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European Journal of Pharmacology 526 (2005) 140–146
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Neural substrates of cocaine-cue associations that trigger relapse

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Accepted 23 September 2005
Available online 25 October 2005

Abstract

Learned associations that occur during the process of repeated drug use in addiction can later manifest as trigger factors in relapse to renewed drug-seeking and drug-taking behavior. The process of conditioned-cued relapse of drug-seeking behavior has been successfully modeled in animals using the reinstatement procedure, in which chronic drug self-administration can be extinguished or withheld, and then reinstated using conditioned stimuli previously paired with the drug. Our laboratory has extensively studied the neural circuitry underlying conditioned-cued drug-seeking during the expression of reinstatement. In order to study the learning process of drug-cue pairings, we further developed a procedure whereby discrete cocaine-cue pairings can be conducted in a single pavlovian training session in animals previously trained to self-administer cocaine. Presentation of these cues during later reinstatement trials produces robust responding over extinction levels at levels similar to those seen when animals experience the cues on a daily basis. In a series of experiments, we have shown that reversible pharmacological inactivation of the basolateral complex of the amygdala just prior to acquisition of cocaine-cue associations blocks the ability of cocaine-paired stimuli to elicit conditioned-cued reinstatement. This learning process is mediated in part by muscarinic acetylcholine and dopaminergic inputs to the basolateral complex of the amygdala, as intra-amygdala infusion of selective receptor antagonists at the time of acquisition significantly affects reinstatement. We have also recently found that disruption of neural activity within the basolateral complex of the amygdala at the time of consolidation (just after cocaine-cue pairings) will disrupt reinstatement. Taken together, these results reveal the importance of the amygdala in the acquisition, consolidation, and expression of drug-stimulus learning that drives relapse to drug-seeking behavior.

Keywords: Addiction; Amygdala; Cocaine; Conditioning; Cue; Reinstatement; Relapse

Contents

1. Conditioned cues and relapse to drugs of abuse

Drug dependence is characterized by high rates of relapse to drug-seeking and drug-taking behavior following periods of abstinence and drug detoxification. While multiple trigger factors can initiate or sustain relapse, evidence has clearly established the ability of drug-associated environmental cues (e.g., associated drug paraphernalia or locations where a drug was previously consumed) to elicit drug craving, and consequently reinstate drug-seeking and drug-taking. Conditioned-cued responses have been demonstrated for a variety of drugs of abuse, including psychostimulants (Ehrman et al., 1992; Foltin and Haney, 2000), opiates (Childress et al., 1994), nicotine

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doi:10.1016/j.ejphar.2005.09.034

(Chiamulera, 2005), and alcohol (Drummond et al., 1990). For example, abstinent cocaine abusers report intense subjective craving and autonomic arousal when exposed to cocaine-paired stimuli (Avants et al., 1995; Ehrman et al., 1992). Furthermore, these conditioned stimuli produce selective, discrete changes in neural activation of corticolimbic brain structures in experienced cocaine users (Childress et al., 1999; Grant et al., 1996; Kilts et al., 2001). Based on these findings in clinical laboratories, it has been theorized that, through a process of associative learning, previously neutral stimuli acquire incentive-motivational properties following repeated pairings with the abused drug (O'Brien et al., 1998). The drug associated stimuli subsequently elicit subjective craving and physiological arousal in a manner that perpetuates a return to further drug use (Gawin, 1991).

2. Animal models of conditioned-cued relapse

Craving as an operationally defined construct presents a major challenge to establish and measure using animal models of addiction (Littleton, 2000; Markou et al., 1993). However, animal models can clearly provide a variety of objective and quantifiable indices of drug-seeking behavior. The well established self-administration paradigm in laboratory animals (Weeks, 1962) has provided an empirical model to study multiple factors in drug-taking behavior, particularly in regards to the acquisition and maintenance of chronic drug-taking for a multitude of abused compounds (Balster and Lukas, 1985; LeSage et al., 1999). In recent years, the self-administration model has been adapted for use as a model of relapse by focusing on the reinstatement of lever pressing previously associated with drug delivery by means of various trigger factors (e.g., cues, stress, or noncontingent drugs). The reinstatement model is now a well established experimental method that can be readily applied to study the behavioral parameters and neural substrates of relapse (See, 2002; Shaham et al., 2003; Shalev et al., 2002). In the conditioned-cued model of reinstatement, stimuli (e.g., lights, tones, odors) previously paired with the self-administered drug can be presented in the absence of drug reinforcement following extinction and/or abstinence. The magnitude of increased operant responding on the previously drug-paired operandum can then be quantified as a measure of conditioned-cued reinstatement of drug-seeking behavior (Fig. 1A). Although further work remains to be done in developing reinstatement models in animals that closely approximate the relapse process in humans (Epstein and Preston, 2003; Katz and Higgins, 2003), the conditioned-cued reinstatement model possesses good face validity for modeling the activation of craving and arousal by environmental conditioned stimuli in drug dependent individuals.

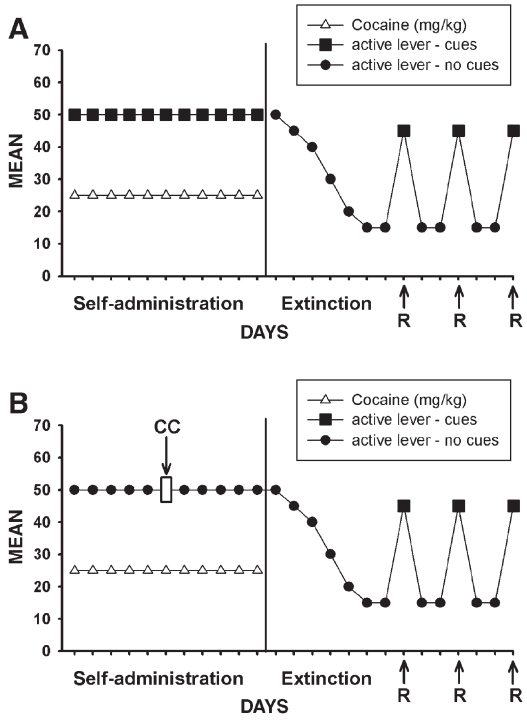

Fig. 1. *Conditioned-cued reinstatement models*. A) Experimental paradigm for reinstatement of drug-seeking behavior showing representative phases of drug self-administration (maintenance), extinction, and reinstatement test days (R). Subjects experience discrete drug-paired cues on each day of self-administration. Cues are then presented at the reinstatement test sessions to determine conditioned drug-seeking behavior. B) Experimental paradigm for assessing acquisition, consolidation, and expression of drug-cue associations. Animals undergo a single classical conditioning session (CC), in which they are passively exposed to cues discretely paired with each i.v. cocaine infusion. Cues are then presented at the reinstatement test sessions to determine conditioned drug-seeking behavior.

3. Associative learning with drugs of abuse

Chronic drug self-administration involves multiple exposures to the drug-taking environment and all of the specific stimuli associated with the drug-taking experience over periods of days to weeks. Thus, there has been limited focus on the specific phases of drug-stimulus learning. In contrast, a number of animal models of aversive conditioning have extensively examined the separate mnemonic processes of acquisition, consolidation, and expression of discrete conditioned associations (Davis et al., 1994; Maren, 1996). Furthermore, appetitive learning models have also been developed for assessing these multiple phases of learning and retrieval using single trial sessions at critical time points, such as consolidation (Salinas and McGaugh, 1996; Schroeder and Packard, 2002). These paradigms have made it possible to assess the neural substrates of acquisition and consolidation by pharmacological manipulation at the time of learning, as well as during retrieval of the learned associations at the time of expression.

We recently developed a modification of our reinstatement paradigm that allows for the assessment of the separate phases of acquisition, consolidation, and expression of stimulus-drug associations that can drive reinstatement (Fig. 1B). As in the standard reinstatement protocol, rats are first trained to lever press for i.v. cocaine infusions over several days in the absence of any programmed stimuli. The subjects then experience a single classical conditioning session, during which they receive passive pairings (i.e., levers are not extended) of a tone+light stimulus complex discretely paired with cocaine infusions. The number of pairings is based on the number of cocaine

infusions that each individual animal injected on the previous two cocaine self-administration sessions. Following acquisition, animals are returned to a pattern of daily cocaine self-administration in the absence of the cocaine-paired stimuli, followed by repeated extinction sessions and subsequent tests of reinstatement responding in the presence of the pavlovian-paired cues delivered during the operant lever responding. In our initial study using this paradigm, we found that discrete stimuli paired with cocaine infusions during the classical conditioning sessions potently reinstated extinguished lever responding at a level virtually identical to subjects who had experienced daily cocaine-cue pairings throughout the chronic maintenance phase of self-administration (Kruzich et al., 2001). Importantly, subjects did not show significant reinstatement if stimuli were a) presented in a completely random fashion (i.e., no consistent contiguity or contingency) at the time of acquisition, or b) presented as a novel stimulus (i.e., first and only experience of the stimulus) at the time of reinstatement testing. The development of this model has provided us the experimental means for discretely assessing the various stages of drug-cue associative learning.

4. Neural substrates of drug-cue associations

Several lines of research have extensively implicated the amygdala in the acquisition and expression of a variety of motivational tasks, both aversive (Cahill and McGaugh, 1990; LeDoux, 2000) and appetitive (Everitt et al., 2000; Gallagher and Chiba, 1996). In our initial studies, we focused extensively on the role of the basolateral complex of the amygdala in reinstatement using animals with an extensive history of drug-cue pairings (i.e., each day of drug self-administration included discrete cue presentation). We found that excitotoxic lesions (Meil and See, 1997) or reversible pharmacological inactivation (Grimm and See, 2000; McLaughlin and See, 2003) of the basolateral complex did not affect cocaine self-administration or cocaine-primed reinstatement, but they profoundly attenuated the ability of cocaine-paired stimuli to reinstate extinguished lever responding. Related findings supporting a critical role of the amygdala in mediating conditioned associations with cocaine reinforcement have been reported with other models of reinstatement (Ciccocioppo et al., 2001; Kantak et al., 2002), conditioned place preference (Brown and Fibiger, 1993), and second order responding for cocaine-paired conditioned stimuli (Whitelaw et al., 1996).

Using the classical conditioning model of drug-cue associations, we have also assessed amygdalar mediation of the acquisition phase of cocaine-paired associative learning. In our initial study (Kruzich and See, 2001), rats received bilateral infusions of the sodium channel blocker, tetrodotoxin, or vehicle in the basolateral complex or central nucleus of the amygdala just prior to the acquisition or expression sessions. Intra-basolateral complex infusions of tetrodotoxin blocked reinstatement under both conditions, suggesting that the basolateral complex is critical in the initial formation of drug-stimulus associations, as well as the expression of cocaine-seeking behavior (Fig. 2). In contrast, tetrodotoxin infused in the central

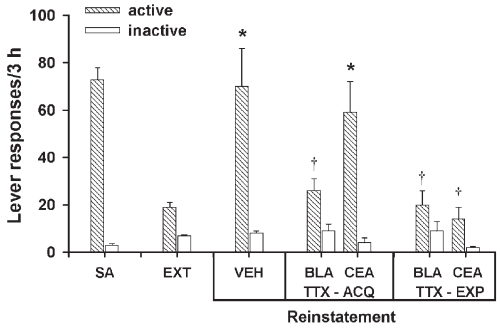

Fig. 2. *Blockade of acquisition or expression of conditioned-cued reinstatement by inactivation of the amygdala*. Active (drug-paired) and inactive lever responses (mean±S.E.M.) are shown for the last day of self-administration (SA), extinction (EXT), and the reinstatement test days for vehicle (VEH) or tetrodotoxin (TTX- 5 ng/side) infusion immediately prior to acquisition (ACQ) or expression (EXP) in the basolateral complex (BLA) or the central nucleus of the amygdala (CEA). Significant differences from extinction level responding (*$P<0.05$) or vehicle responding (†$P<0.05$) are noted. (Adapted from Kruzich and See, 2001.)

nucleus of the amygdala just prior to acquisition failed to significantly decrease subsequent reinstatement, although inactivation just prior to expression effectively blocked reinstatement (Fig. 2). This dissociation between the basolateral complex and central nucleus of the amygdala appears similar to processing of other forms of affective learning that are dependent upon the amygdala, specifically inhibitory avoidance learning (Da Cunha et al., 1999; Parent and McGaugh, 1994). The attenuation of expression by pharmacological inactivation of either amygdalar nucleus suggests that the expression of reinstatement (at least in part) follows a lateral to medial flow of stimulus processing from the basolateral complex to the central nucleus of the amygdala. This interpretation fits with anatomical data on intra-amygdalar connections (Pitkanen, 2000) and previous models of amygdalar activation during emotional stimulus processing (LeDoux, 2000).

In a further application of this acquisition–expression model of reinstatement, we tested the role of cholinergic inputs to the basolateral complex of the amygdala. Acetylcholine has been well characterized as a critical regulator of associative learning processes (Dunnett and Fibiger, 1993; Squire and Davis, 1981). The basolateral complex has a dense innervation of cholinergic inputs (Carlsen and Heimer, 1986; Spencer et al., 1986), with the major cholinergic projections to the basolateral complex arising from the nucleus basalis (Butcher et al., 1992). Previous studies have demonstrated a critical role of muscarinic receptor regulation in amygdala-mediated forms of learning, including passive avoidance learning (Dumery and Blozovski, 1987; Power et al., 2003) and conditioned-place preference (Schroeder and Packard, 2004). We showed (See et al., 2003) that intra-basolateral complex infusion of the muscarinic receptor antagonist, scopolamine, at the time of acquisition produced a dose-dependent attenuation of conditioned-cued reinstatement (Fig. 3). In contrast, scopolamine administered into the basolateral complex just prior to the expression of conditioned-cued reinstatement failed to affect lever responding. These results support the role of cholinergic inputs to muscarinic

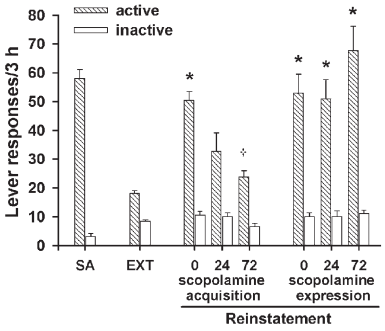

Fig. 3. *Intra-BLA muscarinic receptor blockade of the acquisition, but not expression, of conditioned-cued reinstatement*. Active and inactive lever responses (mean±S.E.M.) are shown for the last day of self-administration (SA), extinction (EXT), and the reinstatement test days for scopolamine (0, 24, or 72 μg/side) given immediately prior to acquisition or expression. Significant differences from extinction level responding (*$P<0.05$) or vehicle responding (†$P<0.05$) are noted. (Adapted from See et al., 2003.)

acetylcholine receptor targets in the basolateral complex in the formation of drug-cue associations, similar to other forms of amygdalar mediated associative learning (Dumery and Blozovski, 1987; Ingles et al., 1993; Schroeder and Packard, 2004).

Using the standard conditioned-cued reinstatement model, whereby rats experience daily exposure to drug-paired stimuli, we previously demonstrated a role of the dopaminergic inputs to the basolateral complex of the amygdala in the modulation of conditioned-cued reinstatement. Infusion of the selective dopamine D1 receptor antagonist, SCH23390, alone or in combination with raclopride, a selective dopamine D2/D3 receptor antagonist, profoundly attenuated conditioned-cued reinstatement, whereas raclopride alone had no effect when compared to vehicle (See et al., 2001). Similar to our results with sodium channel blockade, neither dopamine D1 or D2 receptor antagonists had a significant effect on self-administration when infused just prior to contingent i.v. cocaine access. In an extension of these findings with dopamine receptor antagonists, we found that increasing dopamine by bilateral amphetamine infusions into the basolateral complex produced a significant enhancement of responding in the presence of the cocaine-paired conditioned cues (Ledford et al., 2003). Importantly, intra-amygdala amphetamine had no effect when administered in the absence of the cues, indicating that increased dopaminergic activity in the basolateral complex by itself was not effective at producing reinstatement, but required simultaneous processing of the previously paired drug cues.

We recently assessed the impact of dopamine receptor antagonism at the time of acquisition during single classical conditioning sessions. Our results show that infusion of SCH 23390 into the basolateral complex of the amygdala at the time of acquisition dose-dependently attenuated drug-paired lever responding during reinstatement testing, further supporting the role of the dopamine D1 receptor in regulating cocaine-stimulus associations (Fig. 4). Infusion of raclopride into the basolateral complex suggests a more complicated role for the dopamine D2 receptor in the acquisition of drug-stimulus associations. We found an inverted U dose response curve, whereby raclopride at mid-range doses infused at acquisition actually facilitated the later reinstatement of responding, but higher doses of raclopride resulted in an attenuation of responding (Fig. 4). This effect suggests that varying the occupancy of different dopamine D2-like receptors (possibly both pre- and postsynaptic) can either facilitate or inhibit cocaine-cue associative processing. Collectively, these findings with dopamine receptor agents suggest a critical role of dopaminergic inputs to the basolateral complex, whereby dopamine modulates the acquisition, retrieval, and utilization of drug-stimulus associations. Such a role for amygdalar dopamine in cocaine-cue learning is supported by electrophysiological evidence that dopamine potentiates sensory inputs to the amygdala (Rosenkranz and Grace, 1999) and is critical in maintaining neuronal responses produced during pavlovian conditioning (Rosenkranz and Grace, 2002). The role of dopamine in associative drug-stimulus learning is further supported by evidence that the amygdala exhibits associative long term potentiation (Rogan et al., 1997), and that dopamine regulates the induction of amygdalar long term potentiation (Bissiere et al., 2003).

Consolidation of memory is the process whereby newly created, labile associations become stored in a more persisting form (i.e., long-term memory). Previous work, primarily in the field of fear/aversion conditioning, has demonstrated a substantial role for the basolateral complex of the amygdala in the consolidation of long-term memory (McGaugh, 2004). The

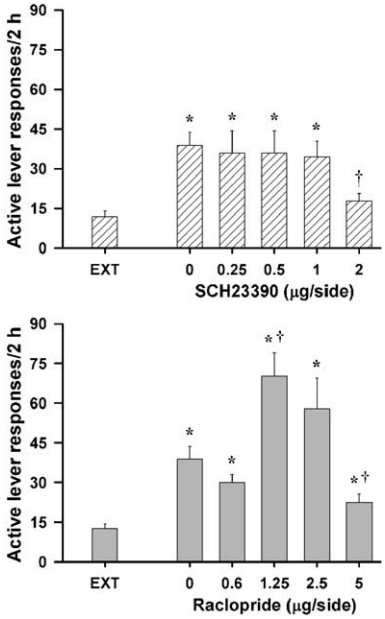

Fig. 4. *Dopamine receptor antagonists administered in the basolateral complex of the amygdala at the time of acquisition alter reinstatement responding*. Active lever responding (mean±S.E.M.) during extinction or conditioned-cued reinstatement tests in animals infused with different doses of the dopamine D1 receptor antagonist, SCH23390 (*top*), or the dopamine D2 receptor antagonist, raclopride (*bottom*), directly into the basolateral complex prior to the classical conditioning session. Extinction data represent the mean for all treatment groups and reinstatement data represent the mean of three separate reinstatement test sessions. (*$P<0.05$, significantly increased responding over extinction; † $P<0.05$, significantly different compared to vehicle.)

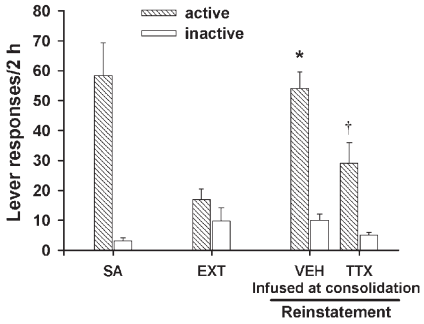

Fig. 5. *BLA inactivation attenuates consolidation of cocaine-cue associative learning*. Active and inactive lever responses (mean ± S.E.M.) are shown for the last day of self-administration (SA), extinction (EXT), and the reinstatement test days for vehicle (VEH) or tetrodotoxin (TTX- 5 ng/side) infusion administered immediately following the classical conditioning session at the time of consolidation. Significant differences from extinction level responding (*$P<0.05$) or vehicle responding (†$P<0.05$) are noted.

importance of the basolateral complex in consolidation of incentive learning with non-drug appetitive reinforcers has also been recently reported (Wang et al., 2005). In an initial test of the neural substrates underlying consolidation of cocaine-cue associations, we found that inactivation of the basolateral complex by tetrodotoxin immediately *after* the single classical conditioning session resulted in significantly attenuated conditioned-cued reinstatement when compared to animals that received vehicle (Fig. 5). This finding thus demonstrates the important role of the amygdala not only in acquisition and expression, but also the consolidation of cocaine-cue associative learning that maintains conditioned-cued reinstatement.

5. Extending the circuitry of drug-cue associations

Most of our previous work using the reinstatement model of relapse has focused on amygdalar mediation of drug-stimulus associative learning that contributes to reinstatement of drug-seeking behavior. The amygdala has widespread connections with a number of forebrain structures, including extensive glutamatergic efferent projections to the nucleus accumbens and prefrontal cortex (Brinley-Reed et al., 1995; McDonald, 1991; Sesack et al., 1989). In regards to the expression of reinstatement, we have shown that pharmacological inactivation (either by tetrodotoxin or GABA receptor agonists) of the dorsal medial prefrontal cortex (anterior cingulate and prelimbic cortex), the lateral orbitofrontal cortex, or the nucleus accumbens core region significantly attenuated cocaine-seeking behavior produced by drug-paired cues (Fuchs et al., 2004a,b; McLaughlin and See, 2003). In contrast, inactivation of a number of other adjacent or distal brain structures had no effect on reinstatement. This circuitry in the rat model of cue-induced relapse (amygdala, prefrontal cortex, nucleus accumbens core) shows striking homology with a number of brain imaging studies in cocaine addicts. In particular, under different test conditions and using various brain imaging methods, cocaine-paired cues have been shown to increase metabolic activation of the amygdala (Childress et al., 1999; Grant et al., 1996; Kilts et al., 2001), the anterior cingulate (Childress et al., 1999; Garavan et al., 2000; Kilts et al., 2001; Maas et al., 1998), nucleus accumbens (Kilts et al., 2001), and the orbitofrontal cortex (Bonson et al., 2002; Goldstein and Volkow, 2002; Wang et al., 1999) in cocaine addicts. Future studies in the animal model will be directed towards these anatomical regions that have extensive afferent and efferent connections with the amygdala in order to assess their roles in the processes of acquisition, consolidation, and retrieval of drug-stimulus associations.

Finally, several other critical issues need to be addressed in regards to the circuitry underlying relapse. First, does the same circuitry underlying cocaine-cue associative processing subserve other drugs of abuse? In a study of the reinstatement of heroin-seeking behavior, we found that pharmacological inactivation of the basolateral complex of the amygdala abolished conditioned-cued reinstatement of heroin-seeking behavior in a manner comparable to that seen with cocaine, suggesting a similar role of the basolateral complex in opiate-paired stimulus learning (Fuchs and See, 2002). Whether this pattern holds true for other abused drugs, such as alcohol and nicotine, remains to be tested. We also predict that there will be similarities in the regional neural substrates underlying acquisition and consolidation of drug-cue associations, although it is quite likely that specific receptor regulatory mechanisms may differ between abused drugs. Second, the selective roles of several critical neurotransmitters/neuromodulators have yet to be examined in the conditioned-cued reinstatement model. For example, norepinephrine is well characterized in the regulation of memory consolidation in the amygdala (McGaugh, 2004), yet norepinephrine has not yet been studied for it's role in the acquisition and consolidation of drug-cue memories relevant to relapse. Finally, the interaction of multiple trigger factors of relapse presents a critical challenge to gaining a "real world" perspective on the neural substrates of relapse. In particular, the interplay of stress and conditioned cues may constitute the most important factor in the process of relapse to drugs of abuse (Goeders, 2002; Sinha et al., 2000). In support of this interaction, we have recently found that acute pharmacological stress activation by the α-2 noradrenergic antagonist, yohimbine, will potentiate cue reactivity in a supra-additive manner during reinstatement (See et al., 2005). These further directions in determining the neural circuitry of relapse to drugs of abuse should ultimately yield new treatment approaches that will help break the patterns of repetitive, compulsive, and destructive drug abuse.

Acknowledgement

The authors' work is supported by the National Institute on Drug Abuse (DA10462, DA15369, DA16511).

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