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Contributions of Non-Human Primates to the Understanding of Cocaine Addiction

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1. Introduction

In this review, we aim to highlight the importance of neuropharmacological data, originated in non-human primate studies, towards our understanding of the mechanisms of cocaine addiction. Most studies in this field are undertaken with rodents as animal models, having provided over the years important knowledge on the behavioral, neurological and pharmacological mechanisms of drug addiction. There are, nonetheless, significant hormonal, neurochemical and neuroanatomical discrepancies between rodents and primates, particularly in reference to humans. Although the phylogenetic distance between humans-rodents, as opposed to humans-non-human primates may seem obvious, the impact this has on research findings is not always very evident. The gap in brain chemistry, neuronal organization and development, as well as behavioral diversity has serious implications in rodent models and limits somewhat their significance and generalization potential when trying to understand cocaine addiction – a phenomenon typical in humans. Due to ethical and important methodological restrictions on human testing, non-human primate (NHP) models are not only insightful, but also crucial to further the current scientific knowledge on this topic.

2. Addiction and cocaine

Cocaine is one of the most prevalent drugs of abuse. Data from the World Health Organization (WHO) estimated that, until 2008, approximately 19 million people worldwide had made use of cocaine (WHO, 2010). While the illicit retail market of cocaine is deemed to be worth around US$ 88 billions per year (WHO, 2009), its economic burden is difficult to measure. In terms of health treatment costs, there were 31,800 drug-related deaths in the United States alone in 2007 – a rate twice as high as that for murder in that year – with cocaine being related to about 40% of this toll. From 2002 to 2007, the WHO estimates that these premature deaths cost around 33 billion dollars. The American Drug Control program's budget for all drug-related control efforts in 2011 corresponds to US$15 billion, including treatment, prevention and illicit trade combat (National Drug Control Budget, 2011). Most of this will be spent on cocaine control, as the USA is the major destination of cocaine exports (WHO). On the other hand, the global cost of cocaine is less clear, considering that data from several countries are less reliable or regular.

Cocaine addiction is a psychological substance dependence where addicts have great difficulty in abstaining from drug-seeking, even at the cost of evident negative consequences (Vanderschuren & Everitt, 2004). It is a relapsing disorder with pervading effects on the human brain (O'Brien, 1997). Repeated use of cocaine leads to sensitization, i.e. enhanced response to the stimulus. In this case, repeated cocaine intake induces increased motor response and motivation (Robinson & Berridge, 2008). Sensitization is a long-lasting behavioral phenomenon with several implications to addiction (Paulson et al., 1991). The enduring sensitization induced by cocaine is linked to the relapsing properties of this disorder. Relapse or reinstatement is the return of drug-seeking or drug-taking behavior after a drug-free interval. In animal models, reinstatement has been shown to take place with priming injections of the drug (de Wit & Stewart, 1981), other compounds (Crombag et al., 2002), re-exposure to environmental cues associated with drug-taking (Meil & See, 1996) or even by stressful events (Anker & Carroll, 2010). In fact, cocaine relapse is one of the most difficult obstacles for the rehabilitation of addicts (O'Brien, 1997), possibly being related to cocaine sensitization of motivation or stimulus salience and not sensitization of locomotor activity (Robinson & Berridge, 2008).

Although progress in understanding the function of the brain and addiction has been made, there is still no pharmacological treatment that effectively blocks cocaine dependence, even after 30 years or so of research. Therefore, it is evident that cocaine addiction is a lingering and crippling health issue that warrants continued attention from the scientific community.

3. The case for non-human primates as models

As in the case of most biomedical fields, rodent models stand as the primary source of data in the study of addiction. Their small size and short reproductive cycle makes them easy to maintain, handle and reproduce, as well as relatively inexpensive in up keeping in laboratories around the world. Nevertheless, rats and mice did not reach this ubiquity in biomedical research on these merits alone. Rodent models have proved reliable in a wide range of topics, from drug screening to cognitive tests (eg. Fouquet et al., 2010; Heinrichs, 2010; Schmidt et al., 2011). Naturally, the versatility of these subjects has reflected on the enormous amount of scientific literature and experimental apparatus that have been generated over the course of the last five decades. The extensive amount of rodent research also spurs a faster refinement of the techniques, which in turn, makes rodents an even more practical and useful model. In terms of cocaine addiction, rats have been employed in several paradigms (self-administration, conditioned place-preference, open field; Mello & Negus, 1996; Ator & Griffiths, 2003) and also make up the majority of cocaine-related studies. Unfortunately, there is a significant genetic gap between humans and rodents: the actual figure being 66-82% homology (Nilsson et al., 2001). This difference has several implications in the understanding of cocaine abuse in humans.

NHP have been employed in addiction paradigms for approximately 40 years (Thompson and Schuster, 1964; Griffiths et al., 1980; Mello and Negus, 1996). Although the primate database on addiction is less abundant than that of rodents', there is considerable information available for comparison and interpretation. The genetic homology between NHP and human falls within 95%, depending on the species considered (Hacia et al., 1998). A greater phylogenetic proximity reflects on a more similar anatomy, physiology and behavior. In the sections below, we will examine the most important discrepancies between rodents and NHP and the contributions of primate research to the understanding of cocaine

addiction. The importance of NHP however does not lie solely on their genetic distance to rodents. There is rather a powerful tool in primate research that allows for a greater and more refined analysis of the intricacies of cocaine effects: primate behavior.

In this sense, one of the most widespread and reliable tests for cocaine addiction is the self-administration paradigm (Griffiths et al., 1980; Ator & Griffiths, 2003). In this model, the animal subject is trained to press a lever or push a button to receive a rewarding stimulus (e.g. electrical stimulation to "rewarding centers" in the brain or a direct infusion of an addictive substance). There are several schemes under which this paradigm may work for both rodents and NHP. Nevertheless, there is a limit to how many response parameters one may expect to gather from rats and mice. The great advantage of primate research is the plethora of behaviors that may be drawn upon, ranging from simple self-directed behaviors, to very complex social behaviors. All apes and monkey species present high cognitive indices and good manipulatory skills (Pouydebat et al., 2009, 2011). They may form large social structures, including even non-kin members. As a result, there are quite complex social situations that entail a variety of social cues and behaviors. For instance, they display (and react appropriately to) facial expressions signaling emotional states or intentions beyond only aggressiveness, as in the case of most non-primates species (Schimidt & Cohn, 2001). They may even engage in very cognitively demanding behaviors such as deception (Reader et al., 2011). Thus, the use of a species-appropriated ethogram may add a wealth of new data even to simple reaction time experiments. Models may be improved to resemble very closely human social conditions or complex cognitive tasks that models human drug-seeking behavior. As pointed out by Nader and coworkers (2008), "…all animal models are, as a minimum, predictive of some clinical outcome… When social behaviors of NHP and cocaine self-administration (for example) are included, these models are homologous models of human drug abuse." Indeed, some paradigms have included social variables in the study of cocaine abuse (Czoty et al., 2005; Morgan et al. 2002).

Furthermore, physical reactions to compounds or the abstinence thereof mirrors very closely those of humans. For example, NHP demonstrate all key signs of opioid withdrawal seen in humans, including retching, hiccups, pallor and abdominal cramps (see Weerts et al., 2007). Rodents, on the other hand, lack those and several other symptoms. Likewise, more subtle and yet relevant drug effects, such as hallucinatory behavior, are only clearly discernible in NHP (Castner & Goldman-Rakic, 2003; Ellison et al., 1981).

In the case of addiction, NHP longevity is also another advantage. Most ape and monkey species tend to live quite long; a few may even live beyond the age of 40 (Judge & Carey, 2000). This has important implications for the study of long-term effects of drug abuse. It means, among other aspects, that long-term effects of cocaine consumption may be more easily modeled for a specific developmental stage, such as adolescence. It also allows studies of a drug's cumulative effects or cross-drug comparisons in the same subject (Ator & Griffiths, 2003). Together with their greater physiological similarities and behavioral diversity, longevity makes NHP models key for addiction research.

At this point, it is important to add a caveat to our argument. Although NHP might prove crucial to research in most biomedical fields, for several reasons it may not always be the ideal model for many laboratories worldwide. First, primates require appropriate facilities that cater to their size, locomotion, habits and social needs. This makes primate research considerably more expensive than working with rats or mice. Longer reproductive cycles and development stages also reduce the pace of any experimental output. Even small species offers difficulty in handling and training. Another restriction refers to the lack of

background research on the behavior and/or physiology for several primate species. Behavioral ethograms, for instance, are not always readily available in the literature. Lastly, ethical considerations regarding the availability of specimens and the threat of extinction for some species may also limit the use of primates. Therefore, we are not advocating the use of primates as the primary source of scientific data. Biomedical research will still rely heavily on rodent studies, and rightly so. One of the aims of the present review is to advise that caution should be taken before generalizing rodent findings to human and to show how NHP research may help bridge the gap between them.

3.1 Dopamine

The primary focus of cocaine research, as well as most drug of abuse, is the brain's dopaminergic system. Dopamine (DA) is a neurotransmitter produced in the substantia nigra, ventral tegmental area (VTA) and hypothalamus. The projection of VTA dopaminergic neurons reaches two main targets in the brain: the prefrontal cortex (mesocortical pathway) and the ventral striatum (mesolimbic pathway). Both comprise what is called the reward system, with the mesolimbic pathway playing a major role (see Berridge, 2007 and Wise, 1996 for review). Not surprisingly, the rewarding and psychostimulant effects of cocaine are mediated by its ability to enhance dopaminergic activity within the meso-cortico-limbic circuit (Roberts et al., 1977). Briefly, cocaine binds to and blocks the pre-synaptic transporter responsible for DA re-uptake (Heikkila et al., 1975; Ritz et al., 1987,). This dopamine transporter is referred to as DAT. As DA reuptake is inhibited, the synaptic cleft is overflown with DA that will bind to post-synaptic receptors, inducing a prolonged or enhance signaling effect.

The DA receptors are classically divided into 5 subtypes, classified as: D_1, D_2, D_3, D_4 and D_5. These subtypes have been further divided and organized into two main groups, the 'D_1-like' receptors: D_1/D_{1a}, D_5/D_{1b}, D_{1c} and D_{1d}; and the 'D_2-like' receptors: $D_{2long\ and\ short}$, D_3, D_4 or $D_{2al\ and\ s}$, D_{2b} and D_{2c} (Sibley and Monsma, 1992). D_1-like and D_2-like are traditionally involved in the rewarding properties of stimuli such as cocaine (Hummel & Unterwald, 2002; Di Chiara et al., 2004). In this regard, several studies have reported critical differences between rodents and primates. NHP post-synaptic D_1-like receptors show higher levels and their laminar distribution is more complex than in rodents, but similar to humans (Smiley et al., 1994). Regarding the densities of D_2-like receptors, Lidow and coworkers (1989) showed a distinct pattern of distribution in the primate cortex: a rostro-caudal gradient, with the prefrontal cortex showing the highest concentration and the occipital cortex the lowest. Rats, on the other hand, were found to have a more diffuse distribution of these receptors. More specifically, the ratio between D_1-like and D_2-like receptors in the NHP striatum is almost 1:1 (Madras et al, 1988; Weed et al, 1998), whereas D_1-like receptors are three times more prevalent than D_2-like (Hyttel and Arnt, 1987; Weed et al, 1998). The density ratio in humans seems to follow the same pattern as that observed in NHP (Hall et al, 1994; Piggott et al, 1999). There is also greater similarity between humans and NHP in the distribution of D_1-like (Hersi et al., 1996) and D_2-like receptors in the hippocampal formation (Kohler et al., 1991). These are also reflected in low ligand efficacy of D_1-like receptor agonists in the primate brain (Izenwasser & Katz, 1993; Pifl et al., 1991; Vermeulen et al., 1994).

The distribution and the organization of DA receptors are not the only discrepancies concerning the DA system. An early review from Berger and coworkers (1991) noted important differences in the organization of primate and rodent DA cells. They indicated

larger and differentially organized terminal fields in the DA mesocortical pathway in primates. DA cells arriving in the rat striatum are clearly organized into two tiers, ventral and dorsal, whereas no such distinction is found in monkeys (Joel & Weiner, 2000). Cytoarchitecture of midbrain DA cells in monkeys and humans is noticeably different with large and dense dendritic plexuses (Gonzalez-Hernandez et al., 2004). The primate cortex shows a higher density of DA innervation, as compared to rodents (Goldman-Rakic et al., 1992; Goldman-Rakic et al., 1989). Goldman-Rakic and coworkers (1992) emphasized that the cortical DA system in rhesus monkeys is near identical to that of humans. Both species show a bi-laminar innervation of the prefrontal cortex with projections reaching upper and deep cortical areas. These discrepancies bear important consequences for cocaine addiction studies. For instance, the development of compounds that may block cocaine addictive effects will probably depend on receptor specificity.

It is noteworthy that greater focus is generally given to rodent pathways that show high homology with humans. Nevertheless, a few promising options may remain unexplored if NHP are not employed. For instance, the rat thalamus is very poorly innervated by DA neurons (Groenewegen, 1988). Only recently has some attention been given to the multiple DA projections to the thalamus in the monkey and human brain (Sanchez-Gonzalez et al., 2005). Likewise, drug screening may be severely restricted by results in rodents. As pointed out by Weerts and coworkers (2007), "unacceptable performance in the rat can result in termination of further examination of a compound or an entire chemical series".

All the physiological and anatomical dissimilarities between primates and rodents seem to bear on the dynamics of DA circuits and its associated metabolism. Cocaine infusion in NHP was shown to reduce glucose metabolism in several brain regions, including the prefrontal cortex and the ventral striatum, in a manner similar to that reported in human studies (London et al., 1990; Pearlson et al., 1993; Lyons et al. 1996). The effect seems to reduce metabolism also in cortical areas projecting to the ventral striatum (Lyons et al. 1996; Porrino et al., 2002). This is in clear opposition to rodent findings, where metabolic activity is increased, not decreased, being also restricted to dopaminergic circuits (Hammer & Cooke, 1994; Porrino et al., 1988).

The pharmacokinetics of the DA system also shows important differences in behavioural profiles. In NHP, rate-increasing effects of cocaine seem not to be important for the reinstatement of behavior after extinction (Banks et al. 2007). Odum and Shahan (2004) had found earlier that also the psychostimulant amphetamine significantly increased extinguished responding. Lile and co-workers also reported that cocaine and DA agonists induce different behavioural effects in monkeys and challenged the accepted influence of neurotransmitters transporters in reinforcement, as previously established in rats (Lile et al. 2003; Roberts et al. 1999). This became clearer when Letchworth and coworkers (2001) found long-term cocaine-induced increases in DAT densities in monkey striatum, which is not seen in rodents but is quite similar to human studies.

Regarding drug abuse in general, the DA system has been the most extensively investigated pathway. Despite this, its causal role in the reward system is still under debate. In short, three competing hypotheses have been put forward: (1) DA mediates the hedonic aspects of reward (i.e. 'liking'; Wise, 1980); (2) DA mediates the prediction of rewards concordant with associative learning (Schultz, 2004); and (3) DA mediate the motivational aspect of drug-seeking behavior by attributing incentive salience to reward-related stimuli (i.e. 'wanting'; Berridge & Robinson, 1998). In a detailed review of mostly rodent literature, Berridge (2007) examined the findings from the last 30 years and concluded that there is more support for

the incentive salience hypothesis. However, there is also support from a few electrophysiological studies in monkeys showing that DA neurons cease to fire after reward-related cues have been learned (Schultz, 2006).

Nonetheless, primate studies have yielded a few other contributions. The study of cocaine-induced response sensitization also showed striking differences between primate and rodents. Rats generally display a dose-dependent sensitization of DA reinforcing responses (Liu et al., 2005). Chronic exposure to cocaine or amphetamine, on the other hand, has failed to produce sensitization in NHP (Castner et al., 2000; Bradberry & Rubino, 2006; Castner & Williams, 2007), which is in agreement with human imaging studies (Volkow et al. 1997; Martinez et al. 2003). Similarly, cocaine-associated cues have been shown to induce DA release in the rat striatum (Ito et al., 2002; Weiss et al. 2000). Similar studies with monkeys were unable to produce significant increases in extracellular DA in either the striatum or cortex (Bradberry, 2000; Kimmel et al. 2005). Human findings, via imaging studies, seem to agree with NHP results, although DA release was not measured directly (see Bradberry, 2007 for review). It is beyond the scope of the present review to try to settle the issue of DA causal role in drug abuse. Instead, the data shown here underscores critical NHP findings that put rodent studies in perspective.

Overall, the data reviewed above indicates that rodent DA system differs significantly from humans'. This is important to keep in mind when analyzing results from rats and mice studies. Although rodent studies provide the initial step of investigation, data obtained from such models are not easily generalized to humans. In some cases they may even bias investigation towards rodent-related issues. As we shall see further, there are also important differences concerning serotonin (5-HT), neuropetides and hormones. However, these systems have been studied less extensively in the framework of cocaine abuse, but their importance is gradually becoming clearer.

3.2 Serotonin

Serotonin or (5-hydroxytryptamine [5-HT]) is an important neurotransmitter in the brain. It is mostly synthesized in the raphe nuclei in the midbrain and from there 5-HT neurons project to several regions in the brain (Kazakov et al., 1993). There are at least 14 types of 5-HT receptors grouped into seven families (see Roth, 2006), with 5-HT_1 and 5-HT_2 being the most relevant and widespread in the human brain (Glennon et al., 2000). The release of 5-HT is modulated by the inhibition of two types of 5-HT auto-receptors: cell body and fiber terminal (Price et al., 1996).

As in the case of DA receptors, discrepancies between rodent and primate 5-HT auto-receptor distribution have been reported. 5-HT_{1A} distribution in rats and humans seem to be highly congruent (Hartig et al., 1992). Autoradiographic assays, however, have shown an abundance of 5-HT_{1A} mRNA expression in the superficial layers of monkeys' prefrontal cortex (de Almeida & Mengod, 2008; Marazziti et al. 1994; Mengod et al. 1996). This suggests that raphe nuclei efference may modulate high-level cortico-cortical communication in primates. In rodents, 5-HT_{1A} mRNA seems to be restricted to the deeper layers of the prefrontal cortex (Pompeiano et al., 1992; Santana et al., 2004) and therefore would not exert the same influence on cortical activity.

Although data on 5-HT_{1A} distribution throughout the brain is still lacking for NHP, there is little reason to suppose it differs much from humans and rodents. The same does not hold true, for example, in the case of 5-HT_{2A} receptors. High densities of this receptor were found

in the rat caudate, putamen and accumbens nuclei, as well as 5-HT_{2A} mRNA in the caudate, putamen and substantia nigra (Lopez-Gimenez et al., 2001). This may reflect the fact that 5-HT neurons in the rat striatum are not as evenly distributed as in NHP (Ikemoto et al., 1996; Van Bockstaele et al. 1993). A similar pattern emerges from immunohistochemical assays on 5-HT transporting proteins (SERT), where rats show a more heterogeneous distribution than primates (Owashi et al., 2004). In spite of some efforts, there is as serious lack of data regarding the distribution specific 5-HT receptors in NHP brains. At this point, the involvement of 5-HT in cocaine behavioral effects still seems quite complicated (eg. Dic Dhonnchadha & Cunningham, 2008) and unfolding the intricacies of serotonergic system in the primate brain may prove crucial.

Nevertheless, the basic interaction between cocaine and 5-HT seems to be the same as DA. Besides its effects on DAT, cocaine is also a potent inhibitor of 5-HT reuptake: it binds strongly to SERT, thereby preventing their reuptake by pre-synaptic cells (Heikkila et al., 1975; Ritz et al., 1987; Ritz et al., 1990). There are, once again, discrepancies in how cocaine affects rodent and primate serotonergic transmission. Work from Miller and coworkers (2001) showed that although both rodents and NHP share a high similarity in DAT sequence homology with humans (≅ 98.9%). In the case of SERT, NHP to human homology is slightly lower (98.3%), and even lower in for rodents (95%). Not surprisingly, SERT inhibition has an inverted effect on rats and primates, where it strengthens the discriminative stimulus of cocaine and has no impact on self-administration on the former (Tella, 1995), while it reduces the discriminative stimulus and self-administration in the latter (Howell & Byrd, 1995; Spealman, 1995).

Although the effects of cocaine on 5-HT inhibition were already well established by the early 1990s (Cunningham & Lakoski, 1990; Cunningham et al., 1992), it was only more recently that 5-HT neurotransmission was implicated in the cocaine-increased locomotor activity in rats (Hergers & Taylor, 1998). These findings were further explored by Carey and coworkers (2000, 2001 and 2005) showing that cocaine-induced locomotor activity in rats was mediated more specifically by 5-HT_{1A} receptors. Although self-administration of cocaine seems unaffected by 5-HT_{1A} manipulations in rats (Parsons, Weiss, & Koob, 1998), low doses of highly selective 5-HT_{1A} antagonist WAY100635 were shown to block cocaine-induced hyperlocomotion, whereas pre-treatment with 8-OHDPAT (5-HT_{1A} partial agonist) enhanced it. These findings were corroborated in NHP, where WAY100635 also blocked increases in locomotion induced by diethylpropion, an amphetamine-like drug (Mello Jr. et al., 2005). Pharmacological antagonism of this particular subtype of receptor showed conflicting results in rodent stress and anxiety tests (Fletcher et al., 1996; Griebel et al., 2000; Bell et al., 1999; Groenink et al., 1996). In monkeys, WAY100635 reduced anxiety behaviors in a confrontation model (Barros et al., 2003). These results are important if one considers the fact that stress and anxiety may trigger relapse in cocaine addicts (Steketee & Kalivas, 2011). Also 5-HT_{1A} agonism has been shown to enhance cocaine's reinforcing effects in NHP (Czoty et al., 2002).

The role of 5-HT on cocaine relapse seems to be related not only to its involvement in anxiety and stress processes. 5-HT may influence cocaine relapse due to its role in memory retrieval (Molodtsova, 2008). In rodents, the non-selective 5-$HT_{1B/1A}$ agonist RU24969 was shown to reduce the retrieval of cocaine induced cues (Acosta et al., 2005). This effect was reversed by 5-HT_{1B} antagonism which indicates prevalence of 5-HT_{1B} receptor in this case. Antagonism of 5-HT_{1B} receptors receptors seems to have no effect of their own on cocaine-related memories or behavior reinstatement. There are no reports on the effects of 5-HT_{1A}

agonists on retrieval of cocaine operant behavior *per se*, but one study found a reinstatement of cocaine-induced locomotor behavior (Carey et al., 2009). Retrieval of cocaine-associated memories in rats was also shown to be impaired by 5-HT_{2A} antagonism (Burmeister et al., 2004; Fillip, 2005) and 5-HT_{2C} agonism (Burbassi & Cervo, 2008; Fletcher et al., 2008; Neisewander & Acosta, 2007).

Although the understanding of 5-HT receptor's modulation of cocaine-related memory is still inceptive, Nic Dhonnchadha & Cunningham (2008) argued that future research should focus on 5-HT_{1B}, 5-HT_{2A} and 5-HT_{2C}. To our knowledge, the effects of 5-$HT_{1A/1B}$ and 5-$HT_{2A/2C}$ pharmacological manipulation on cocaine-associated memories have yet to be tested. Nevertheless, disparities of primate and rodent serotonergic system warrant a broader stance for future research. Although 5-HT_{1B} and 5-$HT_{2A/2C}$ modulation enhance self-administration in both species (Bubar & Cunningham, 2006; Czoty et al., 2005; Fletcher et al., 2002; Howell & Byrd, 1995; Parsons, Weiss, & Koob, 1998), 5-HT_{1A} agonism has shown to enhance the reinforcing properties of cocaine only in primates (Gold & Balster, 1992; Nader and Barrett, 1990). Therefore, differences in 5-HT reinforcing effects between rodents and NHP may very well transpose to cocaine-associated memories or even provide a entirely distinct pattern.

3.3 Peptides

Compared to DA and 5-HT, the role of neuropeptides in the effects of cocaine remains largely unknown. Nonetheless the past 20 years have witnessed important advances, especially in two fronts: tachykinin receptors and cocaine-and-amphetamine regulated transcript (CART). As shown below, the differences in primate and rodent brain regarding these two neuropeptides should exact caution from researchers.

Tachykinins comprise a group of neuropeptides that share a common C-terminal sequence (Phe-X-Gly-Leu-Met-NH2), with five known mammalian tachykinins: substance P - SP, neurokinin A (NKA), neurokinin B (NKB), neuropeptide K and neuropeptide g. They have been shown to bind to three specific tachykinin receptors: NK1, NK2 and NK3. NK1-Rs and NK3-Rs are widely distributed in the brain, while the NK2-Rs are found only in restricted areas. Although SP, NKA and NKB have a high binding affinity to the NK1-R, NK2-R and NK3-R, respectively, all tachykinins bind to all three receptor types (Severini et al., 2002).

In rats, cocaine administration induced the expression of tachykinin-related mRNA in the striatum (Adams et al., 2001; Arroyo et al., 2000; Johansson et al., 1994; Hurd et al., 1992; Mathieu-Kia & Besson, 1998). It also increased SP immunoreactivity in the striatum, substantia nigra and frontal cortex (Alburges et al., 2000). Nevertheless, results from NK1 manipulations on cocaine effects in rodents have been controversial so far. NK1 antagonism was shown to block cocaine-induced hyperlocomotion (Kraft et al., 2001), reverse sensitization (Davidson et al., 2004) and reduce cocaine-induced DA increases in the striatum (Loonam et al., 2003). NK1 agonism reinstated cocaine operant behaviors, yet SP – which binds preferentially to NK1 – failed to replace cocaine (Ukai et al., 1995). NK1 knockout mice showed no difference in cocaine self-administration and sensitization, as compared to controls (Ripley et al., 2002).

In the case NK3 receptors, there are a few reports implicating its activity in alcohol addiction in rats (Ciccocioppo et al., 1998; Massi et al., 2000). Also, NK3 activation in the VTA has been shown to reinstate cocaine-seeking behavior (Placenza et al., 2004) and its antagonism seems to block cocaine sensitization (Nwaneshiudu & Unterwald, 2010). In a joint effort from Huston and Tomaz's groups, a series of comparative studies regarding the involvement of

NK3 receptors in the effects of cocaine in rats and marmoset monkeys has been carried out. In rats, NK3 antagonist SR142801 reduced behavioral effects of cocaine, but increased DA action in the ventral nucleus accumbens and showed no significant effect on conditioned place preference (Jocham et al., 2006). It also had no individual effect on DA content in the striatum. In monkeys, the same antagonist blocked cocaine-induced effects in a range of behaviors, including locomotion and vigilance (De Souza Silva et al., 2006b). It also had no effect *per se*. In contrast, NK3 agonist senktide showed discrepancies between the two species. In rats, senktide increased both cocaine-induced hyperlocomotion and the DA response in the nucleus accumbens (Jocham et al., 2007). Senktide alone induced a brief increase in activity but no neurochemical changes. On the other hand, this same compound blocked cocaine-induced hyperlocomotion in monkeys, although it enhanced cocaine's effects on exploratory activity and some vigilance behaviors dose-dependently (Fig. 1; De Souza Silva et al., 2006a). Furthermore, unlike rats, senktide did not induce significant

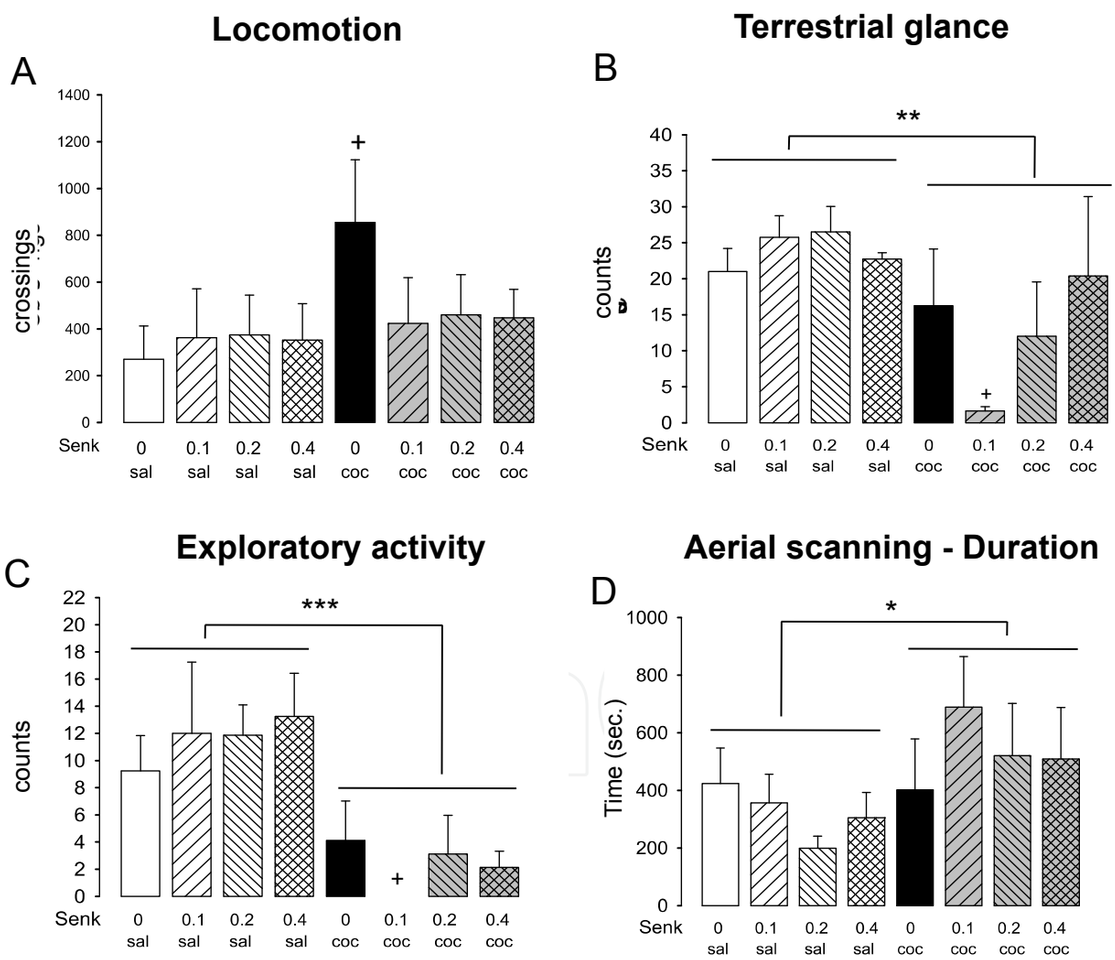

Fig. 1. The effects of cocaine (10 mg/kg, i.p.) on marmoset locomotor activity (A), terrestrial glance (B), exploratory activity (C) and aerial scanning duration (D; mean ± S.E.M.) and its modulation by the NK3-receptor agonist, senktide (0.1–0.4 mg/kg, s.c.), during a 20 min test trial (n = 8). +p < 0.05 vs. saline–saline, *p < 0.05, **p < 0.01, ***p < 0.001, two-way ANOVA (Modified from de Souza Silva et al., 2006a).

behavioral changes on its own (Fig 1A). These conflicting findings may be due to relevant differences in NK3 receptor distribution between rodents and NHP (Langlois et al., 2001). Despite that, NK3 receptor seems to be an interesting target for investigation and future therapeutic intervention of cocaine addiction.

CART is an mRNA identified in 1995, whose transcription seems to be modulated by psychostimulants (Douglas et al., 1995). It encodes two proteins in the rat (short and long CART), but only one in humans (short). In CART knockout mice, cocaine and amphetamine locomotor and reinforcing effects were reduced (Couceyro et al., 2005). The literature on CART research in primates, however, is scarce. There is one recent comparative report on the cocaine-induced expression of CART in the rat and monkey brain (Fagergren & Hurd, 2007). They report a higher expression of CART mRNA in the primate frontal and temporal cortices, positive labeling confined to the shell-like region of the striatum, different distribution in the hippocampal formation and more markedly differences in the thalamus. These aspects are different from those in rats, yet seem to be in agreement with human studies. Limbic distribution of CART mRNA was overall very similar to that of rodents'. However, the authors point that they were unable to investigate the nucleus accumbens where cocaine had been shown to induce increases in CART mRNA in humans (Albertson et al., 2004).

In summary, neuropeptidic involvement in cocaine-induced effects is beginning to provide important insights. The scarcity of primate studies on the subject is unsettling, considering that the discrepancies with rodents' anatomy and physiology are not trivial. There is, for instance, an absence of co-localization of several neuropeptides with DA in primates (Gaspar et al., 1990; Oeth & Lewis, 1992). Although the discovery of CART is fairly recent, compounds acting on NK1- and NK3-receptors have been under investigation for quite some time. Regardless, the understanding of tachykinins' influence on cocaine addiction seems to be progressing in a very slow pace.

3.4 Hypothalamic-pituitary-adrenal (HPA) axis

Another key aspect of psychostimulant effects concerns the neuroendocrine system. Stressful stimuli or situations trigger a series of neuroendocrine steps in the HPA axis; i.e., the release of corticotropin-releasing factor (CRF) from the hypothalamus, adrenocorticotropic hormone (ACTH) from the pituitary gland and finally glucocorticoids from the adrenal cortex. There is increasing evidence that this physiological response to stress is related to several aspects of drug addiction (Piazza & Le Moal, 1997; Sinha, 2001; Spealman et al., 2004). The work from Piazza and coworkers revealed that glucocorticoids were implicated in the DA response to cocaine and opioids (Marinelli et al., 1998; Marinelli et al., 1997; Piazza &Le Moal, 1997) and, therefore, the HPA axis was a possible target for addiction treatment. Glucocorticoid stress response seems to be essential for the acquisition, maintenance and reinstatement of stimulant self-administration (Goeders, 2002; Piazza et al., 1991; Piazza and Le Moal, 1998).

There are major and pervasive differences in the rodent and primate HPA system. First, the activation of the HPA in rodents relies predominantly on corticosterone, as opposed to cortisol in humans and NHP. There also seems to be discrepant age-related influences on hormones and cocaine. Rats display an increase in basal glucocorticoids as they age (Haugert et al., 1994; Meany et al., 1992), whereas no such difference was observed in NHP or humans (Goncharova & Lapin, 2002). More importantly, the distribution of corticotropin-

releasing-factor (CRF) reactivity and that of corticoid receptors in the brain show great discrepancies in the amygdala (Bassett & Foote, 1992; Sanchez et al., 1999), hippocampus and pre-frontal cortex (PFC; Sanchez et al., 2000). The discrepancies in the amygdala and hippocampus are similar to the differences in the distribution of norepinephrine in those regions (Smith et al., 2006). These structures are important for learning and memory (McGaugh 2002; Tomaz et al., 1992) which, in turn, are also implicated in addictive behaviors (Garavan et al., 2000; Kilts et al., 2001; O'Brien et al., 1998). The amygdala also sends critical inputs to the striatum and PFC.

The discrepancies in receptor distribution in the PFC are of particular interest. The PFC is another area relevant for cocaine effects. It is a critical structure in decision-making and is involved in stress responses (Weinberg et al., 2010). It has undergone a massive expansion in primates, with NHP sharing a high similarity with humans in terms of structure, neurochemistry and connections (Carmichael and Price, 1994, 1996; Hardman et al., 2002; Ongur et al., 2003; Porrino & Lyons, 2000). The predominance of glucocorticoid receptors in the primate PFC, compared to the hippocampus, suggests that in humans and NHP this structure plays an important role in the HPA negative feedback through GR-mediated mechanisms (Sanchez et al., 2000). Furthermore, increasing evidence has implicated PFC asymmetry with stimulant use and hormonal changes. Activity in the right PFC was positively correlated with elevated levels of cortisol and cocaine craving (Kalin et al., 1998; Volkow et al., 1999). Chronic use of cocaine was also correlated with greater volume loss of the right PFC (Liu et al., 1998).

Despite these differences, cocaine-induced effects have shown a considerably similar response in rodents and primates. Plasma levels of ACTH, endorphin and corticosterone in rats increase in response to cocaine administration (Forman & Estilow, 1988; Levy et al., 1991; Moldow & Fischman, 1987; Saphier et al., 1993) as also seen in NHP (Lima et al., 2008; Sarnyai et al., 1996). This same pattern is seen in humans, where ACTH and adrenaline levels were increased with cocaine infusions, along with its subjective effects such as euphoria (Mendelson et al., 2002). On the other hand, glucocorticoids show reinforcing properties of their own in rodents, whereas no such effect has been observed in primates (Broadbear et al., 1999). Broadbear and coworkers (2004) also reported that increases in ACTH and cortisol in NHP in response to cocaine infusion were in line with rodents studies, but the same did not hold true for opioid drugs, which induced an inhibition of HPA activity in monkeys.

Although rodent and primate research presents direct mechanisms for the cocaine-induced activation of HPA axis, the impact that stress may have on the maintenance and relapse into drug seeking behavior is not so clear (Sinha, 2001). Initial studies with footshock paradigms in rodents have suggested that corticosterone may play a role in relapse (Deroche et al. 1997; Shaham et al. 1998; Mantsch and Goeders 1999). Rodent studies on reinstatement, however, yielded conflicting results (Erb et al., 1998; Goeders, 2003; Lu et al., 2001). Studies with squirrel monkeys by Spealman and coworkers suggest that the HPA axis is not involved in cocaine relapse (Lee et al., 2003). Rather, their following work indicated that the noradrenergic system is more likely to mediate stress response in cocaine reinstatement (Lee et al., 2004; but see Platt et al., 2007). Nevertheless, a recent study with rats suggests that cocaine reinstatement may be dependent on the interplay of both the HPA and noradrenergic systems (Graf et al., 2011).

4. Current and future strategies against cocaine addiction

As mentioned above, an effective pharmacological treatment for cocaine addiction is still lacking. A recent study has attempted to implement a novel cocaine vaccine trial, with limited results (Martell et al., 2009), yet other trials are currently under way (Kinsey et al., 2010). There are, nonetheless, several ongoing efforts to develop pharmacological strategies in primates to block or reduce the reinforcing properties of cocaine. From the findings discussed above, DA and 5-HT receptors and their respective transporters seem to currently be the most likely candidates for such an endeavor. In fact, the co-administration of DAT and SERT inhibitors has yielded encouraging results in primates (Howell, 2008), with such joint infusion leading to a better outcome, when compared to DAT alone. Strategies that influence CART transcription may also exert an important modulatory effect on stimulant-seeking behavior and thus should not be overlooked in primate studies. On the other hand, NK1 and NK3 receptors seem to be more involved in the hyperlocomotor property of cocaine, even if the present lack of studies limits such a prediction, while the interaction of the stress response, via HPA axis, with the noradrenergic system seems promising in terms of preventing a relapse.

The development of drugs with such mechanisms will require confirmation and further testing in NHP models. Well-established testing paradigms are just now being combined with neuroimaging techniques in monkeys, such as PET scans (Howell, 2008; Howell & Murnane, 2011) and fMRI (Jenkins et al., 2004; Brevard et al., 2006). Besides the several aspects already pointed out in this chapter, other advantages for using NHP (specifically related to imaging studies) are worth mentioning, including a similar cerebral metabolism and pharmacokinetics profile between humans and NHP, as opposed to rodents (Banks et al., 2007; Lyons et al., 1996; Porrino et al., 2002). Therefore, the translational value of NHP neuroimaging is unparallel to any other animal model.

In summary, there is compelling evidence for the importance of NHP in cocaine research. In all neural pathways analyzed, the discrepancies detected between rodents and humans warrant some caution when generalizing the results observed in the former. Nevertheless, there are several lines of research related to cocaine that have few or no corresponding studies being held with primates. Besides the difficulty in handling and research costs, this may also be due to restrictions in the use of these animals for research, especially for large primates. The findings discussed in this chapter indicate that NHP will remain crucial for biomedical research for several years to come, as substitutes have not yet been made available. Therefore, the development of a clinically effective anti-cocaine or anti-relapse drug/vaccine will very likely depend on our ability to cope with the lack of studies and ever-mounting pressure against the use of animals in research.

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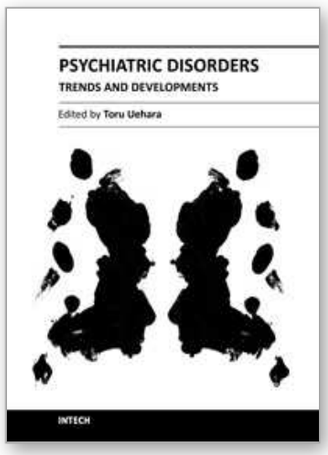

Psychiatric Disorders - Trends and Developments

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Due to their prevalence, pervasiveness and burden inflicted on men and women of today, psychiatric disorders are considered as one of the most important, sever and painful illnesses. This impairment of cognitive, emotional, or behavioural functioning is in some cases tragic. Aside from knowing the physical organic factors, such as infections, endocrinal illnesses or head injuries, the aetiology of psychiatric disorders has remained a mystery. However, recent advances in psychiatry and neuroscience have been successful in discovering subsequent pathophysiology and reaching associated bio-psycho-social factors. This book consists of recent trends and developments in psychiatry from all over the world, presented in the form of multifarious and comprehensive articles. The first two sections of the book are reserved for articles on schizophrenia and depression, two major illnesses present in this field. The third section of the book is reserved for addiction psychiatry, related not only to socio-cultural but also biological alterations. The last section of the book, titled Biological Neuropsychiatry, consists of three topics - updated molecular biology, fundamental neuroscience and clinical neuropsychiatric conditions. Doubtlessly, this book will be fruitful for future developments and collaboration in world psychiatry.

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