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Journal of Substance Abuse & Alcoholism

Review Article

Cocaine Interaction with Dopamine Transporter in the Prefrontal Cortex and Beyond

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Submitted: 18 March 2017

Accepted: 28 February 2018

Published: 28 February 2018

ISSN: 2373-9363

Keywords
- Cocaine
- Monoamine transporters
- Prefrontal cortex
- Nucleus accumbens
- Bed nucleus of stria terminalis

Abstract

Although the relevant research investment in understanding the mechanism of action of cocaine and its role in altering brain circuits and behaviour, an efficacious therapy for cocaine addiction has not been found yet. Thus, cocaine use, dependence, abuse and addiction are still a relevant health, social, and economical problem. Cocaine interacts with three different monoamine transporters and increases the extracellular level of dopamine, norepinephrine and serotonin in many brain areas as well in periphery. The aim of this review is to evaluate the interaction of cocaine with the dopamine transporter (DAT) but also with the norepinephrine transporter (NET) and the serotonin transporter (SERT) in several brain areas. In addition, it will be discussed some of the receptor interaction the are involved in the complex alteration of brain circuitry that in turns produces the feeling and the behaviours sought by addicted. The areas that will be considered are: i) the prefrontal cortex (PFC), being the area in which the process of decision making is elaborated; ii) the NAcc shell because its involvement in the reinforcing and motivational properties of cocaine; iii) the bed nucleus of stria terminal is (BNST), due to its involvement in the stress response and in the relapse of cocaine consumption. It will be also considered the effect of prenatal exposure to cocaine and the target role of monoamine transporters in the search of a therapy for cocaine addiction.

ABBREVIATIONS

NAcc: Nucleus Accumbens; DAT: Dopamine Transporter; NET: Norepinephrine Transporter; SERT: Serotonin Transporter; PFC: Prefrontal Cortex; mPFC: medial Prefrontal Cortex; BNST: Bed Nucleus of Stria Terminalis; VTA: Ventral Tegmental Area; LC: Locus Coeruleus; DRN: Dorsal Raphe Nucleus; PNCE: Prenatal Cocaine Exposure; GD: Gestational Day; PD: Postnatal Day

INTRODUCTION

Although the relevant research investment in understanding the mechanism of action of cocaine and its role in altering brain circuits and behaviour, an efficacious therapy for cocaine addiction has not been found yet. Failure in finding suitable pharmacological tools to prevent abuse or to treat cocaine addiction is probably due to the complexity of its interaction with brain circuits that are involved in the process of the decision formation. Thus, cocaine use, dependence, abuse and addiction are still a relevant health, social, and economical problem.

Even though the prevalence of cocaine use among high school seniors is much lower than alcohol use or smoking [1,2], emergency room visits for cocaine consumption are twice as much as for heroin or marijuana consumption (Thedea.org/US Substance Abuse and mental health Service Administration). In addition, the prevalence of acute coronary syndrome (ACS) associated with cocaine use increased from about 6 % in 2001 to 22 % in 2008 and interestingly, more than 25 % of hospitalized were younger than thirty [3]. Number of deaths from cocaine use is also increasing (2014) after a decline in 2010 [2,4].

Generally speaking, people begin to use drugs of abuse for recreational purposes, when the novelty seeking behaviour prevails over a prudent conservative behaviour, often under the influence of a challenging environment. The repeated exposition, motivated by the reinforcing property of abuse substances, leads to dependence and addiction. Cocaine use did not differentiate from other substances until the seventies, when its use became popular among businessmen, art-performers and other people who deal with high demanding roles, for improving their effectiveness and self-confidence.

Thus, if alcohol, cannabis or heroin were regularly abused to 'escape from everyday life', cocaine was frequently used to reach better performances in demanding activities as well as social life. Later on, this type of use spread among lower classes because of the increasing number of drug dealers and the consequent drop of drug prices. Again, cocaine was often

used to enhance performances and, as a result, more violent crimes were accomplished under its effect [5]. Hence, although cocaine shares many features with many other drugs of abuse, we believe that its peculiar motivational properties have a crucial role in cocaine addiction. In particular, cocaine ability to be self-administered by experimental animals and its property to stimulate dopamine transmission in the nucleus accumbens (NAcc) [6-8], allows its inclusion in the large group of addictive substances. Yet, the peculiar use among addicted people suggests that the neurobiological mechanisms and the alteration of brain circuits observed in animal models should be evaluated with caution, along with the translation of research findings into clinical practice. The aim of this review is to evaluate the interaction of cocaine with the dopamine transporter (DAT) but also with the norepinephrine transporter (NET) and the serotonin transporter (SERT) in several brain areas, in addition, the relative consequences that generate the complex alteration in brain circuitry that in turns produces the feeling and the behaviours sought by addicted will be discussed. The areas that will be considered are: i) the prefrontal cortex (PFC), being the area in which the process of decision making is elaborated; ii) the NAcc shell because its involvement in the reinforcing and motivational properties of cocaine; iii) the bed nucleus of stria terminalis (BNST), due to its involvement in the stress response and in the relapse of cocaine consumption.

COCAINE MECHANISM OF ACTION: MONOAMINE TRANSPORTERS

Understanding cocaine mechanism of action is apparently an easy task. Earlier studies on genetically modified mice have suggested that the primary site of cocaine action is the presynaptic DAT [9]. Being DAT the main mechanism of synaptic dopamine removal, cocaine blockade of DAT increases the extracellular dopamine concentration, thus strengthening the effects mediated by dopamine. In particular, the increase of extracellular dopamine in specific brain areas (i.e. NAcc) is a distinctive mark of drugs of abuse in rodents and in humans [10,11]. Therefore it appears obvious that cocaine is rewarding and addictive because by blocking DAT, it consequently stimulates dopamine transmission in the NAcc. Nonetheless this feature seems to be necessary but not sufficient, as i.v. injection of methylphenidate that has comparable efficacy to that of cocaine in blocking DAT in human brain in vivo, has not been reported to produce a self-report of 'feeling high' in several subjects [12]. In addition, the role of cocaine in rising dopamine levels in the PFC has been debated. Earlier it was found that rats self-administered cocaine in the mPFC but not in the NAcc or in the ventral tegmental area (VTA), [13].Moreover, it was found that i.p. cocaine administration increased dopamine output to a larger extent in the PFC as compared to NAcc [14]. Yet, the affinity of cocaine for DAT is 0.2 - 0.7 μM and surprisingly it is not different from the affinity for NET (0.4 - 0.7 μM) and that for SERT (0.4 - 0.5 μM) [15]. Thus one may wonder why the effect of cocaine on norepinephrine and serotonin transmission received much less attention. In this review we will try to go beyond this simple assumption and we will try to explain the effect of cocaine on these three monoamine uptake systems in brain and in turn on monoamine receptors involved.

DOPAMINE RECEPTORS AND COCAINE EFFECTS

Even if we consider that cocaine monoamine reuptake blockade is the primary mechanism of its action, we have to take into account that the higher synaptic levels of monoamine will produce a plethora of effects by interacting with multiple types of receptors. Thus, one may wonder which receptors mediate cocaine effects and in which brain area they play their role. We will consider here a few significant reports, out of their vast number that do not allow an exhaustive evaluation in this paragraph. Although numerous studies on dopamine receptors had the aim to find an efficacious therapy for cocaine addiction, the results are still unsatisfactory [16-18]. Nonetheless, these studies contributed to a better understanding of the mechanisms of cocaine effects. As regards dopamine D2 receptors, it has been reported that vulnerability to the reinforcing effects of cocaine is higher when D2 receptor number is reduced [19], and that chronic cocaine exposure reduces their number in monkeys and humans [20] while, in general, blockade of D2 receptors can reduce the strength of cocaine reinforcing effects [21]. Among D2 receptors a minority are autoreceptors and their role is somehow different. In fact, Bello et al. [22], have showed that mice with the selective loss of D2 autoreceptors exhibits increased place preference for cocaine. Thus we could hypothesize that an individual has a higher vulnerability for cocaine due to existence of increased dopamine transmission and due to possibly reduced number of D2 receptors and in particular to autoreceptor function reduction. Therefore cocaine, by increasing synaptic dopamine levels should also increase stimulation of D2 receptor. On this basis, it is very unlikely that a subject will find acceptable a therapy with D2 antagonists while a therapy based on dopamine agonists should better reproduce the effects of cocaine. Unfortunately, the therapy for cocaine addiction, based either on dopamine agonists or antagonists, is not adequate [16,18,23]. Furthermore, D3 receptors are also involved in cocaine addiction (see [24] for a short review). Peculiarly, this receptor has a higher affinity for dopamine and results fully occupied when D1 or D2 are occupied only by about 25 % [25]. They are located in limbic areas and may mediate motivational and emotional functions [26], and it has been shown that their number increases in cocaine dependent individuals [24]. Moreover, D3 antagonists significantly decrease cocaine self-administration [27-29]. In addition, it has been reported that D3 autoreceptors can regulate cocaine potency on DAT in NAcc core slices [30] through a physical interaction with DAT as assessed by coimmunoprecipitation and in situ proximity ligation assay [31]. On the other hand, the role of D4 dopamine receptors and its involvement in cocaine addiction has been reviewed recently [17]. Here we report few salient points discussed by these authors. In particular, D4 receptors density is lower than D2 and D3 and is mostly present in regions associated with executive and cognitive functions (PFC), emotions (amygdala) and memory (hippocampus and entorhinal cortex), while their expression is relatively low in reward-related regions. Studies on D4 knock-out mice, investigation on polymorphisms and studies on the effect of several antagonists, agonists or partial agonists of D4 receptor, in models of cocaine addiction did not produce a clear indication of its role. On the other hand, it appears promising the fact that a new D4 antagonist (NGD-94-1) reduced cocaine self-administration without affecting other behavioural functions [17].

COCAINE EFFECTS: DIFFERENCES BETWEEN EXPERIMENTAL ANIMALS AND HUMANS

A common and puzzling characteristic of cocaine addicts is that almost 80 % of them do not seek treatment [32,33] which might reflect that they neither feel ill nor that they need nothing else but the drug they abuse. No matter if they want to avoid abstinence or to achieve an emotive gain, addicts consider the abused substance as an essential ingredient of their life, regardless of consequences associated with abuse. Studies performed to evaluate the role of mPFC in drug dependence have been conducted in both humans and non-human mammals. In particular, it is of a great interest a comparison of the results obtained in the different segments of drug dependence (i.e. chronic drug exposure, drug abstinence, drug seeking, cue or drug induced relapse and stress induced relapse). Such comparison can provide useful insights in terms of brain areas and circuitry involved, but it is necessary to distinguish the behaviour of a man from that of other primates and obviously of rats. Indeed, drug addiction in humans can be considered as a disorder of self-control because the reinforcing properties of drugs of abuse prevail on the conscious awareness of the negative consequences of addiction behaviour (legal, health or social consequences). At variance with humans, drug intake in animals is supported mostly by the direct reinforcing property of the drug, and the memory of it. Consequently, behaviour is largely governed by instinct and by learned activities and is selected on the basis of its intrinsic and rather immediate reinforcing or punishing value. A second important difference between humans and experimental animals deals with the beginnings of drug use. The beginning of drug taking in man is often a consequence of a complex psychological motivation and it is strictly dependent on a group pressure and other circumstances, such as the age of the subject, which plays a crucial role. In fact, the incomplete brain maturation at adolescence age can offer a fertile ground to the strong reinforcing properties of drugs of abuse. In addition, even at adult age drug use can be started as a reaction to a stressful situation, thus the altered status of brain circuitry can play a relevant role in the response to cocaine. When a drug of abuse is administered to animals, the effects observed are those produced on a brain circuitry ensemble that is in a balanced basal condition (unless specific treatments has been applied previously), therefore a great caution should be taken before comparing the results obtained in experimental animals with those obtained in men.

BRIEF OVERVIEW OF PREFRONTAL CORTEX FUNCTION IN ADDICTION

The prefrontal cortex is involved in cognitive processes [34], in the regulation of emotions [35] in working memory, as well as in executive functions such as motor planning, inhibitory response control and sustained attention [36-38]. PFC functional or anatomical abnormalities are frequently found in individuals with drug abuse disorders ([39-41]. Also, clinical studies report that when traumatic brain injury damages the PFC, drug use disorders often result [42,43], and interestingly damage of PFC can be the result of drug addiction [7, 44].

The prominent role of PFC in motivated behaviour and decision-making is also supported by its anatomical and functional connection with other important areas of the brain, such as the nucleus accumbens and the ventral tegmental area ([45]. A synthetic view of the global function of PFC in addiction has been provided by Chambers et al.[46]. They stated that PFC plays a determining role in the representation, execution and inhibition of motivational drives by influencing patterns of neural ensemble firing in the nucleus accumbens and that poor PFC function could increase the probability of performing inappropriate motivated drives viewed clinically as impulsive. Considering the prominent role of NAcc in addiction by [6,47], it can be hypothesized that the process of addiction is developed through a progressive adaptation of the PFC functioning to the drives mediated by the NAcc. Nevertheless, cocaine is taken with a specific and clear aim (e.g. to improve performances, to facilitate the execution of violent crimes etc.), thus it is hard to consider the motivation as an impulsive drive. Therefore, if from a parsimonious point of view it is mandatory to consider a common circuit of addiction, in which the ability of PFC to evaluate the decision process is somehow impaired, understanding cocaine addiction represents a harder challenge because its direct action on the PFC circuits that are involved in the elaboration of the response.

ROLES OF PREFRONTAL CORTEX IN COCAINE ACTIONS

In this paragraph we will not try to describe exhaustively the deep involvement of the PFC in addiction as substantial evidence confirms the direct involvement of the mPFC in cocaine addiction. We will just point to a few significant reports that support this evidence. Very early it was reported that rats were able to self-administrate cocaine in the mPFC, most likely through a dopamine mechanism [48], although cocaine was shown to increase also norepinephrine levels in the mPFC [49]. It was also found that the i.v. cocaine injection increased dopamine in the rat PFC [50], but also that a lesion of mPFC did not prevent i.v. cocaine self administration [51]. Moreover, dopamine lesion of mPFC was found to enhance cocaine self-administration [52], while excitotoxic lesions of mPFC determined facilitation of cocaine self-administration [53]. From this early evidence and further on the contribution of the PFC to the effects of cocaine was not clarified. The finding that intra PFC cocaine self-administration increased dopamine levels in the NAcc [54] and that intracranial injection of the D1 antagonist SCH 23390 in the mPFC increased the rate of cocaine self-administered injections [55], somehow allowed us to consider the involvement of these two regions in the effect of cocaine as interdependent. The importance of this dependence was investigated [56] and it appeared clear that the complexity of cocaine effects was due to interaction with the glutamatergic transmission [56-57]. In particular, the main source of dopaminergic innervations of the mPFC is the VTA, and VTA dopamine neurons interact directly and indirectly with the pyramidal cells of the PFC [58]. Specifically, the majority of D1 and D2 type receptors in the medial PFC appears to be located on these pyramidal cells, with the density of D2 apparently considerably lower than that of D1 (see the review by Tzschentke [59]. The increase in dopamine extracellular concentration can determine the inhibition of the firing of dopamine neurons through an action on D2 receptors, which in turn increases K^+ conductance at cell body level [60]. The simultaneous reduction

of firing and increase of transmitter at terminal level in the mPFC cortex and other brain areas, produced by psychostimulants and cocaine, determines a complex effect on cognition, attention and learning circuitry. Indeed, either an increase or a decrease in dopamine transmission in the PFC may lead to dysfunction of the ability to inhibit inappropriate actions or thoughts and plan effective action [61]. The alteration of brain circuit that support these activities have been strongly involved in cocaine addiction [15,62,63]. Furthermore, it is interesting to note that on the same dendritic spine of postsynaptic pyramidal cells of the mPFC, dopaminergic terminals arising from the VTA are localized in close opposition to the glutamatergic terminals originating from both, the mediodorsal thalamus and the controlateral medial PFC. The former is not affected by VTA activation, which instead inhibits the excitation of pyramidal cells generated by the input from recurrent collaterals of efferent glutamatergic output [59]. A plethora of further reports extended the effects of cocaine in the PFC. Among them it was reported that i.v. cocaine infusion produced electroencephalographic desynchronization when cocaine and dopamine levels were highest in mPFC, an effect that could be blocked by both D1 and D2 antagonists [64]; furthermore, it was shown that an i.v. cocaine injection can increase the mPFC firing [65].

ROLES OF PREFRONTAL CORTEX IN COCAINE ABSTINENCE, CRAVING AND RELAPSE

Among segments that can be recognized in drug addiction, drug abstinence should produce rather similar changes in man and in experimental animal as both will experience the lack of drug effect upon interruption of its administration. This effect cannot be trivial considering the strong impact of drug effects in brain. Nevertheless, once the acute abstinence has been overcame, strong differences may be found between men and other mammals. In general, mPFC has a critical role in drug seeking, craving and relapse either triggered by drugs or by stress or by cues associated with drug taking in both, humans or in animals [66-68]. As far as it regards global functioning of the PFC, imaging studies allowed to observe a reduction in blood flow and cellular metabolism in dorsal PFC of individuals who abused psychostimulant; on the contrary, an increase has been observed when addicts are exposed to drug associated cues [69]. In addition, a reduction in blood flow and cellular metabolism in ventral PFC has been observed in cocaine abusers upon exposition to cocaine related cues [70].Taken together, these reports support the view that drug addiction negatively affects the function of the PFC in determining the value of natural reinforcers, while it may increase the motivational value of drug associated cues [44]. Nevertheless, although the dorsal mPFC is critically involved in the reinstatement of drug seeking behaviour after abstinence, pharmacological inactivation of the dorsal mPFC had no effect on cocaine seeking induced by cocaine cues [71-72]. Furthermore, Gourley and Taylor [73] recently suggested that the prelimbic PFC is essential for developing a goal-directed strategies, while the infralimbic PFC supports habitual behaviour. In addition, they suggested that some functions of the orbital PFC are parallel with those of the mPFC in the regulation of response selection. On a side of these observations there is an interesting fact: chronic cocaine use can disrupt mesocortical learning [62]. These authors proposed that cocaine elevates dopamine concentration and signalling in the cortex, thus prolonging dopamine signalling at D1 receptors and in turn, the consequent activation of intracellular signalling cascades could induce a long-lasting maladaptive plasticity.

Hereafter, looking at the overall abstinence meaning, we can summarize that abstinence in rats is initially associated with the devaluation of the reinforcement linked to the operant administration mechanism (e.g. lever pressing, nose poke etc.).This devaluation will activate a parsimonious process that drives rat behaviour to ignore the ineffective lever pressing making it going back to its routine cage activity. Although it is hard to appraise in rats the role of memories associated with drug administration, it is likely that a rat will not go through the experience of choosing whether going or not going back to the drug a choice that will be continuously pondered by a cocaine addict. Thus, abstinence and craving in men are most likely sustained by an internal equilibrium, not only generated by the unmotivated disappearance of the drug, but also strictly dependent to the internal struggle between the desire of the reward associated with drug taking and the evaluation of the consequences of that behaviour that heavily involves money, social life and health. Therefore, craving for drugs in animals is characterized by an initial stereotyped search for drug that ends relatively quickly, with reaching a relatively stable brain circuitry equilibrium, whereas in men the mPFC brain circuitry reaches only a pseudo-equilibrium that is the sum of the disappearance of drug effects and ability of self-controlling of environmental stimuli, that often were those that had generated drug addiction. In this scenario, the result of the exposition to cues associated with drug taking can trigger relapse in both, animals and humans.

COCAINE ACTIONS IN THE NUCLEUS ACCUMBENS

Our early microdialysis work suggested that several psychostimulants (e.g. amphetamine, cocaine, nomifensine) have in common the ability to increase dopamine levels in the NAcc [74] an effect shared by other drugs of abuse such as nicotine, morphine, alcohol, and cannabinoids that do not act directly on DAT, NET or SERT [10,75-77]. Once DAT was cloned and expressed in cells in culture, it was proved that cocaine blocked [^{3}H] dopamine uptake with high affinity (244 nM), [78]. This effect was shared by the compound GBR12909 [79], with even higher affinity (52 nM). Once this interaction was ascertained, it was easy to explain the mechanism of action of cocaine in producing the increase of extracellular dopamine concentration in the NAcc. These observations strengthened the “dopamine theory of addiction” [80] which, with highs and lows, has been a reference point in drug addiction studies for over 30 years [81]. Rewarding effects of cocaine and the dopamine theory went under the magnifying lens when Rocha et al. [82] demonstrated that DAT knock-out mice surprisingly self-administered cocaine. These authors hypothesized that cocaine interaction with targets other than DAT, possibly the serotonin transporter, could initiate and sustain cocaine self-administration in DAT$^{-/-}$ mice. To support the fact that reward can take place in absence of dopamine they showed, through microdialysis, that cocaine did not increase dopamine levels in the striatum of DAT$^{-/-}$ mice. In addition, they showed that cocaine binding sites, labeled with C- [125^{3125}I] RTI-

55, a potent cocaine congener, could be displaced by 1 μM of the SERT inhibitor alaprociate. Although these results allowed the authors to propose a role of serotonin in the addictive effects of cocaine, somehow this was in a contrast to the evidence that drugs which block only SERT are not self-administered [83,84] In addition, we investigated cocaine effects in DAT$^{-/-}$ mice and observed that cocaine did not increased dopamine output in the dorsal striatum [85]. Surprisingly, we observed that cocaine could increase dopamine output in the NAcc of DAT$^{-/-}$ mice. We hypothesized that the increase in dopamine output was probably due to NET blockade, as a similar effect was also produced by the administration of reboxetine, a selective NET blocker. Thus we suggested that dopamine output in the NAcc of DAT$^{-/-}$ mice was still playing its role in the reinforcing mechanisms of cocaine by an adaptation of the NET accumbal neurotransmitter reuptake system.

BED NUCLEUS OF STRIA TERMINALIS AND COCAINE ACTIONS

The Bed nucleus of stria terminalis (BNST) is a forebrain nucleus included in the extended amygdala positioned to relay between cortical, hippocampal and amygdalar inputs, and stress and reward centres [86]. BNST is densely innervated by norepinephrine neurons [87], serotonin neurons [88], and dopamine neurons [89]. All three monoamines make contact with corticotrophin releasing factor (CRF) neurons, supporting the role of the BNST in adaptive response to stress [90]. In particular, norepinephrine neurons make synaptic contacts with dendrites of the CRF neurons in the ventrolateral BNST, dopamine neurons innervate soma and dendrites of the CRF neurons in the dorsal part [89], while serotonin neurons innervate CRF neurons in both areas [88]. Consequently, in this nucleus cocaine can interact directly on DAT, NET and SERT. We observed that cocaine increased dose-dependently dopamine output in the BNST [91] but also norepinephrine (Jadzic et al., in preparation). In addition, the BNST sends a dense set of projections to the VTA (reviewed by Silberman [92], that become activated during reinstatement of cocaine seeking [93]. Interestingly, it has been showed that reinstatement of cocaine seeking caused by acute foot-shock stress can be blocked by inactivation of the BNST with sodium channel blockers [94], or gamma-aminobutyric acid (GABA) receptor agonists [95] as well as with beta norepinephrine receptor antagonism [96]. On the other hand, Erb and Stewart [94] reported that CRF antagonism completely blocked reinstatement of cocaine-seeking induced by presentation of foot-shock stress. Moreover, cocaine can increase CRF concentration in blood [97-99], and it also can change CRF peptide or mRNA levels within the extended amygdale [100-102]. Intriguingly, adrenergic beta-1 receptor activation within BNST produces an enhancement of excitatory synaptic transmission that requires CRFR1 signalling and this link was transiently disrupted by chronic cocaine use, although this disruption extinguished with time but could be reactivated by cocaine challenge [103]. Altogether, the neuronal peculiar feature of the BNST and its relationship with the reward and the stress systems is giving to this nucleus a crucial role in all the segments of cocaine transition, from use, over abuse and towards addiction. Thus, it can be hypothesized that the stressful experience of drug addiction can increase the intrinsic power of cocaine in altering the delicate equilibrium of stress control in the BNST and that this part of the brain cannot be excluded as a potential target for cocaine therapy.

DOPAMINE, NOREPINEPHRINE AND SEROTONIN TRANSPORTERS AND COCAINE ADDICTION THERAPY

The interaction of cocaine with three different neuronal transporters (e.g. dopamine, norepinephrine and serotonin transporter) is a major limitation in finding a drug for cocaine addiction therapy. The direct effect of cocaine on monoamine transporters results in the interaction of monoamines with a plethora of dopaminergic, adrenergic and serotoninergic receptors, making a search for such a drug even harder. The role of adrenergic receptors (antagonists and agonists), as well as the role of various alterations of the noradrenergic system in a multiple effects of cocaine is elegantly been reviewed recently [104]. Nevertheless, the extension and the complexity of the central and peripheral adrenergic system make very hard the selection of a drug to be used for cocaine addiction. On the other hand, the selective NET inhibitor desipramine was one of the first medications reported to be effective in humans in reducing relapse to cocaine use [105], but these data were not confirmed [106,107]. The new interesting NET inhibitor atomoxetine, introduced recently for ADHD therapy [108,109], as tested in cocaine dependence, but results were unsatisfactory [110]. At this regard we would like to highlight that the three monoamine systems interact profoundly (see previous sections) and investigations aimed to evaluate a specific receptor interaction in the behavioural or biochemical effects of cocaine (e.g. extracellular monoamine levels in a specific brain area) can produce unpredicted results. In particular, recently we have observed that i.p. administration of the selective blocker of serotonin transporter (citalopram) was able to increase the extracellular concentration of dopamine and norepinephrine in the BNST [111]. This effect was most likely achieved through the synaptic 5-HT elevation and receptor interaction with catecholamine system. These interactions are sustained by a reciprocal innervation of the three most important monoamine nuclei (VTA, LC and DRN) [112], On the other hand, desipramine can increase dopamine output either in the PFC [113,114] or in the BNST [114] through different mechanisms. Therefore, we can expect that cocaine effects on monoamine interaction could be complex. As for serotonin receptors, the most investigated one is the 5-HT1A receptor that in general may influence local feedback mechanisms. Muller et al., [115], reviewed this issue and concluded that 5-HT (1A)-autoreceptors mainly facilitate psychostimulant addiction-related behaviours. This effect is probably due to a limitation of the 5-HT response in terminal areas, whereas in contrast postsynaptic 5-HT (1A)-receptors predominantly directly inhibit the expression of various addiction-related behaviours. An interesting example of dopamine-5-HT interaction is the ability of the 5-HT1A receptors agonist (6)8-OH-DPAT to reduce a discharge rate of mPFC fast-spiking GABAergic interneurons. The consequent disinhibition of pyramidal neurons, in turn leads to downstream excitations of subcortical structures reciprocally connected with the PFC, such as midbrain dopaminergic neurons [116].

The interaction of cocaine with three different transporters has enormously complicated the search for a drug that could be used for the therapy of cocaine addiction, thus drugs that could block specifically only one transporter have been investigated. The identification of a drug that could selectively block DAT allowed dissecting the role of DAT in the effects of cocaine. GBR 12909 [117] and similar compounds were tested extensively. It has been shown that these substances were able to reproduce behaviours typical for cocaine and to reduce cocaine self-administration [118,119]. On the other hand, compounds that selectively increase serotonin neurotransmission didn't show cocaine typical behavioural effects and didn't maintain self-administration behaviour [120,121]. In particular, the major problem of DAT blockers has been the liability potential, thus compounds with slower onset of neurochemical and pharmacological effects such as RTI-366 have been developed [122]. RTI-336 is a highly selective DAT inhibitor with a selectivity 1,000- fold higher than that for SERT and 400 folds higher than that for NET [123]. RTI-366 and RTI 177 were compared with cocaine and resulted to have weaker reinforcing properties [124]

A series of studies conducted in non-human primates, for the evaluation of the effectiveness of DAT inhibitors in reducing cocaine self-administrations, in absence or in presence of selective SERT inhibitors have also been performed. Administration of a SERT inhibitor has little effect on cocaine self-administration, however, co-administration with the ED50 dose of RTI-336 completely suppressed cocaine self-administration behaviour in all subjects tested [125].

In summary, we can say that the potential of DAT blockers as a therapy of cocaine addiction is limited because their reinforcing properties predict an abuse liability, while NET blockers or SERT blockers are inefficacious. On the other hand it could be interesting to investigate their potential in slowing or regressing the evolution from cocaine abuse to addiction in humans.

PRENATAL COCAINE AND TRANSPORTER INTERACTION

Cocaine readily crosses the placenta but is metabolized slowly in the uterus [126], therefore the fetus can be exposed to high cocaine concentrations and for a long period of time. Moreover cocaine shows a high affinity binding that can be displaced by dopamine, norepinephrine and serotonin, in fetal rat brain synaptosomes [127]. The most common consequences of prenatal cocaine exposure (PCE) in humans are low birth weight [128], respiratory problems, reduced head size and increased risk of seizures. However, many effects on brain function appears during early childhood and in adolescence, while in adulthood the neuronal circuitry alterations are somehow repaired [129]. On this basis, one may wonder whether PCE effects in offspring are generated by the increase of dopamine, norepinephrine and serotonin availability during prenatal life or by withdrawal syndrome after birth. Looking at cocaine-DAT interactions it has been shown that cocaine, as well as GBR 12909, could inhibit neurite outgrow when stimulated by NGF in PC-12 cell [129]. This effect was reproduced by dopamine but not with norepinephrine or acetylcholine. On the other hand, serotonin stimulated it. In addition, the D1 antagonist SCH 23390 blocked this effect. As regards changes produced by PCE in the offspring animals, it was found that DAT was increased at postnatal day (PD) 1 through the PD 5, but was reduced at PD 14 and 35, while no changes in dopamine receptors were observed in the striatum [131] A reduce DAT immulabeling was also found in the striatum of the offspring exposed to PCE at gestational day 8-21 [132]. From a functional point of view, PCE can produce a long term effect in the size of the presynaptic, amphetamine releasable cytoplasmic pool of dopamine in the striatum of adult rabbit offspring [133]. As regards norepinephrine system, there is a substantial evidence of the effects of PCE on NET, on receptor and on locus coeruleus (LC) neuronal outgrowth, and of the alterations that support the appearance of cognitive deficits at youth age. In particular, it has been found that norepinephrine turnover was elevated in the PFC of juvenile offspring of rats exposed to cocaine at 10-20 gestation day (GD), an effect probably due to a reduction of alpha-2A adrenergic autoreceptors in the [134]. In addition, an up-regulation of alpha-2 adrenergic receptors was found in the PFC of adolescent PCE rats although a reduction was observed in the amydala and in the hippocampus) [135]. It has been also found that cocaine reduces LC neuronal neurite formation and extension outgrowth in vitro [136].

PCE has also multiple and complex effects on serotonergic system, that has been extensively reviewed by [129] These authors suggested that the alterations in serotonin signaling are dependent on timing of exposure, test regimens and sex. In particular, PNCE over gestation day (GD) 7-20 does not change 5-HT levels but decreases stimulated release in the striatum and nucleus accumbens of 7 days old rats [137] while low levels of 5-HT where found in cerebral cortex and hippocampus of PNCE (13-20 GD) of adult offspring [138]. In addition, PCE decreased 5-HT reuptake sites in cortical and hippocampus sites from 1-7 post-natal day (PND) [139,140], whilst an increased number of SERT binding was observed in juvenile in the NAcc. As regards the effect of serotonin receptors, the 5-HT1A has received the highest attention because of its multiple roles. In particular, the number of 5-HT1A receptors was higher in raphe nuclei, basal ganglia and forebrain at infancy [141-142]. As a conclusion it can be said that the multiple effects of PCE on behavior involve the complex role of serotonin innervation at different stages of development.

As regards humans, it has been recently reported that PNCE newborns at 5 weeks of age exhibited lesser total gray matter than controls [143]; PCE increased plasma norepinephrine levels in the newborns, that were found associated with neurobehavioral disturbances at day 1 or 3 of life, but not at 2 weeks [144] though in a previous study an increase of catecholamine precursor dihydroxyphenylalanine was observed [145]. Another study observed a reduction in homovanillic acid in a cerebrospinal fluid, the main metabolite of dopamine [146]. In conclusions, we can say that the PCE has a profound effect on morphology and development of brain circuits, thus the observed behavioral abnormalities could be justified by the profound cocaine interaction in multiple sites in the brain of the fetus.

DISCUSSION & CONCLUSION

A search on Pub Med for cocaine produces 38572 results. Nevertheless, NIDA states that presently there are no medications approved by the U.S. Food and Drug Administration

to treat cocaine addiction, though researchers are exploring a variety of neurobiological targets (https://www.drugabuse.gov/publications/research-reports/cocaine). Considering that about 90 % of all papers published on cocaine have been published in the last 35 years, one may wonder why this huge effort has produced so modest results. Why the better understanding of cocaine addiction mechanisms didn't bring to a suitable therapy? What went wrong? One of the targets of many researchers has been the identification of the circuit of addiction, with the hope that this knowledge would have allowed us to find a panacea for addiction, included cocaine addiction. Most of the experiments have been performed on experimental animals, and those circuits have been explained in details, but the therapy for cocaine addiction didn't receive a strong impulse. We can thus conclude that the major obstacle in finding a suitable therapy for addiction is cocaine itself. The fact that cocaine does not act on a receptor but acts blocking the transporter for three of the most important neurotransmitters in brain, is a problem hard to face. Furthermore, cocaine does not produce an effect by its intrinsic properties, but rather it modifies the extracellular concentration of the released monoamine on the basis of the monoamine amount that is released either spontaneously or under physiological or environmental stimulation. Cocaine effect is thus an effect that depends on the activation state of brain circuitry. The ideal drug for cocaine addiction should be a drug that binds the monoamine transporter, prevents cocaine binding without affecting transporter functioning. Such drug should work perfectly, as it could diminish cocaine self-administration, driving dependence to extinction. It should also be efficacious in humans although one may wonder if cocaine consumers and addicted are willing to take it. In fact, looking at statistics on cocaine addiction, it appears that only 17 % of those who used cocaine become addicted and about 80 % of users (addicted) do not look for therapy. Thus we may also wonder why we are looking for a therapy. Alternatively, the research effort to find a therapy for cocaine abuse and addiction should be oriented towards the understanding of the motivations that push an individual to use cocaine. These motivations could have a genetic or environmental origin, but the condition of cocaine abuse has to be considered pathological before it evolves in addiction. Thus, it is necessary to have better definition and better acknowledgement of this condition, in order to apply either pharmacological or psychological or even social interventions to prevent addiction.

ACKNOWLEDGEMENTS

The authors thank the University of Cagliari for the financing of this work PRID 2015. The authors express their gratitude to Mr. Giuseppe Satta for the English revision of this manuscript.

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Cite this article

Carboni E, Carboni E, Jadzic D (2018) Cocaine Interaction with Dopamine Transporter in the Prefrontal Cortex and Beyond. J Subst Abuse Alcohol 6(1): 1074.