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1. Abstract

Cocaine is a powerful CNS (central nervous system) psychostimulant, being highly addictive. There is staggering evidences that the stress, and particularly his major effector CRF (corticotropin-releasing factor), has a crucial role in drug addiction, including to cocaine.

In this review it will be analyzed the role of CRF in the cocaine-induced neuroadaptations, underlying the chronic consumption of cocaine and the behaviour propitiating relapse.

Finally, it will be characterized the potencial role of CRF receptor antagonists as pharmacological tools for the treatment of cocaine addiction.

CRF_1 selective antagonists CP154.526, antalarmine and MPZP have potential to be used in cocaine addiction treatment whereas, R121919 and NBI-27914 do not. In relation to CRF_2 selective antagonist AS-30 and Astressin-2B there are not sufficient data do analyze its potential. Non selective CRF antagonists α-helical CRF and D-Phe CRF_{12-41} have also potential to be used in cocaine addiction treatment. This data strongly support that both CRF_1 and CRF_2 contribute to cocaine addiction.

The relevance of this review stems from the fact that there is no pharmacological therapeutics approved to cocaine addiction.

Resumo

A cocaína é um poderoso estimulante do SNC (sistema nervoso central). Existem evidências de que o stress, incluindo o seu principal mediador, o CRF (factor de libertação de corticotropina), tem um papel crucial na adição à cocaína. Esta hormona hipotalâmica aumenta os efeitos agudos da cocaína e dirige a neuroplasticidade induzida pela cocaína que caracteriza a adição.

Neste artigo de revisão, irá ser analisado o papel do CRF nas neuroadaptações no cérebro desencadeadas pela cocaína que condicionam o seu consumo crónico incluindo o comportamento de recaídas.

Por último, serão analisados quais os antagonistas dos receptores do CRF que têm potencial para serem utilizados no tratamento farmacológico da adição à cocaína. Este trabalho é crucial visto que não existem terapêuticas farmacológicas disponíveis para o tratamento da adição à cocaína.

Os antagonistas selectivos dos receptores CRF_1 CP154.526, antalarmine e MPZP têm potencial para serem utilizados no tratamento da adição à cocaína, ao contrário de R121919 e de NBI-27914. Relativamente a antagonistas selectivos do CRF_2, AS-30 e Astressin-2B, não existe informação suficiente sobre o seu putativo interesse terapêutico. Os antagonistas não selectivos do CRF α-helical CRF e D-Phe CRF_{12-41} também evidenciam potencial terapêutico na adição à cocaína.

2. Introduction

Cocaine is a methyl ester of benzoylecgonine (EMCDDA), which is an alkaloid that can be extracted from coca leaves of *Erythroxylon coca* Lam (coca leaves) or synthesized from ecgonine (UNODC 2011). This substance has been consumed by humans for a long time. The antiquity of the cocaine use is well documented through archaeological findings across South and Central America (Stolberg 2011), having been found several remnants of coca leaf in Bolivian and Peruvian tombs with the date of 600 AC (Boghdadi & Henning 1997).

Cocaine is included in the psychostimulants substance class. These substances generally raise the activity of the brain monoamines (catecholamines and serotonin), stimulating intensely the Central Nervous System (CNS).

Cocaine was included in the Controlled Substances Act 1970 list, and belongs to the Schedule II, along with opioids and other psychostimulants (amphetamine-type stimulants) (NIDA 2009). Cocaine is envisaged as a substance of accepted (limited) medical use but with high abuse potential, that can induce serious physical and psychological dependence.

Its therapeutic use is owned to his anaesthetic and vasoconstrictor properties. Cocaine is used in topical anaesthesia in ophthalmologic surgery (Grynkiewicz & Gadzikowska 2008), nevertheless in this practice area its use has been reduced due to its corneal toxicity (NIDA 2009). Also it is used in the otorhino-laryngoscopic interventions as local anaesthetic of the nasal, oral and laryngeal mucosa (NIDA 2009). For example, its topical use in fiberoptic bronchoscopy allows the procedure to be accomplished with less resource to systemic narcotics (Festic et al. 2010).

Cocaine has also been used in a method of local topical anaesthetic, added to tetracaine and adrenaline, in a combination called TAC. This is used mainly in the hospital emergency department for small dermal lacerations suture, in paediatric patients. The rational for using TAC is to avoid the need for local injections (Noorily et al. 1995), however there are reports of rare but serious adverse effects of TAC in children, including a death case attributed to the fast absorption by mucous membranes (Bush 2002).

The routine use of cocaine has been criticized because of its increasing cost, less availability and difficulties in the storage because of its controlled substance feature and addictive potential and dangerous adverse side effects (Noorly et al. 1995; Eidelman et al. 2005).

The compulsive use of drugs of abuse, in particular the use of cocaine, provides negative humour stages in which the dependents feel agitation and anxiety, not only with repeated use, but especially in the early withdrawal (24h-48h), during the so called “crash” period.

After the crash, in protracted abstinence, it was obvious from pre-clinical studies that there was high responsiveness to stressor elements. (Erb 2010).

There are clear evidences that stress has crucial role in addiction, being the Corticotropin-Releasing Factor (CRF) the major stress effector (Guan et al. 2009). This hypothalamic hormone has a biphasic role in distinct structures of the mesocorticolimbic dopaminergic during chronic drug consumption. By one hand it increases the acute effects of drugs of abuse, and in the other hand, it potentiates drug induced neuroplasticity that leads to relapse following withdrawal.

Several studies revealed that cocaine stimulates the release of CRF (Basso et al. 1999), being evident that chronic cocaine consumption causes dysregulation not only of the hypothalamic-pituitary-adrenal axis (HPA), but also of the brain stress systems, which are both CRF mediated (Koob 2009).

At the present moment there is no pharmacologic therapies approved by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) for the treatment of cocaine dependence (Rocio et al. 2004; Shorter & Kosten 2011).

For the cocaine’s addiction treatment there are only behavioural therapies available, but they have narrow efficiency (Shorter & Kosten 2011). The behavioural therapies available are Cognitive-behavioural therapy and the Community Reinforcement Approach Plus Vouchers (CRA Plus Vouchers). The first one consists in the learning of a set of self-control strategies, which allow the patients to identify and correct problematic behaviour. The CRA

Plus Vouchers is a 24h-lasting therapy in ambulatory, in which one participates in counselling sessions where the improvement of family relationships and of the social network is encouraged, and where skills that minimize the abuse are learned (NIDA 2009).

This review is going to address the epidemiology of cocaine, the properties of cocaine (chemistry, pharmacokinetics and phamacodynamics), the health risks associated with its consumption, and therapeutic for cocaine addiction. It will specially analyze the role of CRF in cocaine-induced brain changes underlying the behaviour leading to addiction.

Finally, and as major purpose, it will be reviewed the potential role of the antagonists of CRF as pharmacologic tools for cocaine addiction treatment.

3. Methodology

The following database available in *Biblioteca Central dos Serviços de Documentação dos Hospitais da Universidade de Coimbra* were consulted: Cochrane Library, Pubmed and Science Direct.

The search strategy included the following key-words: cocaine, addiction OR dependence, CRF OR CRH, CRF antagonist OR CRH antagonist, withdrawal, relapse and stress and was limited to articles written in English. No time limitation was imposed.

I have also consulted publications from *National Institute on Drug Abuse* (NIDA), *United Nations Office and Crime* (UNODC), European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), World Health Organization (WHO), Instituto de Drogas e Toxicodependência (IDT).

4. Epidemiology

Cocaine ranks as the fourth most abused illicit drugs in the world, with a global prevalence estimate between 14 and 21 millions of consumers, the equivalent to 0.3 -0.5% of the population aged between 15 and 64 years old. In this list, cannabis is in the first place, amphetamine type stimulants (ATS) in second and opioids in third (UNODC 2011).

After heroin, cocaine is considered the most problematic drug, not only in what concerns health consequences, but also in terms of trafficking-related violence (UNODC 2011).

North America has the larger number of consumers in the world, about 5.7 millions, which stands for one third of the total consumers. Outside America, Europe has the most developed market, especially Central and Western Europe (UNODC 2011).

Cocaine is the second illicit drug most consumed in Europe, after cannabis, and despite the great number of dependence treatments that correspond to opiods consumers, cocaine consumers represent already a quarter of all new addicts admitted to treatment (EMCDDA 2010).

In this continent the number of consumers arises to 4.3 - 4.8 millions, which corresponds to 0.8 – 0.9% of the population aged between 15 – 64 years old, and about 14 millions of Europeans have consumed at least once in life, which means 4.5% of the population aged between 15 – 64 years old. It is estimated that about 5.9% of the young adults (15 – 34 years old) have already consumed at least once in life (EMCDDA 2010).

Regarding Europe, the great number of consumers (1.2 – 1.3% of the populations aged between 15 – 64 years), is found in Western and Central Europe compared with East Europe

(0.1 – 0.3% of the populations aged between 15 – 64 years). Two thirds of European consumers live in UK, Italy and Spain (UNODC 2011).

Whereas the number of consumers has been continuously decreasing in the USA since 2006, the number of consumers doubled between 1998 and 2006 in Europe, having then stabilized between 2006 and 2009 (UNODC 2011). On the contrary, one is facing an increase in cocaine consumption both in Africa and Asia.

In Portugal cocaine is the second most consumed drug in the adult population, 1.9% consumers are between 15 – 64 years old, and 2.8% of consumers are between 15 – 34 years old. Algarve and Lisbon are the regions with the highest consume prevalence, above the national average (IDT 2009).

There are different consume patterns: the occasional consumer, the regular social integrated consumer and the marginalized consumer, being the last one frequently drug addicted (EMCDDA 2010).

5. Cocaine Pharmacology

5.1 Cocaine Chemistry

Cocaine is a methyl ester of benzoylecgnine (UNODC 2011; EMCDDA), having the following molecular formula C17H21NO4 and systematic name (IUPAC): [1*R*-(exo, exo)] -3-(benzoyloxy)-8-methyl-8-azabicyclo [3.2.1] octane-2-carboxylic acid methyl ester (EMCDDA).

Cocaine represents 0.6 to 1.8% of all substances extracted from coca leaves (Rocio et al. 2004). An organic solvent (eg. Kerosene) can be used in the extraction process and therefore a cocaine paste can be formed with a 40 – 80% level of pure alkaloid cocaine base (Rocio et al. 2004; Golstein et al. 2009). When one adds hydrochloric acid to the cocaine paste the hydrochloride cocaine salt is formed. This pharmaceutical form is water soluble and isnot only used in local anaesthesia but can also be abused by intravenous injection and by absorption thought mucous membranes, namely nasal mucosa snorting (Rocio et al. 2004). This pharmaceutical form is highly susceptible to pyrolysis (Rocio et al. 2004), decomposing at 195^{o}C, thus cannot be heated to be consumed (Boghdadi & Henning 1997).

Both cocaine base (or freebase) and crack, have a crystalloid form, being insoluble in water, but soluble in alcohol, acetone or ether (Boghdadi & Henning 1997). Its fusion point is 95^{o}C (Boghdadi & Henning 1997), and it is highly resistant to pyrolysis (Rocio et al. 2004), thus being heated until it vaporizes, to be inhaled (Boghdadi & Henning 1997).

Cocaine freebase and crack have a slightly different manufacturing process, even though being the same chemical form of cocaine. In fact crack manufacture is simpler and less expensive, becoming more popular than cocaine base. Furthermore, it is safer to consume crack because this does not have the risk of burning as cocaine base (Boghdadi & Henning 1997; Golstein et al. 2009).

Cocaine can be consumed combined with heroin, forming the so called ‘speedball’ (Golstein et al. 2009).

5.2 Routes of cocaine administration

Cocaine can be consumed in several ways: It depends if it is in a water soluble form – hydrochloride cocaine, or in a crystalloid form, soluble in alcohol, acetone or ether- cocaine base or crack (Boghdadi & Hennnig 1997).

Hydrochloride cocaine can be consumed by intravenous way or by absorption through mucosa, including nasal mucosa (Boghdadi & Hennnig 1997).

Cocaine in a crystalloid form has to be heated to be consumed. Cocaine base has to be mixed with tobacco and smoked, or can be heated and then inhaled in special pipes. Crack can be smoked mixed with tobacco or marijuana, or can be smoked in usual pipes or glass pipes (Boghdadi & Hennnig 1997).

Cocaine base can be inhaled by using heated pipes, or smoked mixed with tobacco. In the same way crack can be inhaled by using heated pipes, or even smoked mixed with marijuana or tobacco. The origin of the name ‘crack’ comes from the sound of the crystals cracking while it is being smoked (Boghdadi & Henning 1997). When smoked cocaine has a bigger addictive effect (Rocio et al. 2004).

5.3 Half-life, metabolization and elimination of cocaine

Smoking cocaine base or crack allows the cocaine to reach the cerebral circulation in 6 to 10 seconds (Boghdadi & Henning 1997; Rocio et al. 2004), much faster than consuming it by intravenous injection, which takes twice the time, or by intranasal absorption (snorting). Intranasal cocaine takes 3 to 5 minutes to reach the cerebral circulation, but on the other hand prolongs the duration of effects. Cocaine’s half- life time is short: 0.5 to 1.5 hours (Boghdadi

& Henning 1997; Rocio et al. 2004). This stimulant reaches the higher concentrations in the brain, kidneys and spleen (Boghdadi & Henning 1997).

After absorption, 90% of the cocaine binds to blood proteins. Its distribution volume is 1.96-2.7 L/Kg (Goldstein et al. 2009). Then 75 – 80% of the cocaine is metabolized into benzoylecgonine, and in lesser extension into ecgonine methyl ester (Boghdadi & Henning 1997; Rocio et al. 2004). Some metabolites are metabolized in ecgonine and then eliminated by renal excretion (Goldstein et al. 2009).

Benzoylecgonine has vasoconstrictor effects but does not seem to cross blood-brain barrier quickly, while ecgonine methyl ester has low pharmacologic activity and crosses the blood-brain barrier in low quantity (Goldstein et al. 2009).

The ecgonine methyl ester is formed by an enzymatic hydrolysis by liver and plasma colinesterases, and benzoylmethylecgonine is formed in a bigger extension by spontaneous hydrolysis [therefore in a non enzymatic manner (Boghdadi & Henning 1997; Rocio et al. 2004)]. These two metabolites have plasmatic half-lives of 4 and 6 – 7.5 h respectively (Boghdadi & Henning 1997).

About 5% of the cocaine is metabolized into norcocaine, which is metabolically active (Rocio et al. 2004). Norcocaine is formed in the liver by N-demetilation; this metabolite does not cross the blood-brain barrier (Goldstein et al. 2009).

Other minor compounds are formed, such as p-hydroxycocaine, m-hydroxycocaine, p-hydroxybenzoylecgonine, m- hydroxybenzoylecgonine and norbenzoylecgonine (Goldstein et al. 2009).

9.5 to 20% of cocaine is not metabolized, being depurated directly in the urine and detected till 24 – 36h post-consumption (Goldstein et al. 2009).

Cocaine and metabolites can be detected in several samples, such as urine, blood, hair, sweat, meconium and amniotic liquid. The urine multi-enzimatic immunoassay is the first test applied. Since cocaine has a fast half-life elimination, the urine tests analyzes the metabolite benzoylecgonine. The positive results are confirmed with chromatography gas mass spectrometry (Golstein et al. 2009).

5.4 Pharmacodynamics of cocaine

Cocaine operates by inhibiting the dopamine, noradrenaline (catecholamines) and serotonine uptake transporters in pre-synaptic terminals, resulting in the impedance of the neurotransmitters reuptake and, by this way, in an increase in the neurotransmitter availability in the cleft. Therefore the synaptic transmission is altered and the monoaminergic activity gains emphasis (Carrera et al. 2004; Schmidt et al. 2005; Treadwell & Robinson 2007; Goldstein et al. 2009).

Due to reuptake blockage of catecolamines in the pre-synaptic terminal, cocaine has simpaticomimetic effects, resulting in the raise of the arterial pressure, heart rate, hyperhidrosis, shaking, palpitation and hyperthermia (Treadwell & Robinson 2007).

Hyperthermia can also be owed to the cocaine-induce dysregulation of the heat centre, localized in the hypothalamus (Goldstein et al. 2009).

In high doses it has also anticholinergic effects, by the inhibition of the muscarinic receptors (in doses approximately 20-fold higher than the plasma concentration required to produce euphoria). Therefore cocaine can delay the gastric motility increasing the trend to gastroduodenal ulcer, and ensuing perforation (Boghdadi & Henning 1997).

The major effect in the CNS, and specially sought by the consumers, is euphoria. This comes from the cocaine influence in the mesocorticolimbic area of the brain, which causes the sustained stimulation of the dopamine receptors. By this way the consumer experiences intense euphoria, high energy, awareness, raised self-trust, indefatigability and mild to moderate anorexia. Also the sexual pleasure is amplified (Treadwell & Robinson 2007). Moreover, it inhibits the activity on the pontine nucleus locus coeruleus (LC), which brings down fear and panic, giving highlight to wellness and euphoria (Boghdadi & Henning 1997).

These positive reinforcing effects are experienced with low to moderate consumption doses. The evolution to a heavy and chronic consumption pattern brings about a progression of the positive into negative effects (Carrera et al. 2004), with aggressiveness, disorientation, hallucinations (Goldstein et al. 2009), total insomnia, exhaustion and serious anorexia (Carrera et al. 2004).

The continued inhibition of the dopamine reuptake in the synaptic cleft will consume organism dopamine storage, causing the increase of the dopamine receptor type 2 (dopamine D_2 receptor; Tsukada et al. 1996) in particular D_2 receptors in high-affinity state (D_2 High; Briand et al. 2008). This phenomenon produces the craving behaviour (Boghdadi & Henning 1997) and the "washed-out" syndrome, characterized by anhedonia, lethargy and moving muscles difficulty (Goldstein et al. 2009).

The raised serotoninergic activity is also responsible for major possibilities of having seizures (Goldstein et al. 2009).

With repeated use the CNS will become tolerant to the cocaine's euphorigenic effects. This way the consumer needs to consume a higher cocaine dose to obtain the initial euphoria. The higher the consume is the higher is the dose needed to satisfy the consumer. However, the same tolerance does not occur (or it occurs only partially), in the other parts of the organism.

Thus the dose increase will raise the cardiovascular and CNS toxicity (Boghdadi & Henning 1997).

Cocaine blocks competitively the sodium channels voltage- gated in the neurons as well as in the heart. Therefore it suppresses the conduction and the initiation of the electric impulse in both CNS (Treadwell & Robinson 2007; Goldstein et al. 2009) and heart (Boghdadi & Henning 1997). This conduction blockage allows its use as local anaesthetics.

This cardiotoxicity translates into decreases in the depolarization rate and in the amplitude of the action potential, delaying the conduction, thus causing ventricular arrhythmia, QRS prolongation, QT/QTc prolongation (Goldstein et al. 2009) and sudden death (Boghdadi & Henning 1997). Also its vasoconstrictor effect contributes to sudden death, and can cause massive myocardial infarction (Boghdadi & Henning 1997).

Its vasoconstrictor effect is owed to the inhibition of the local reuptake of noradrenaline, the raise of the endothelin 1 and the decrease of the nitric oxide production (Goldstein et al. 2009). This effect can not only cause myocardial infarction, but is also responsible for arterial hypertension and infarction of several other tissues (Goldstein et al. 2009).

Cocaine intake can also cause miscarriage, placenta abruption, placenta previa and stillbirth in a pregnant woman. Additionally cocaine can cause foetal intrauterine growth retardation, prematurity, congenital anomalies and cerebral infarction or haemorrhage. Still in the neonatal period the baby can experience withdrawal, convulsive disorders, arterial coronary spasm and ventricular tachycardia (Boghdadi & Henning 1997).

6. Addiction

6.1 Addiction definition

Drug addiction is a substance dependence condition which manifests as a compulsion to seek and consume drug, loss of self-control in limiting intake, and emergence of a negative emotional state when drug access is not possible (Koob & Le Moal 2008).

6.2 Reward System

When a non-dependent individual consumes for the first time, e.g. cocaine, this psychoactive substance stimulates reward cerebral circuits, obtaining wellbeing sensations like euphoria and raised humour, thus promoting positive reinforcement (Zangen 2010). In fact, acute psychoactive drug administration, including cocaine, initially facilitates the dopamine and glutamate neurotransmission in the nucleus accumbens (Heidbreder 2005; Koob & Le Moal 2008).

In a normal regulated organism, the individual neither can directly manipulate his sensibility to sensorial stimulus, nor can change voluntarily the responsiveness of his reward system, in order to amplify wellbeing. This positive state of humour is physiologically obtained by natural reward-seeking behaviours, like eating or having sex (Ahmed & Koob 2005).

The positive impact of cocaine on dopamine works as a facilitator of the reward system, raising its responsiveness, and therefore the sensorial stimulus has a greater impact in the hedonic motivation (Ahmed & Koob 2005).

6.3 Homeostasis and allostasis

The organism is an open system, seeking permanently the stability in a dynamic equilibrium. In an attempt to maintain the homeostasis, it opposes to any induced disruption (Fig1). It is believed to exist brain systems which are responsible for maintaining the brain in a hedonic neutral condition, by triggering negative feedback, thus opposing to any stimuli that affects the affective state (Koob & Le Moal 2008). The Solomon's opponent-process motivation theory conceives that when hedonic, emotional or affective states get started, they are automatically modulated by mechanisms within CNS that reduce the intensity of positive feelings (Koob & Le Moal 2008).

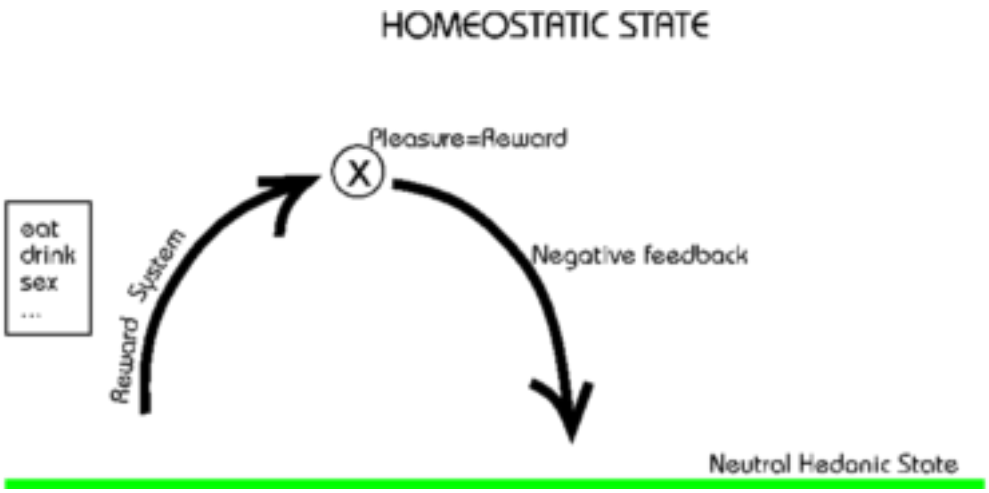

Fig 1: Normal homeostatic state.

But when the addictive drugs acts, this simple counteradaptative process is limited compared with the powerful drug effect, quickly entering in a dysregulation stage, in which it is no longer possible to reach normal threshold of reward function, achieving allostasis (Koob & Le Moal 2008). Therefore bigger doses are necessary to obtain the same responsiveness of the reward system, including the desired pleasure effects, thus emerging tolerance to the drug (Ahmed & Koob 2005).

The allostasic brain uses a feed-forward mechanism rather than negative feedback processes as in homeostasis, thus generating new neuroadaptations in the brain circuits (Koob & Le Moal 2008; Fig 2).

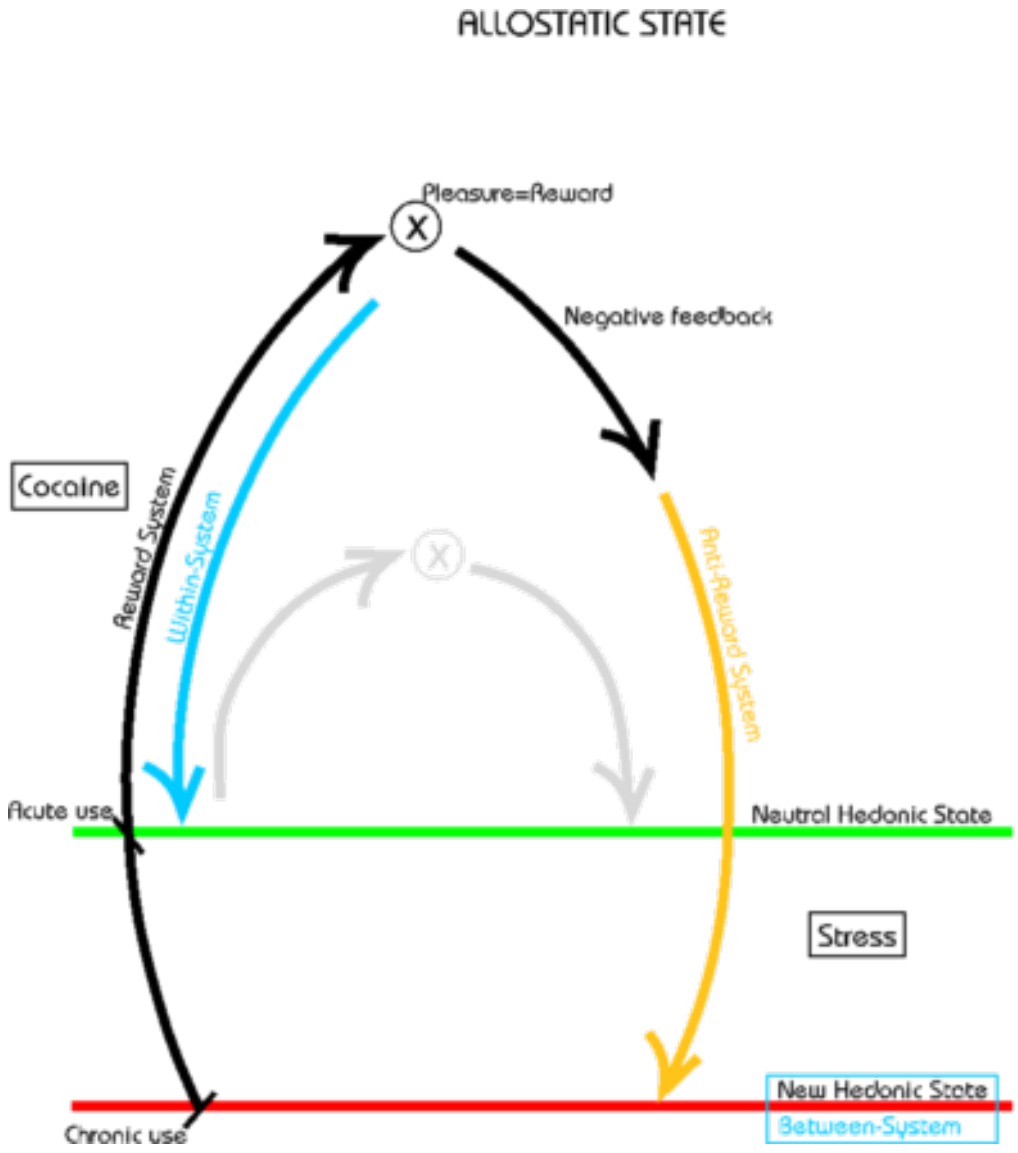

Fig 2: Allostatic state induced by chronic cocaine consumption.

6.4 Neuroadaptation mechanisms

There are two neuroadaptation mechanisms, the Within-System and the Between-System that act at different levels.

The initial mechanism acting is the Within-system, which implies cellular or molecular neurodaptations on reward circuit. It consists on the declining of the reward system responsiveness by the decreasing of the dopaminergic and glutaminergic neurotransmission in the nucleus accumbens. These neuroadaptations contribute to protracted abstinence syndrome and to the vulnerability to relapse, by causing long-standing neurochemical changes (Ahmed & Koob 2005). In fact, this decrease of neurotransmission in reward system is thought to contribute strongly to a negative motivational state associated with acute abstinence (Koob & Le Moal 2008).

Imagiological studies further confirmed that, not only there was a decrease in the amount of released dopamine, but also there were decreases in the quantity of high-affinity dopamine D2 receptors in dependent individuals.

It is thought that these dopaminergic deficits contribute to the decrease of sensibility to reward-seeking activities in the dependent individual, therefore contributing to continuous drug consumption in an attempt to compensate these deficits (Volkow et al. 2010).

In addition to within-system, different brain circuits including brain stress circuits that act in the opposite way to the reward system can be recruited, supplying additional negative hedonic valence – this is the anti-reward system (Koob & Le Moal 2008). The excessive activation of the anti-reward system induces a neurodaptation in which persistent elevation of the basal thresholds of activation of reward system occurs. This represents the Between-System mechanisms (Ahmed & Koob 2005).

The cerebral neurocircuits implicated in Between-System neurodaptations are the same involved in stress modulation: HPA axis and extrahypothalamic CRF-stress neurocircuits (Ahmed & Koob 2005; Specio et al. 2007). The HPA axis is composed by the paraventricular nucleus of the hypothalamus, anterior lobe of pituitary gland and adrenal glands (Koob 2009). The activation of the HPA axis begins with the synthesis of CRF by neurosecretory neurons in the medial parvoventricular subdivision of the paraventricular nucleus of hypothalamus, followed by its release in the pituitary portal system.

CRF can be also found outside the HPA axis, namely in the neocortex, extended amygdala, medial septum, thalamus, cerebellum and in the autonomic midbrain and hindbrain nuclei, including the ventral tegmental area (extrahypothalamic CRF-stress neurocircuits). By this way CRF influences autonomic and behavioural responses to stressors. Among these extrahypothalamic CRF systems, the extended amygdala is particularly related with motivational changes in addiction (Koob 2010).

With chronic drug consumption these systems are dysregutaled, raising the levels of the adrenocorticotropic hormone (ACTH), corticosterone (CORT) and CRF in the extended amygdala in acute withdrawal (Crespo et al. 2003; Koob & Le Moal 2008).

The extended amygdala is an entity separated from the basal forebrain, composed by the bed nucleus of stria terminalis, central medial amygdala and a transition zone in the posterior part of the medial nucleus accumbens (posterior shell) (Koob 2009). This structure receives afferents from limbic cortex, hippocampus, and sends efferent to posterior medial (sublenticular) ventral pallidum, ventral tegmental area, brainstem and a great volume of efferent to hypothalamus lateral (Koob 2009). In the extended amygdala there is a great number of CRF terminals, cellular bodies and CRF receptors, which suggests an important

role of CRF in the Between-System neuroadaptations, and so, in the addiction state (Koob & Le Moal 2008; for further details on CRF please see section 8.)

6.5 The Addiction Cycle

In behavioural terms the drug addiction is a control disorder with impulsive and compulsive characteristics. In an early stage of drug use, in which the impulse control disorder dominates, the individual feels a rising tension before committing the act, feeling pleasure, relief or gratification in the moment he commits it; he can regret it or not afterwards. As the individual progresses in the addiction cycle, the control disorder becomes compulsive, and he feels stress and anxiety before committing the act, and stress relief when committing the compulsive act (Koob & Le Moal 2008).

The addiction cycle is composed by three stages: binge/intoxication; preoccupation/anticipation; and withdrawal/negative affect. These stages evolve in positive feedback-within this cycle, allowing the progress from impulsivity into compulsivity. Therefore this cycle brings about a change from positive reinforcement into negative reinforcement (Koob 2009).

The binge/intoxication stage essentially signals a positive reinforcement trigged by drugs of abuse. The preoccupation/anticipation stage underlies craving that may lead to chronic relapse in humans. The orbitary cortex, cingulate anterior cortex and temporal lobe, where amygdala is included are involved in craving (Koob 2009). This is a subjective memory effect of the reward stimuli, provided by the drug consumption, superimposed to a negative emotional state (Koob & Le Moal 2008).

High craving levels predispose to poor treatment response (Back et al. 2010).

In the withdrawal/negative affect stage the reward threshold is increased, leading to negative reinforcement characterized by irritability, dysphoria and loss of motivation to natural rewards, that will drive the individual to drug-seeking compulsive behaviour (Koob & Le Moal 2008). Cocaine addicted subjects meet most DSM criteria for substance dependence, including tolerance and withdrawal (APA 2000).

6.5.1 Pre-clinical evidences

Several animal models can be used in the addiction studies, even though none could fully represent the human condition of drug dependence. Thus we have several animal models of addiction that try to simulate different aspects and different phases in the addiction cycle (Kobb & Le Moal 2008).

Animal models of binge/intoxication stage of the addiction cycle consist in the evaluation of the positive reinforce of the drug which depends on the reward power. These models are extensive and well validated (Kobb & Le Moal 2008). The animals can be drug dependent or not. In fact animals will readily self-administer drug in the non-dependent state. Therefore we can measure directly the reward drug effect through animal's effort in accomplishing tasks in order to obtain the drug. Such increased self-administration in dependent animals has now been observed with cocaine (O'Dell & Koob 2007). The drugs that are self-administrated by animal match perfectly with those with high abuse potential in human (including cocaine; Kobb & Le Moal 2008).

Alternatively we can measure indirectly drug reward through conditioned place preference procedures in which animals will prefer places where they can obtain the drug, and also through the measure of brain reward thresholds, that we know drugs reduce. These models are predictive of the drug potential of abuse (Kobb & Le Moal 2008). These effects in

brain reward threshold have already been observed in the withdrawal from cocaine, methamphetamines, opioids, ethanol, tetrahydrocannabinol (THC) and nicotine (Koob 2003).

The negative reinforcing models are similar to reward models, but instead of using rewards, we use negative reward valence through withdrawal. This way, animals will have an increase of brain reward thresholds and conditioned place aversion with withdrawal (Kobb & Le Moal 2008).

The animal models of transition to addiction qualify the ability of the drug to induce transition to addiction. These can measure drug self-administration in dependent animals with extended access to drug (rather than short-term access); it can measure the effort of dependent animals to obtain drug during withdrawal; or can analyze the drug consumption in dependent animals even when the consumption brings punishment. The escalation of drug consumption with extended availability was verified with cocaine, methamphetamines, nicotine, alcohol and heroin (Kobb & Le Moal 2008).

Finally, there are preoccupation/anticipation stage models (craving) that are related to drug motivational modifications and cue paired with drugs during abstinence in dependent animals. At first place, we vanish drug-seeking behaviour (lever pressure) in dependent animals. Then, we can induce reinstatement of cocaine seeking behaviour drug induced through a priming cocaine injection, or reinstatement of cocaine seeking behaviour cue-induced through presentation of a cue-paired with drug, or even reinstatement of cocaine seeking behaviour stress induced with the presentation of stressor stimulus that could restart consumption. So, we measure the latency time until the animal retakes drug seeking behaviour or the amount of drug-seeking behaviour itself (number of lever pressures; Kobb & Le Moal 2008).

The discriminative stimuli is a model of craving related with the presentation of cue-paired with the drug. The discriminative stimuli attribute the quality cue-paired with drug to behaviour/situations. It has robust results as a craving model for cocaine (Weiss et al. 1999).

7. Corticotropin-Releasing Factor, Stress and Cocaine Addiction

The importance of stress and all its components in the initiation and perpetuation of cocaine consume lies in four elements: 1-acute drug use activates HPA stress axis through hypothalamic as well as extrahypothalamic CRF release (Sarnyai et al. 2001; Koob & Le Moal 2008); 2-CRF has a role in the mediation of the organism response to environmental stress (Heinrichs et al. 1998; Valentino RJ et al. 2010); 3-CRF system stimulation induces reinstatement of cocaine seeking behaviour (Specio et al. 2007) and 4-CRF system induces negative emotional states during withdrawal in pre-clinical studies (Heinrichs et al. 1998).

CRF [a straight-chain 41-residue peptide (Sarnay et al. 2001)] has a bilateral role in the response to cocaine induced stress, acting by one hand as impeller of the endocrine answer through HPA axis, and on the other hand as a neurotransmitter through extrahypothalamic CRF system (Erb et al. 2001; Wang et al. 2007; Koob & Le Moal 2008).

CRF binds to CRF receptors in the pituitary gland, causing ACTH release in systemic circulation (Specio et al. 2007; Koob 2009). When ACTH reaches the adrenal gland, it induces synthesis and secretion of glucocorticoids by the adrenal cortex (Sarnyai et al. 2001; Koob 2009).

Chronic consumers experiencing withdrawal at early stages show elevation of the CRF levels in the extended amygdala (Erb 2010) and therefore, elevation of basal levels of CORT,

underlying persistent anxiety-type behaviours (Sarnyai et al. 2001). On the other hand these consumers show minimal levels of craving.

However, in protracted abstinence, the basal levels of CORT and anxiety normalize and the individual shows a higher tendency to react to aversive stimuli or drug associated-cues with anxious behaviour, facilitating the reinstatement of cocaine-seeking behaviour underlying craving (Erb 2010).

The normalization of basal levels of CORT could be due to the increase of glucocorticoids receptors density in the hippocampus with chronic consume, which can induce negative-feedback (Sarnyai et al. 2001). This hypothesis justifies the high responsiveness to stressors, as referred previously. Therefore, the exposure of dependent individuals to stressors can trigger a subjective answer of CRF that is associated to augmented risk of consume, severity of consume and predisposition to relapse even after protracted abstinence (Erb et al. 2001; Lu L et al. 2001; Sarnyai et al. 2001; Crespo et al. 2003; Erb & Brown 2006). However, it was demonstrated that there is maintenance of cocaine self administration in rats after bilateral adrenalectomy, what confirms that the key element in addiction is CRF (Specio et al. 2007).

There are three distinct classes of CRF receptors, subtype 1 (CRF_1), subtype 2 CRF receptors (CRF_2) and CRF binding protein (CRF-BP), that are heterogeneously distributed in the CNS (Sarnyai et al. 2001). CRF_1 has high affinity to CRF, and CRF_2 has lesser affinity and possesses different forms: CRF2 α, CRFR2 α-tr, CRF2 β, and CRF2 δ. It is thought that both receptors have distinct roles (Lu et al 2001), in which CRF_1 might have importance in anxiety type-behaviours and in the cocaine dose escalade in self-administration, and CRF_2 appears to be more related to the appetite regulation and possibly with modulation of anxiety-type behaviour (Specio et al. 2007; Boyson et al. 2011). CRF-BP it is a high affinity plasma

protein existent during pregnancy, which binds CRF, and neutralizes its ability to induce ACTH release (Sarnyai et al. 2001).

Beyond CRF, also the noradrenaline has a role in anxiety expression during withdrawal. There is evidence that its activity in the central nucleus of the amygdala, in cocaine-withdrawal early stage, contributes to the increase of local CRF (Erb 2010).

CRF is definitely an important element in behaviour long-lasting effects with chronic cocaine abuse (Lu et al. 2001; Erb & Brown 2006). Data confirmed that indeed the use of CRF antagonists blocks anxiety behaviour during cocaine-withdrawal in rats (Crespo et al. 2003; Specio et al. 2007).

7.1 Corticotropin-Releasing factor antagonists

Next we will review CRF antagonists that have potential use in cocaine addiction treatment. Studies that test the effects of CRF antagonists in animals with a cocaine consumption history were selected (Table 1). There are no clinical trials yet.

Table 1

REFERENCES	ANIMALS	RECEPTORS BLOCKAGE	ANTAGONISTS	RESULTS
Goeders & Guerrin 2000	Wistar rats	CRF_1	CP154.526; 10 – 40 mg/kg (ip)	It reduces cocaine self-administration in 2h behavioural sessions with 1 h access to cocaine sessions.
Erb et al. 2001	Long-Evans rats	CRF	D-Phe CRF_{12-41}; 50 ng (intra-BNST injection)	It attenuates reinstatement of cocaine-seeking behaviour induced by footshock.
Gurkovskaya & Goeders 2001	Wistar rats	CRF_1	CP154.526; 20 mg/kg (ip)	It reduces the lever answer during cocaine extinction.
Lu et al. 2001	Sprague-dawley	CRF	α-helical CRF; 10 µg (icv)	It attenuates the reactivation of place preference cocaine-conditioned induced by cocaine. It blocks the reactivation of place preference cocaine-conditioned induced by footshock.
		CRF_1	CP154,526; 1-10 mg/kg (ip)	It does not attenuate the reactivation of place preference cocaine-conditioned induced by

				cocaine. It blocks the reactivation of place preference cocaine-conditioned induced by footshock.
		CRF_2	AS-30; 1-10 µg (icv)	It does not attenuate the reactivation of place preference cocaine-conditioned induced by cocaine. It does not block the reactivation of place preference cocaine-conditioned induced by footshock.
Przegalinski et al. 2005	Wistar rats	CRF_1	CP154.526; 5-20 mg/kg (ip)	It decreases the reinstatement of cocaine-seeking behaviour induced by cocaine. It does not influence the cocaine discriminative stimulus. It does not alter the self-administration of cocaine in 2h/day access sessions.
Mello et al. 2006	Rhesus	CRF_1	Antalarmine; 1-10	It does not reduce the self-

	monkeys		mg/kg IV	administration of cocaine in 2h/day access sessions. It does not alter cocaine discrimination.
Wang et al. 2007	Long-Evans rats	CRF_2	AS-30; 1 µM (intra-VTA injection)	It prevents the reinstatement of cocaine seeking-behaviour induced by footshock.
		CRF_1	R121919; 1-10 µM (intra-VTA injection)	It does not prevent the reinstatement of cocaine-seeking behaviour induced by footshock.
			NBI-27914; 1-10 µM (intra-VTA injection)	It does not prevent the reinstatement of cocaine-seeking behaviour induced by footshock.
Specio et al. 2008	Wistar rats	CRF_1	Antalarmine; 6.3-25 mg/kg [intraperitoneal injection (ip)]	It reduces the self-administration of cocaine in the higher dose in the group with long access (6h/day), but not in the group with short access (1h/day).
		CRF_1	MPZP 3.6-27.5 mg/kg [subcutaneous injection (sc)]	It reduces the self-administration of cocaine in both long (6h/day) and short (1h/day) access.

				It had effect in long access group at lower dose that in the short access group.
Blacktop et al. 2011	Sprague Dawley	CRF_1	Antalarmine; 1 µg (intra-VTA injection)	It blocks footshock-induced reinstatement.
		CRF_2	Astressin-2B; 1 µg (intra-VTA injection)	It does not block footshock-induced reinstatement.
Boyson et al. 2011	Long-Evans rats	CRF_1	CP154.526; 20 mg/kg (ip)	It prevents social stress-induced locomotor sensitization to a cocaine challenge. It prevents the escalade of cocaine self-administration during a 24h-binge, after repeated social stress events.

Pre-treatment with antalarmine (a CRF_1 selective antagonist; ip) is capable of reducing cocaine self-administration in rats with extended access to cocaine (6 hours sessions/day), but not in the group with short-term access (1 hour session/day) after a period of eleven days of daily infusion of the drug (Specio et al. 2008). Also, pre-treatment with antalarmine intra-VTA injected is capable of blocking footshock-induced reinstatement in rats with long-access administration (6 hours sessions/day) after 14 day of self-administration followed by a 10 days extinction period. However, astressin-2B (CRF_2 selective antagonist; intra-VTA

injection), does not block footshock-induced reinstatement in the same conditions (Blacktop et al. 2011). In addition, Mello et al. 2006 verified that antalarmine pre-treatment (i.v) before a self-administration session does not significantly decrease the number of self-administrations in Rhesus monkeys with restricted access to cocaine (2 hours sessions/day). However, in the highest dose, antalarmine reduced the number of cocaine administrations. However these authors did not try cocaine-extended access (Mello et al. 2006). Moreover the authors reported the lack of effect of antalarmine in the discriminative stimulus of cocaine in this study.

Specio et al. (2008) have also tested MPZP which is a selective CRF_1 antagonist as well. They further verified that unlike antalarmine, MPZP (sc) reduced the amount of self-administrated cocaine in rats with both restricted (1 hour sessions/day) and extended access (6 hours session/day) to the stimulant.

The difference of results obtained with antalarmine and MPZP seems to be due to the different pharmacologic profile of both molecules, once both have high affinity do CRF_1. MPZP has larger bioavailability than antalarmine (Specio et al. 2008).

These authors further suggest that the CRF system is more sensitive to CRF_1 blockage if the access to cocaine is more extended (Specio et al. 2008).

Przegalinski et al. (2005) consistently reported that CP154.526 (ip; an antalarmine analogue) pre-treatment neither reduced cocaine self-administration in rats with restricted access (2 hour sessions/day) nor produced changes in the discriminative stimulus of cocaine in rats. The ability of CP154.526 to prevent cocaine-induced reinstatement behaviour was also tested, and it was established that this antagonist reduced the reinstatement behaviour after vanishing the cocaine access, in a dose-dependent way (Przegalinski et al. 2005). On the other hand, Boyson et al. (2011) established that treatment with CP154.526 (ip) before social

stress events, prevented dose escalade in a 24 hour self-administration session in rats. Also in a model of cue-induced craving, Gurkovskaya & Goeders (2001) established that pre-treatment with CP154.526 (ip) decreased, but did not abolish completely the reinstatement behaviour (Gurkovskaya & Goeders 2001). Using higher doses than Przegalinski et al. 2005, Goeders & Guerrin 2000 observed that pre-treatment with CP154.526 (ip) reduced cocaine self-administration in rats, in a 2 hours behavioural session/day regimen (total of 1h access to cocaine/day).

Lu et al. (2001) tested three types of CRF antagonists: α-helical CRF (non selective CRF antagonist), CP154.526 and AS-30 (CRF_1 and CRF_2 selective antagonists, respectively). It was verified that the α-helical CRF (icv) was able to attenuate the cocaine-induced reactivation of cocaine-induced conditioned place preference. On the contrary, CP154.526 (ip) and AS-30 (icv) had no effect in cocaine-induced reactivation of cocaine-induced conditioned place preference (Lu et al. 2001). The effect of these antagonists in the reactivation of cocaine-induced place preference by footshock was also tested. It was seen that both CP154.526 (ip) and α-helical CRF (icv) significantly blocked the reactivation induced by footshock. However, AS-30 (icv) was devoid of effect (Lu et al. 2001). Wang et al. (2007) had different results with AS-30. In fact, AS-30 injection in the ventral tegmental area (VTA) blocked the reinstatement of cocaine-seeking behaviour induced by footshock. However the selective blockage of CRF_1 with the selective antagonists R121919 and NBI-27914 injected in the VTA did not prevent the same reinstatement behaviour (Wang et al. 2007).

Erb et al. 2001 also demonstrated that non selective CRF receptors antagonist D-Phe CRF_{12-41} injected in the BNST of one brain hemisphere (the blockage of the sodium channels (TTX) in the amygdala of the other hemisphere was simultaneously applied) attenuated the reinstatement behaviour induced by footshock.

8. Discussion

Antalarmine and MPZP have only been tested in animal addiction models of transition to addiction. Antalarmine seems to be useful in the treatment of dependence to cocaine in animals with extended access to cocaine (Specio et al. 2008), not being effective in animals with short access to cocaine (Mello et al. 2006; Specio et al. 2008). Additionally, antalarmine does not have effect in cocaine discrimination in primates (Mello et al. 2006). This suggests that antalarmine efficacy might be dependent upon the stage of cocaine addiction. The MPZP seems to be more effective than antalarmine in rats with extended access, being also effective following short-access cocaine sessions (Specio et al. 2008). Both antalarmine and MPZP are promising, particularly MPZP not only because of its superior efficacy, but also because of its administration route (subcutaneously).

CP154.526 is the most tested antagonist in different experimental settings. It is capable of decreasing cocaine-induce reinstatement behaviour in doses 5 – 20 mg/kg ip in transition to addiction animal models (Przegalinski et al. 2005). CP154.526 was also tested in craving models. For example, it is capable of reducing the number of self-administrations in rats in long-access cocaine sessions (Boyson et al. 2011). Additionally, the positive effect of this antagonist is dose-dependet in shorter sessions (2h/day) (Przegalinski et al. 2005; Goeders & Guerrin 2000). CP154.526 is also able to block the reactivation of cocaine-induced conditioned place preference by footshock, but not by cocaine (Lu et al. 2001). This suggests that cocaine- and stress- induced reinstatement of cocaine seeking are differently modulated by CRF_1 receptors.

Other CRF_1 antagonists (R121919 and NBI-27914) were scarcely tested and showed discouraging results. In fact, they did not have effect in reinstatement of cocaine-seeking behaviour induced by footshock (Wang et al. 2007).

The CRF_2 selective antagonist AS-30 was capable of blocking the reinstatement of cocaine-seeking behaviour induced by footshock (Wang et al. 2007); however, it does not attenuate the reactivation of cocaine-induced conditioned place preference by footshock or cocaine (Lu et al. 2001). This conflicting data does not shed light upon its potencial use in cocaine addiction. More studies are clearly needed.

Other CRF_2 selective antagonist astressin-2B was also tested in only one experiment, obtaining negative results. Astressin-2B fails to alter footshock-induced reinstatement (Blacktop et al. 2011). More studies are needed.

At last, non-selective CRF antagonists were tested too. α-helical CRF had positive effects, being able to attenuate cocaine-induced reactivation of place preference induced by cocaine and to significantly block footshock-induced reactivation of place preference induced by cocaine in rats (Lu et al. 2001). D-Phe CRF12-41 is also able to attenuate reinstatement of cocaine seeking-behaviour induced by footshock (Erb et al. 2001). This suggests that both CRF_1 and CRF_2 contribute to cocaine addiction.

9. Conclusion

Further pre-clinical studies with CRF_1 selective antagonists (CP154.526, MPZP and antalarmine) and with non selective antagonists (α-helical CRF and D-Phe CRF_{12-41}) are warranted to confirm that this is a promising strategy for cocaine addiction treatment.

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