. The most common PRR, the Toll-like receptors (TLRs), are primarily expressed on microglia, although variable combinations of TLRs are also expressed by astrocytes, neurons, and other non-neuronal cells (i.e., endothelial and oligodendrocytes) (Hanamsagar et al., 2012). There are approximately a dozen TLR family members in mammals, which respond to specific stimuli. Activation of all TLRs (with the exception of TLR3) induces MyD88 activation, leading to the induction of nuclear factor κ B (NFκB) and pro-inflammatory cytokine release (i.e., IL-1β, IL-6 or TNFα) (Brown et al., 2011). In contrast, TLR3 induces a TRIF-dependent pathway leading to IRF3 activation and secretion of other cytokines, such as IFNγ, although this signaling pathway can also be triggered by TLR4 through an adaptor protein, TRAM. Both MyD88 and TRIF-dependent pathways also stimulate mitogen-associated protein kinase (MAPK) including ERK, p38, and JNK (Brown et al., 2011). These neuroinflammatory pathways exert a critical influence on memory processes. The two following sections summarize the literature on this topic, focusing on pro-inflammatory cytokines expressed by both glia and neurons (i.e., IL-1, IL-6 and TNFα) (for a more detailed review, see Yirmiya and Goshen, 2011).

4.2. Detrimental effects of neuroinflammation on memory
The majority of literature on neuroinflammation and memory supports the idea that neuroinflammation has detrimental effects on memory, which have been demonstrated, primarily, by observations in neurodegenerative diseases (Bader and Winklhofer, 2019). More specifically, neuroinflammation has been associated with memory impairment in various animal paradigms that match consolidation. For example, exogenous IL-1β induces alterations in biological processes that support LTP, thereby preventing the emergence of LTP (Katsuki et al., 1990). Moreover, exogenous IL-1β or bacterial infection that increases IL-1β, do not affect acquisition of spatial learning in the Morris water maze, but reduce performance in the retention phase (Oitzl et al., 1993; Gibertini et al., 1995). In the same way, lipopolysaccharide (LPS) injections (Pugh et al., 1998), or IL-1β intracerebroventricular or intrahippocampal administration (Barrientos et al., 2002) induce impairments in contextual fear conditioning. Moreover, this effect is reversed by IL-1ra (i.e., natural antagonist of IL-1 receptor) injections (Pugh et al., 1998). Importantly, animals pre-exposed to the context before conditioning showed no deficit suggesting that the impairment resulted from an alteration of the context-associated consolidation processes, but not from the association between the context and the aversive stimulus (Pugh et al., 1998; Barrientos et al., 2002). Finally, chronic neuroinflammation in transgenic mice overexpressing IL-1β has been revealed through up-regulation of inflammatory mRNAs molecules in the hippocampus (Moore et al., 2009; Hein et al., 2010). These mice show impairments in contextual, but not auditory, fear conditioning (Hein et al., 2010), as well as deficits in spatial learning in the water maze, which were negatively correlated with gene regulation (Moore et al., 2009).
Chronic neuroinflammation, induced by repeated LPS infusions, has been linked to increases in TNFα, TNFR2, and IL-1β hippocampal expression (Belarbi et al., 2012). Impairments of both acquisition and consolidation in a spatial water maze, following chronic LPS, were rescued by DT 3,6′dithiothalidomide, a blocker of TNFα activity (Belardi et al., 2012; Russo et al., 2012). Together, these results indicate that elevated level of IL-1β and TNFα, inducing neuroinflammatory processes, have a detrimental effect on contextual memory. Noticeably, high doses of pro-inflammatory cytokines, such as IL-1β, IL-6, or TNFα, or administration of pathogens, can induce a state of “sickness behavior” (Lacosta et al., 1999). Mice injected with IL-1β display spatial deficit only in a warm-water maze (i.e., 23°C) and not in cold-water maze (i.e., 18°C) from which they may have a stronger motivation to escape (Gibertini, 1998) (for a review, see Cunningham and Sanderson, 2008). This state of sickness could partly account for altered memory through state-dependency processes or a change in motivation.

4.3. Beneficial effects of neuroinflammatory markers on memory

Studies examining the role of pro-inflammatory markers in memory suggest that a balance of several cytokines is necessary for the establishment and maintenance of a memory trace. Tetanic bursts that induce LTP, ex vivo or in vivo, lead to hippocampal up-regulation of mRNA for a number of cytokines, such as IL-1β, IL-6 and IL-1ra, although TNFα expression is not altered (Schneider et al., 1998; Balschun et al., 2004; del Rey et al., 2013); these effects were observed only in rats displaying persistent LTP for more than 3 hours. Importantly, prior administration of AP-5 (i.e., an NMDAR antagonist) prevented this upregulation. These data suggest
that cytokines are involved in LTP mechanisms at a time point that matches a consolidation phase. The IL-1β cytokine plays a critical role in these processes, as no LTP could be measured in mice deficient for the IL-1 receptor (IL-1RrKO) (Avital et al., 2003). Pharmacological intervention showed that inhibition of IL-1β, via administration of the IL-1ra antagonist 90 min after tetanic bursts, reduced population spikes to pre-LTP values (Schneider et al., 1998). This effect was not observed when the antagonist was administered 30 min prior to, or 5 min after, LTP induction, indicating that IL-1β is necessary for LTP maintenance, but not induction. An opposite effect was observed with an antibody that blocks IL-6, resulting in sustained maintenance of LTP for a longer time and increased spatial memory (Balschun et al., 2004). In sum, both cytokines display time-dependent effects on memory, with IL-1β being implicated in LTP maintenance and IL-6 in LTP duration. This dual action of IL-1 and IL-6, at a time point corresponding to consolidation, reveals a complex mechanism of cytokine activation in the healthy brain. The establishment of a balance may result in a more coherent memory trace. Behavioral experiments also support this idea. Mice deficient for the IL-1 receptor (Avital et al., 2003) or overexpressing an IL-1 receptor natural antagonist (IL-1raTG) (Goshen et al., 2007) display impairments in spatial learning and contextual fear conditioning, but show no difference in non-spatial learning (i.e., visible platform in water maze) or auditory fear conditioning. Up-regulation of transcripts for IL-1β and IL-6, but not IL-1ra or TNFα, are observed in the hippocampus, 2 hours following spatial learning (e.g., Y-maze) (del Rey et al., 2013) and 24 hours following fear conditioning (Goshen et al., 2007). The latter effect was observed in WT, but not in IL-1rKO and IL-1raTG, mice. Taken together, these results indicate a role for IL-1β and IL-6 in contextual memory (i.e., consolidation).
The neuroinflammatory marker, TNFα, has been implicated in cognitive-associated diseases such as Alzheimer’s disease (Decourt et al., 2017), but its role in memory processes is more controversial. Neuronal cell cultures exposed to TNFα displayed an increased number of AMPAR at the membrane, arguing for the involvement of TNFα in AMAPR trafficking and therefore in synaptic strength modulation (Beattie et al., 2002). Also, mice deficient for TNFR show decreased LTP and LTD in hippocampal slices (Albensi and Mattson, 2000). In contrast, no TNFα transcript modification was observed in the hippocampus following either LTP-induction or learning (del Rey et al., 2013), suggesting that further research is required to unravel the specific role of TNFα in memory.

The signaling pathway for NFκB, a transcription factor initially described in the immune system but actually expressed in brain parenchyma, plays a central role in immune and inflammatory responses. NFκB can be activated by several pro-inflammatory cytokine signaling pathways (Bonizzi and Karin, 2004) and by LTP-inducing protocols (Freudenthal et al., 2004). Indeed, NFκB regulates LTP-induced plasticity (Albensi and Mattson, 2000) and, among genes regulated by NFκB, some are coding proteins located at the synapses, such as PSD95, NCAM or AMPA receptor subunits (Engelmann and Haenold, 2016). These findings suggest that NFκB is involved in long-term memory, a proposal that has been verified in behavioral experiments. For example, NFκB is rapidly activated in the hippocampus by contextual emotional memory (Freudenthal et al., 2005) and in the amygdala by conditioned fear (Yeh et al., 2002). In addition, altering NFκB activation or disrupting NFκB activity during consolidation/reconsolidation produce memory
impairments during a retention test (Freudenthal et al., 2005; de la Fuente et al., 2011; de la Fuente et al., 2014). Moreover, NFκB is inhibited following cue-extinction, suggesting a complex role for this transcription factor (de la Fuente et al., 2011). Collectively, these results indicate that extracellular signals, initially related to inflammation, could in fact play a role in physiological processes of memory consolidation and reconsolidation.

In conclusion, both detrimental and beneficial effects of cytokines on memory processes have been described, and this differential consequence is dependent on the dose of cytokines, specifically physiological (low) versus pathological (high) states (see above). In line with this idea, some studies emphasize an inverted U-shape dose-effect of IL-1 on memory (Brennan et al., 2003; Goshen et al., 2007). Indeed, high doses of IL-1β impair contextual fear conditioning in mice, whereas low doses enhance it (Goshen et al, 2007), confirming that neuroinflammation plays a role in spatial and contextual memory. Hippocampus-dependent memory is clearly modified by neuroinflammation markers, but no convincing data exist on whether other types of memories, such as cue-associated or emotional memory, are also modulated. Further exploration will bring insight into the neuroinflammatory mechanisms involved in different kind of memories. Also, as all the data on cytokines summarized here were obtained following learning (i.e., consolidation), it is critical to explore the role of these cytokines in memory retrieval. This would uncover a potential role of these cytokines in reconsolidation.

5. Cocaine and neuroinflammation
Drugs of abuse, and in particular alcohol, trigger neuroinflammation, although less is known about the effects of cocaine on neuroinflammation (see reviews Clark et al., 2013; Lacagnina et al., 2017). Table 2 summarizes these few studies, highlighting the regulation of neuroinflammatory markers, both in vitro (cell culture) and in vivo (rodent, primate and human). In humans, chronic cocaine use is associated with increased serum levels of the pro-inflammatory cytokine, IL-6, and decreased serum levels of the anti-inflammatory cytokine, IL-10 (Moreira et al., 2015), pointing to a global pro-inflammatory effect. This idea is supported by evidence of enhanced microglia activation in post-mortem brains of cocaine users (Little et al., 2009). In contrast, no difference in microglia activation in grey matter was observed in living cocaine users, using a positron emission tomography (PET) imaging technique (Narendran et al., 2014). Patients in the PET study were abstinent for a minimum of 14 days, whereas individuals in the post-mortem study had used cocaine at least once in the 2 weeks prior to death. Neuroinflammation induced by cocaine, therefore, may not persist beyond a 2-week interval. The discrepancy could also reflect differences in the brain region investigated (grey versus white matter). Indeed, microglia activation in living nonhuman primates increased, specifically in white matter, following cocaine use (Smith et al., 2019).

Further work has examined potential mechanisms involved in pro-inflammatory consequences of cocaine use. The cocaine-induced “xenobiotic hypothesis” proposes that cocaine is recognized by the immune system as a foreign xenobiotic component (see review Hutchinson and Watkins, 2014). Indeed, cocaine binds directly to the MD2 domain of TLR4 in the VTA (Northcutt et al., 2015), a PRR known to be triggered by xenobiotic components (Hutchinson and Watkins, 2014). The
interaction with TLR4 further increase DA release in the NAc (Northcutt et al., 2015), which suggests a synergetic effect with the direct action of cocaine on monoamine-reuptake transporters. Furthermore, several downstream elements of a TLR4 pathway are up-regulated by cocaine, both in vitro and in vivo (see Table 2), including NFκB, IL-1β, IL-6, IL-12, TNFα, MAPK, IRAK1, MyD88, and TRAF6. In addition, downregulation of IL-10 has been reported following cocaine intake (Ang et al., 2001; Russo et al., 2009; Lin et al., 2011; Moreira et al., 2015; Liao et al., 2016; Brown et al., 2017; Zhu et al., 2018b; Periyasamy et al., 2018), again supporting a global proinflammatory process. Cocaine also indirectly enhances pro-inflammatory markers through other TLRs, including TLR2 and TLR3 (Liao et al., 2016; Zhu et al., 2018b), that could participate in the downstream regulations observed. In sum, targeted approaches have revealed the importance of TLRs pathways in inflammatory processes following cocaine exposure.

Interestingly, genome-wide approaches have also pointed to regulation of a wide variety of inflammatory molecules following cocaine intake. For example, analysis of genomic data (Clark et al., 2013) obtained from whole RNA sequencing studies (Ahmed et al., 2005; Renthal et al., 2007 and Piechota et al., 2010) highlight gene expression increases in inflammatory modulators in several brain reward structures (e.g., dorsal striatum, NAc, PFC, amygdala, septum, lateral hypothalamus, and VTA), following acute or chronic cocaine intake in rats. A global increase in neuroinflammatory marker expression was confirmed in an RNAseq study of both NAc and VTA samples from cocaine self-administering nonhuman primates (Vallender et al., 2017). Pro-inflammatory cytokines, cytokine receptors, chemokines, TLRs, MMPs, ADAMs, PDGFs, and MCSF are among the genes up-
regulated by cocaine. These data highlight novel candidates involved in cocaine-induced adaptations, in addition to those identified in targeted approaches.

Overall, cocaine intake is consistently associated with increases in a number of neuroinflammatory markers. Several drugs of abuse cause activation of microglia and astrocytes through signaling of neuroinflammatory markers, which influence neuronal function (Lacagnina et al., 2017). Blocking this brain reaction to cocaine by anti-inflammatory strategies, both in rodents and humans, has shown efficacy in alcohol abuse treatment by acting on drug intake, craving, or relapse (see reviews Ray et al., 2014; Konho et al., 2019). Few studies have examined the effect of anti-inflammatory agents in cocaine addiction, although these have produced intriguing results. For example, administration of (+)naltrexone, a specific TLR4 antagonist, prevents the development of cocaine place preference in rats (Northcutt et al., 2015). N-acetylcysteine is an antioxidant and anti-inflammatory agent which has been examined for treating several psychiatric and neurological disorders associated with dysfunction in oxidative stress, neuroinflammation, as well as, glutamate and dopamine dysregulation (see review Deepmala et al., 2015). Interestingly, N-acetylcysteine displays promising anti-relapse effects both in pre-clinical and clinical studies (for a review, see Nocito Echevarria et al., 2017). Indeed, in clinical studies, N-acetylcysteine decreased desire and interest toward cocaine when given after a cue-reactivity procedure (i.e., slides depicting cocaine and cocaine-use) (LaRowe et al., 2007). The drug also increases time to relapse and reduces craving in abstinent addicts, whereas it had no effect on craving or drug intake in cocaine consumers at the time of the experiment (LaRowe et al., 2013). These results are supported by pre-clinical studies in rodents. In a long-access paradigm inducing escalation, N-
acetylcysteine prevents increased cocaine intake and blocks cocaine-induced locomotor sensitization as well as cocaine-induced reinstatement (Madayag et al., 2007). In contrast, it had no effect on cocaine intake per se in humans (Madayag et al., 2007). Altogether, N-acetylcysteine represents a good candidate for intervention in cocaine abstinent patients. Further investigation exploring other inflammatory markers induced by cocaine could provide informative data for developing novel strategies to reduce cocaine-relapse.

6. Conclusions

The idea that addiction may reflect maladaptive memory has emerged, with an emphasis on developing therapeutic strategies to counter recurrent relapse in cocaine addiction. Numerous animal studies confirm that disruption of cocaine-associated memories (i.e., reconsolidation) decreases cocaine-seeking behavior. Based on this evidence, a combination of behavioral and pharmacological treatments should be further investigated in human clinical trials. Uncovering the underlying mechanisms of cocaine-associated memories will help to target pathways and time points of effective therapeutic strategies. Indeed, some of the results summarized above suggest that mechanisms other than reconsolidation (e.g., disruption in extinction or impairment in retrieval) may contribute to this process. Therefore, the retrieval protocol and the time window within which pharmacological or behavioral interventions occur are essential elements in the ensuing alterations of cocaine-seeking behavior.

Among potential lines of investigation, neuroinflammation is an intriguing possibility. Indeed, many neuroinflammatory markers, such as pro-inflammatory
cytokines or their upstream regulator NFκB, are up-regulated by cocaine intake. Development of a pro-inflammatory state has been confirmed by targeted and whole-genome approaches. Such cytokines are crucial players in memory processes, with the specific impact depending on the intensity and duration of the inflammatory process. Further work is required in this area, but it is now clear that interactions between memory processes and neuroinflammation following cocaine use could represent new targets for therapeutic interventions to reduce relapse. Among molecules involved in both neuroinflammation and memory, factors like NFκB represent an appealing target. We have previously shown that rats that self-administer cocaine display differential epigenetic regulation of genes organized around this transcription factor (Fonteneau et al., 2017). Moreover, genome-wide association studies in cocaine users, focusing on genes related to learning, memory, and synaptic plasticity, have highlighted two single nucleotide polymorphisms on nfkb1, encoding for NFκBp105/p50 (Levran et al., 2015). In addition, investigations of reconsolidation processes have revealed that inhibition of NFκB can disrupt fear-associated reconsolidation (de la Fuente et al., 2011) or morphine-CPP associated reconsolidation (Yang et al., 2011). Hence, acting on the NFκB pathway may be an appropriate approach to disrupt cocaine-associated reconsolidation and, therefore, decrease relapse.

Among the strategies proposed to directly impact reconsolidation of cocaine memories, the β-adrenergic blocker, propranolol, is under investigation at the clinical level and displays promising effects. Another target for cocaine-associated memory could be N-acetylcysteine. Indeed, the anti-reinstatement effect of this compound could also be explained by the restoration of neuroplasticity at cortico-striatal synapses induced through its action on the cysteine-glutamate exchanger (Madayag
et al., 2007; Moussawi et al., 2009). This inability to use neuroplasticity could explain, at least partially, the difficulties of addict individuals to learn new behaviors to reduce cocaine intake. Moreover, as N-acetylcysteine decreases craving in humans when given after cue-retrieval (LaRowe et al., 2007), it could provide beneficial effects on cocaine-associated reconsolidation. Remarkably, both propranolol and N-acetylcysteine also have anti-inflammatory properties that could account for their ability to reduce relapse. As with many mental health disorders, pharmacological treatments for cocaine abuse are often more effective when combined with behavior modification programs. Of these, cognitive behavioral therapy (CBT), is one of the most effective, particularly in terms of increasing treatment retention and reducing relapse (Penberthy et al., 2010). Although it has yet to be tested, principles of reconsolidation could be incorporated into CBT treatment by raising patient awareness of cue-drug associations and how these are modified with repeated memory reactivation. Altogether, it appears that developing a strategy combining anti-inflammatory agents, cocaine-associated memory manipulations, and CBT could hold promising treatment for altering cocaine-seeking behavior.

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<td>Rat</td>
<td>CPP (10mg/kg)</td>
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<td>Context reactivation, All compartments, 15min</td>
<td>Propranolol and nadolol</td>
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<td>Daily tests</td>
<td>o</td>
<td>Otis <em>et al.</em>, 2013</td>
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<td>Context</td>
<td>Compartment</td>
<td>Drug</td>
<td>Effect</td>
<td>Test</td>
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<td>Context reactivation, All compartments, 15min</td>
<td>Nadolol</td>
<td>DH</td>
<td>Daily tests</td>
<td>Cocaine priming test 2</td>
<td>Otis et al., 2014</td>
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<td>Mouse</td>
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<td>Test 2</td>
<td>Yan et al., 2013</td>
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<td>Liu et al., 2016</td>
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<td>Rat</td>
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<td>Forced abstinence</td>
<td>Context reactivation, Drug-paired compartment, 10min</td>
<td>Cannabidiol</td>
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<td>de Carvalho and Takahashi, 2016</td>
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<td>Rat</td>
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<td>Extinction, Context B</td>
<td>Context reactivation, Context A, 15min</td>
<td>PP2</td>
<td>DH</td>
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<td>Wells et al., 2016</td>
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<td>Rat</td>
<td>CPP (10mg/kg)</td>
<td>None</td>
<td>Context reactivation, Drug-paired compartment, 10min</td>
<td>Calpain inhibitor mixture + Cue (contingents) + context reactivation, Context A, 15min</td>
<td>NAc core</td>
<td>Test 2</td>
<td>Liang et al., 2017</td>
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<td>Context reactivation, Drug-paired compartment, 10min</td>
<td>Sal003</td>
<td>BLA</td>
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<td>Context reactivation, Drug-paired compartment, 10min</td>
<td>β-butyrolactone</td>
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<td>Test 2</td>
<td>Li et al., 2010</td>
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<td>Context reactivation, Drug-paired compartment, 10min</td>
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<td>Test 2</td>
<td>Lin et al., 2014</td>
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<td>Context reactivation, Drug-paired compartment, 10min</td>
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<td>Rat</td>
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<td>Context reactivation, Drug-paired compartment, 10min</td>
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<td>NAc core</td>
<td>Test 2</td>
<td>Ding et al., 2013</td>
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Table 1: Summary of research findings on cocaine-associated reconsolidation

Self-administration (SA), conditioned place preference (CPP). Context A corresponds to context of SA, Context B and C to a novel context. Test1 and test2 correspond to CPP post-conditioning measurements. Medial prefrontal cortex (mPFC), prelimbic cortex (PrL), infralimbic (IL), nucleus accumbens (NAc), caudate

<table>
<thead>
<tr>
<th>Stress-response system</th>
<th>Cognitive system</th>
<th>Extinction, Context B</th>
<th>Novel context induce stress (no reaction), Context C, 15min</th>
<th>Mifepristone</th>
<th>Context-induced reinstatement</th>
<th>Stringfield et al., 2017</th>
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<tbody>
<tr>
<td>Rat SA (0.15mg/inj)</td>
<td></td>
<td>Extinction</td>
<td>Context reaction, Context A, 15min</td>
<td>BLA</td>
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<tr>
<td>Mouse CPP (10mg/kg)</td>
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<td>None</td>
<td>Social defeat stress</td>
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<td>Context reaction, All compartments, 20min</td>
<td>Cycloheximide</td>
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<td>Test 2</td>
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<tr>
<td>Mouse CPP (20mg/kg)</td>
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<td>7-nitroindazole</td>
<td>Propranolol</td>
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<td>Rat SA (0.5mg/kg)</td>
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<td>Extinction</td>
<td>Cocaine (0.5mg/kg, i.v. or 10mg/kg, i.p.) reaction, Context B, 2x or HC</td>
<td>Garcinol</td>
<td>Systemic</td>
<td>Cue-induced reinstatement</td>
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<td>Rat SA (1mg/kg)</td>
<td></td>
<td>Extinction</td>
<td>Cocaine (contingents) reaction, Context B, 3x</td>
<td>Garcinol</td>
<td>Systemic</td>
<td>Cue-induced reinstatement</td>
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<td>Rat SA (0.75mg/kg)</td>
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<td>Extinction</td>
<td>Cocaine (contingents) reaction, Context A, 15min</td>
<td>5-AZA</td>
<td>Systemic</td>
<td>Cue-induced reinstatement</td>
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</table>

Table 1: Summary of research findings on cocaine-associated reconsolidation

Self-administration (SA), conditioned place preference (CPP). Context A corresponds to context of SA, Context B and C to a novel context. Test1 and test2 correspond to CPP post-conditioning measurements. Medial prefrontal cortex (mPFC), prelimbic cortex (PrL), infralimbic (IL), nucleus accumbens (NAc), caudate
putamen (CPu, dorsal striatum), basolateral amygdala (BLA), central amygdala (CeA), lateral amygdala (LA), dorsal hippocampus (DH), - decrease, + increase, and o no change.

<table>
<thead>
<tr>
<th>Species</th>
<th>Cocaine exposure/protocol</th>
<th>Localisation</th>
<th>mRNA/protein</th>
<th>Inflammation marker/modulators</th>
<th>Effect</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Human</td>
<td>Cocaine users</td>
<td>Serum levels</td>
<td>protein</td>
<td>IL-6</td>
<td>+</td>
<td>Moreira et al., 2015</td>
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<td>IL-10</td>
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<tr>
<td>Human</td>
<td>Cocaine users, Post-mortem</td>
<td>Striatum, hippocampus, and entorhinal cortex</td>
<td>protein</td>
<td>CD68, RCA-1 (activated microglia)</td>
<td>+</td>
<td>Little et al., 2009</td>
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<tr>
<td>Human</td>
<td>Cocaine users</td>
<td>dlPFC, OFC, mPFC, ACC, striatum, sensorimotor cortex, amygdala and hippocampus</td>
<td>protein</td>
<td>18kDa translocator protein (activated microglia)</td>
<td>o</td>
<td>Narendran et al., 2014</td>
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<td>Primate</td>
<td>SA (0.3mg/kg, i.v., 15months)</td>
<td>Striatum</td>
<td>protein</td>
<td>18kDa translocator protein (activated microglia)</td>
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<td>Smith et al., 2019</td>
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<tr>
<td>Rat</td>
<td>10mg/kg i.p., 1x</td>
<td>vmPFC, NAc, VTA</td>
<td>mRNA</td>
<td>IL-1β</td>
<td>+</td>
<td>Northcutt et al., 2015</td>
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<tr>
<td>Rat</td>
<td>SA (0.5 µg/kg, i.v., 15days)</td>
<td>VTA</td>
<td>mRNA</td>
<td>IL-1β, GFAP, IκBα, CD11b</td>
<td>+</td>
<td>Brown et al., 2018</td>
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<td></td>
<td></td>
<td>TNFa</td>
<td>o</td>
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<tr>
<td>Rat</td>
<td>SA (0.5mg/kg, i.v., 6h, 10days) + traumatic brain injury</td>
<td>PFC, OFC, NAc, Striatum</td>
<td>protein</td>
<td>IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, IL12, TNFa, IFNγ</td>
<td>o</td>
<td>Vonder Haar et al., 2019</td>
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<tr>
<td>Mouse</td>
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<td>NAc</td>
<td>mRNA</td>
<td>NFkBp65, NFkBp105, IκBp70</td>
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<td>Ang et al., 2001</td>
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<td>Mouse</td>
<td>20 mg/kg, i.p., 5x</td>
<td>Striatum</td>
<td>protein</td>
<td>NFkBp65, NFkBp105</td>
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<td>IκBα, IκBβ</td>
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<tr>
<td>Mouse</td>
<td>CPP (20mg/kg, i.p., 3x)</td>
<td>mPFC, NAc</td>
<td>protein</td>
<td>TNFa</td>
<td>-</td>
<td>Lin et al., 2011</td>
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<td>IL6</td>
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<td>IL-1β</td>
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<td>Cell (HBMECs) - Mouse</td>
<td>10µM - 20 mg/kg i.p., 7x</td>
<td>NAc core</td>
<td>mRNa and protein</td>
<td>TNFα, Iba1</td>
<td>Lewitus et al., 2016</td>
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<td>Mouse CPP (20mg/kg, i.p., 3x)</td>
<td>NAc</td>
<td>protein</td>
<td>p-NFκBp65, p-IκBα</td>
<td>+</td>
<td>Zhu et al., 2018 b</td>
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<td>Cell (BV2) - Mouse</td>
<td>10 µM for 1 h - 20mg/kg i.p., 7x</td>
<td>Microglia</td>
<td>mRNa and protein</td>
<td>PDGF</td>
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<tr>
<td>Mouse 10 and 100 mM for 24 to 48h - 20mg/kg i.p., 7x</td>
<td>Microvessels</td>
<td>mRNa and protein</td>
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<td>Guo et al., 2016</td>
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<td>Mouse 10 µM for 24h - 20mg/kg i.p., 7x</td>
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<td>Mouse 10µM for 24h - 20mg/kg i.p., 7x + miR124 overexpressing</td>
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<td>TLR4, IRAK1, TRAF6, MyD88, KLF4, TNFα, IL6, IL1β, NOS2, CCL2</td>
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<td>Cell (pericytes) - Mouse</td>
<td>10µM for 1 to 10h - 20mg/kg i.p., 7x</td>
<td>Brain capillaries</td>
<td>mRNa</td>
<td>CXCL10, VEGF, CCL2</td>
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<td>Niu et al., 2019</td>
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</table>

**Table 2: Summary of research findings on cocaine-induced neuroinflammation**

Self-administration (SA), conditioned place preference (CPP), prefrontal cortex (PFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), nucleus accumbens (Nac) + increase, - decrease, o no change