THE ROLE OF SEROTONIN IN CRAVING: FROM BASIC RESEARCH TO HUMAN STUDIES

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Abstract — Increasing evidence suggests that craving may play a central role in the mechanisms of addiction. The experience of craving is largely characterized by obsessional thoughts about drugs, triggering compulsive drug-seeking and drug-taking behaviour. In the present article the possible involvement of brain 5-hydroxytryptamine (5-HT) in the mechanisms of craving and relapse is discussed by integrating the results of basic research with those obtained in human studies. Based on studies suggesting that the brain serotonergic system plays a central role in the regulation of impulse-control mechanisms, it is proposed that 5-HT deficiency may contribute to the loss of control over drug-taking, which is a crucial factor for the maintenance of addictive behaviour.

INTRODUCTION

A large body of evidence suggests that craving plays a central role in the maintenance of addictive behaviour. Nevertheless, various methodological problems have severely hampered researches in this field. Most of these problems are related to the fact that craving is a subjective state, which may largely differ among drug abusers, may depend on the drug used and may be strongly influenced by the psychophysiological condition of the individual (Kozlowski et al., 1989; Pickens and Johanson, 1992). This has severely limited the development of standard procedures providing reliable and objective measures of craving in humans.

Recently, experimental animal models, mainly based on drug-maintained responding, have been proposed as tools to study drug-seeking behaviour and relapse (Markou et al., 1993). Whether these models may have validity as indicators of human craving is not clear; nevertheless, their use may be helpful in investigating the neurochemical basis of craving.

The present article discusses the possible role of the brain indolylamine 5-hydroxytryptamine (5-HT), also referred to as serotonin, in the process of craving, by integrating the results of basic research with those obtained in human studies. Attention has been focused on the involvement of the 5-HT system in the regulation of impulse-control mechanisms. Indeed, it is believed that the loss of control over drug-taking is an important factor in the maintenance of the addictive syndrome (Koob et al., 1998).

THE CONCEPT OF CRAVING

The incentive motivational theory of behaviour predicts that some natural stimuli, such as food or sex, but also some artificial stimuli (drugs) may possess incentive motivational value, owing to their ability to activate the neuronal substrates for pleasure. Following the attribution of salience, the stimulus acquires incentive properties and becomes attractive and wanted (Bolles, 1967, 1972; Bindra, 1976).

The incentive-sensitization theory of addiction predicts that repeated drug experience induces progressive neurochemical adaptation (sensitization), resulting in a pathological enhancement of the incentive salience attributed to drug-taking events (Robinson and Berridge, 1993; Kalivas et al., 1998). The act of drug-taking becomes increasingly attractive, the desire of a drug evolves into craving and drives individuals to a compulsive, uncontrolled drug-seeking behaviour (Robinson and Berridge, 1993). Neutral stimuli that have
been repeatedly experienced in association with drugs (place, actions, objects) acquire secondary incentive value, through associative learning processes. Therefore they become capable of eliciting craving and of triggering drug-seeking behaviour (Ehrman et al., 1992; Newlin, 1992; Robinson and Berridge, 1993; Ranaldi and Roberts, 1996; O’Brien et al., 1998).

Although the incentive-sensitization theory can provide an important theoretical substrate for craving and drug-seeking behaviour, it does not provide an exhaustive explanation for the whole addictive syndrome. For instance, it does not consider which is the contribution of the negative state associated with drug withdrawal for the development and maintenance of addictive behaviour (Koob and Le Moal, 1997). In this regard, the counteradaptation theory of drug addiction suggests that repetitive drug administration induces adaptive physiological processes that counteract the effect of the drug (Koob and Bloom; 1988; Koob et al., 1989; Koob and Le Moal, 1997). When the drug is discontinued these adaptive processes are left unopposed resulting in a withdrawal state. Withdrawal results in a long-lasting psychological dysregulation (dysphoria, anxiety, depression, anhedonia) that can contribute to motivate drug-taking (Childress et al., 1994; Koob and Le Moal, 1997). Indeed, a state of withdrawal can enhance the incentive-motivational value of a drug resulting in an increase in craving and drug-seeking behaviour (Koob and Bloom, 1988).

Stress and adverse life events can contribute to the development of addictive behaviour and to an increased rate of relapse (Brown et al., 1995; Phillips et al., 1997; Piazza and Le Moal, 1998). Several studies reported that exposure to stressors may result in sensitization towards drugs of abuse and vice versa (Antelman et al., 1980; Ahmed and Koob, 1997; Prasad et al., 1998). Indeed, both stressors and drugs of abuse are able to stimulate the mesolimbic dopamine (DA) system. Thus it is possible that stress may reinstate drug self-administration (relapse), by ‘priming’ for the drug (Robinson and Berridge, 1993; Le et al., 1998; Piazza and Le Moal, 1998). An alternative explanation is that repeated exposure to stressors may generate mood disorders, such as anxiety and depression (File, 1996; Graef et al., 1996). These negative affective states may increase the motivational value of the drug that is taken in the attempt to alleviate distress symptoms (Koob and Le Moal, 1997; Stewart et al., 1997).

THE 5-HT SYSTEM

Serotonin is a neurotransmitter widely distributed in the central nervous system. Neurochemical and neuroanatomical studies have provided evidence that the cell bodies of brain 5-HT neurons are mostly located in the medial and the dorsal raphe nuclei. From these nuclei, 5-HT fibres project to the forebrain and terminate in several cortical areas, as well as in other brain structures such as the striatum, the nucleus accumbens, the ventral tegmental area, the hippocampus (Jacobs and Azmitia, 1992).

Seven 5-HT receptor subtypes have so far been described. The 5-HT1, 5-HT2, 5-HT3 and 5-HT4 receptors have been pharmacologically well characterized, while 5-HT5, 5-HT6, and 5-HT7 have been identified, but not completely characterized. The 5-HT1 and the 5-HT2 receptors can be subclassified into 5-HT1A, 5-HT1B/D, 5-HT1E, and 5-HT1F and into 5-HT2A, 5-HT2B and 5-HT2C, respectively. In the brain all the above-mentioned receptors are located postsynaptically. The 5-HT1A and the 5-HT1B subtypes are also located presynaptically in the raphe nuclei (somatodendritic autoreceptors) and in terminal areas (axon terminal autoreceptors), respectively (Hoyer et al., 1994; Hoyer and Martin, 1996). Administration of drugs stimulating postsynaptic receptors or treatments with selective serotonin reuptake inhibitors (SSRIs), serotonin releasers and serotonergic precursors may lead to an increase in central 5-HT function. By contrast, administration of the neurotoxin 5,7-dihydroxytryptamine (5,7-DHT), which damages 5-HT fibres, or of the tryptophan hydroxylase inhibitor para-chlorophenylalanine (PCPA), as well as of compounds stimulating presynaptic receptors, results in a decrease in central 5-HT neurotransmission.

There is evidence that drugs of abuse may influence brain 5-HT activity and that 5-HT may have a role in the regulation of specific aspects of addictive behaviour. Modulation of brain 5-HT neurotransmission has been shown to influence drug self-administration (Lyness et al., 1980; Lyness, 1983; Lyness and Moore, 1983; Lyness and Smith, 1992; Peltier and Schenk, 1993) and
altered regulation of brain 5-HT function can be detected in drug withdrawal (Cunningham et al., 1992; Nevo et al., 1995; Parsons et al., 1995, 1996; Kleven et al., 1995; Rasmussen and Czachura, 1997). Moreover, it has been well documented that alcohol abuse and dependence may, in some cases, be related to central 5-HT deficiency (Cloninger, 1987; Sellers et al., 1992; Virkkunen and Linnoila, 1997). In addition, both animal and human studies suggest that treatment with drugs increasing 5-HT neurotransmission may result in reduction of alcohol consumption (Sellers et al., 1992; Naranjo et al., 1992, 1994, 1995; Naranjo and Bremner, 1994).

5-HT AND DRUG SELF-ADMINISTRATION

Self-administration is currently considered the most reliable experimental procedure to assess the abuse potential of drugs and it possesses a high predictive validity as an animal model of human drug abuse (Marku et al., 1993).

As suggested by several self-administration studies, manipulation of the brain 5-HT system may influence the motivational properties of drugs. Administration of the SSRI fluoxetine may decrease either oral, intragastric or intravenous ethanol self-administration (Murphy et al., 1988; Haraguchi et al., 1990; Lyness and Smith, 1992). By contrast, depletion of brain 5-HT following treatment with the tryptophan hydroxylase inhibitor PCPA increases responding for intravenous ethanol (Lyness and Smith, 1992). Also amphetamine, cocaine and morphine self-administration is reduced by treatment with agents such as SSRIs or the 5-HT precursor tryptophan, which stimulate central 5-HT activity (Lyness, 1983; Smith et al., 1986; Porrino et al., 1989; Richardson and Roberts, 1991; McGregor et al., 1993; Peltier and Schenk, 1993) On the other hand, 5-HT depletion following central injections of the neurotoxin 5,7-DHT results in increased drug self-administration (Lyness et al., 1980; Lecese and Lyness, 1984).

Although 5-HT may be involved in drug self-administration, it is extremely difficult to understand what is the exact role played by this system in the regulation of the motivational aspect of drug-taking. Indeed, most of the studies investigating the effects of manipulations of the 5-HT system were performed using the fixed ratio (FR) schedule. Using this paradigm, it is not clear whether changes in the rate of drug intake may reflect an increase or a decrease in the reinforcing effects of the drug that is being self-administered (Arnold and Roberts, 1997). More recently, the role of the 5-HT system was examined by employing the progressive ratio (PR) schedule (Loh and Roberts, 1990; Richardson and Roberts, 1991; Roberts et al., 1994). In this paradigm, which has been proposed as a valid animal model to study drug-craving and relapse, the cost (number of lever pressing) of a drug injection is progressively increased over sessions until the subject fails to receive an injection within a predetermined interval of time. The largest ratio value successfully completed is defined as the breaking point.

The breaking point can be taken as a measure of drug-craving. The decrease or increase in the breaking point can be interpreted, respectively, as a reduction or a potentiation of the motivational value of the drug (Marku et al., 1993; Richardson and Roberts, 1996). Loh and Roberts (1990), using the PR schedule, observed that the injection of the neurotoxin 5,7-DHT into the amygdala or into the medial forebrain bundle increases the breaking point for cocaine self-administration. These data led the above authors to suggest that depletion of brain 5-HT increases the motivational value of cocaine. In a subsequent study, Roberts et al. (1994) observed that brain 5-HT depletion results in an increase of the breaking point also when food is used as a reinforcer. Moreover, compared to non-lesioned controls, 5,7-DHT-lesioned rats showed a higher level of responding during extinction. Altogether, these results led the authors to suggest that depletion of brain 5-HT increases the motivational value of cocaine. In a subsequent study, Roberts et al. (1994) observed that brain 5-HT depletion results in an increase of the breaking point also when food is used as a reinforcer. Moreover, compared to non-lesioned controls, 5,7-DHT-lesioned rats showed a higher level of responding during extinction. Altogether, these results led the authors to suggest that depletion of brain 5-HT increases the motivational value of cocaine.

5-HT AND IMPULSE CONTROL

It is known that manipulations of the 5-HT system may influence cognitive and learning processes, which may have implications for the role played by this system in the control of operant behaviours (i.e. self-administration). Indeed, there is evidence suggesting that 5-HTergic mechanisms are particularly important in maintaining the
effectiveness of motivated responses towards either negative or positive reinforcers (Soubrie, 1986; Wogar et al., 1993; Harrison et al., 1997). Soubrie (1986), reconsidering the role of 5-HT in the regulation of these motivated responses, suggested that 5-HT may be involved in the control of 'impulsive' behaviour.

Animal models to study 'impulsivity' are based on the ability of the animals to choose between a small immediate reward and a larger delayed reward. An exaggerated preference for small immediate reward over larger delayed reward may be regarded as indicative of 'impulsiveness'. Using operant tasks in which animals were trained to choose between these two rewards, it was observed that depletion of 5-HT reduces the ability of the animal to wait for the delayed reward (Wogar et al., 1991, 1993). By contrast, rats treated with SSRIs showed an increase in their ability to wait for a larger reward (Bizot et al., 1988). Further evidence of the involvement of brain 5-HT in the regulation of 'impulsivity' has been recently provided by Harrison et al. (1997). These authors, using the five-choice serial reaction time task, observed an increase in premature responding in rats injected with 5,7-DHT, while their accuracy and attentional performance were unaffected. The authors suggested that such an increase in premature responding is consistent with the idea that depletion of 5-HT results in decreased impulse control. The animal studies confirm the observation that human subjects exhibiting pathological impulsive behaviour have lower than normal concentration of the 5-HT metabolite 5-hydroxyindol-3-ylacetic acid (5-HIAA) (Linnoila and Virkkunen, 1992). Indeed, it has been shown that drug treatments which increase central 5-HT neurotransmission may improve the ability of individuals to maintain 'self-control' (Murphy et al., 1992; Lopez-Ibor, 1992; Asberg and Martensson, 1993).

CRAVING AND IMPULSE CONTROL: A POSSIBLE ROLE OF BRAIN 5-HT

As mentioned above, drug-craving is the consequence of attribution of excessive incentive salience to an external stimulus (drug) or its mental representation. The conscious product of this process is the subjective experience of 'wanting', which may result in uncontrollable, compulsive drug-seeking behaviour. Within this theoretical framework, it has been postulated that the mesolimbic DA system is the neurochemical substrate for the process of incentive salience attribution (Robinson and Berridge, 1993; Kalivas et al., 1998). On the other hand, the 5-HT system, owing to its role in impulse-control mechanisms, could contribute to behavioural disinhibition and could facilitate the emission of goal-directed behaviour (drug seeking and drug-taking behaviour). A deficit in brain 5-HT function may therefore increase the vulnerability to drug abuse and possibly also the frequency of relapse episodes (Fig. 1).

Indeed there is evidence of a strong correlation between drug abuse, hypofunction of the 5-HT system and impairment of self-control mechanisms (Higley et al., 1996; Higley and Linnoila, 1997; Brunner and Hen, 1997; Virkkunen and Linnoila, 1997). In particular, deficiency of brain 5-HT activity has been directly correlated with specific forms of alcohol abuse and dependence. Cloninger (1987) described a subgroup of alcohol abusers (type II) who have low cerebrospinal fluid

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Fig. 1. Schematic illustration of the hypothetical two-stage process of craving.

First stage: the increase in mesolimbic DA (dopamine) activity, which is apparently involved in drug-induced sensitization and in the incentive learning processes (Robinson and Berridge, 1993; Di Chiara, 1995, 1998) may play a central role in the process of incentive salience attribution to drug-related stimuli. The attractiveness of a drug progressively increases evolving into craving. Second stage: reduction of brain 5-hydroxytryptamine (5-HT) activity may contribute to loss of control associated with craving, which results in compulsive drug-seeking and relapse. This is a simplified DA- and 5-HT-based model of craving and relapse. The possibility that other neurochemical systems could be involved in these processes should not be excluded.
levels of 5-HT and its metabolite 5-HIAA. These subjects, characterized by impulse-control deficits and violent behaviour, are known to suffer from severe alcohol dependence with frequent episodes of craving and relapse.

A high co-morbidity has been also observed between drug abuse and bulimia nervosa, which is characterized by compulsive behaviour and loss of control over food consumption (Bulik, 1987; Lilenfield et al., 1997). Interestingly, there is evidence to suggest that dysfunction of the brain 5-HT system is an important neuropsychopathological component of this disorder (Brewerton, 1995; Jarry and Vaccarino, 1996).

Co-morbidity between alcohol abuse and obsessive compulsive disorder (OCD) has also been reported (Helzer and Pryzbeck, 1988; Zetin and Kramer, 1992; Schuckit et al., 1997). Patients suffering from OCD are characterized by poor self-control and obsessional thoughts, triggering repetitive and compulsive behaviour (Murphy et al., 1992; Zetin and Kramer, 1992). Interestingly, a decreased concentration of 5-HIAA, which may reflect the possible deficiency of brain 5-HT, was found in the cerebrospinal fluid of these patients (Murphy et al., 1992; Zetin and Kramer, 1992; Stein et al., 1996). The hypothesis of 5-HT deficiency in OCD is further supported by the observation that pharmacological treatments aimed at increasing central 5-HT neurotransmission represent effective therapies in the management of OCD (Murphy et al., 1992; Zetin and Kramer, 1992; Barr et al., 1993; Tollefson et al., 1994). Nevertheless, it is known that SSRIs are also effective in the treatment of alcohol abuse. Following SSR1 administration alcoholics reported ~20% reduction of ethanol drinking and reduction of craving (Naranjo et al., 1992, 1994; Naranjo and Bremner, 1994; Lejoyeux, 1996; Tiibonen et al., 1996). This effect of SSRIs has often been attributed to their antidepressant action and to mood improvement in alcoholics undergoing treatment. However, there are studies showing that there is no correlation between SSRIs-induced ethanol intake reduction and the expression of pathological co-morbid depression (Naranjo et al., 1992, 1994; Naranjo and Bremner, 1994). Moreover, the inhibitory action of SSRIs on ethanol intake occurs rather promptly (few days), whereas their antidepressant action can be observed only after rather long periods of treatment (Kasper et al., 1992; Blier and de Montigny, 1994). Thus, it can be speculated that SSRIs might reduce ethanol intake through a similar mechanism to that involved in OCD, rather than in depression. Further evidence for a correlation between OCD and alcohol abuse comes from pharmacological studies on the effects of the selective 5-HT2C/1B agonist meta-chlorophenylpiperazine (mCPP). In fact, mCPP treatment may provoke both a transient exacerbation of symptoms in patients suffering from OCD and an increase in alcohol-craving and relapse episodes in alcoholic subjects (Zohar et al., 1987; Murphy et al., 1992; Barr et al., 1993; Pigott et al., 1993; Krystal et al., 1994; Kalkman, 1997).

GENERAL CONCLUSIONS AND COMMENTS

At present, experimental evidence for the involvement of the brain 5-HT system in the process of drug-craving is largely incomplete. There is mainly indirect evidence suggesting that hypofunction of the brain 5-HT system could be positively correlated with increased craving and relapse rate.

There are animal studies showing that repeated administration of drugs of abuse, such as alcohol, nicotine or cocaine, may result in specific neuronal adaptation of the brain 5-HT system resulting in supersensitivity of raphe 5-HT1A receptors (Cunningham et al., 1992; Kleven et al., 1995; Nevo et al., 1995; Rasmussen and Czachura, 1997). Such an adaptation may produce an overall attenuation of the serotonergic activity which is particularly pronounced during withdrawal (the absence of the drug leaves the neuronal changes unopposed) (Parsons et al., 1995, 1996; Weiss et al., 1996). Indeed, many psychiatric conditions associated with drug withdrawal, such as depression, insomnia and aggression, may arise because of a dysregulation of the central 5-HT system (File, 1996; Graeff et al, 1996). These brain disturbances may contribute to the 'psychological distress syndrome' produced by discontinuation of drug use, which may increase the motivational value of the drug (Koob and Le Moal, 1997). Moreover, as was postulated in this article, deficiency of brain 5-HT activity may result in a decreased impulse-control over drug-taking, which may contribute to an increased rate of relapse. In this regard, it is interesting to note
that an impairment of self-control mechanisms is a common factor observed in both the addictive syndrome and other brain disorders (e.g. bulimia, obsessive-compulsive disorder and violent behaviour) characterized by dysregulation of the central 5-HT system (Moss, 1987; Murphy et al., 1992; Jarry and Vaccarino, 1996; Koob et al., 1998).

It is possible to speculate that drugs which stimulate central serotonergic activity (i.e. SSRI agents) may be useful to control craving and to reduce relapse rates. However, because 5-HT could be specifically involved in the regulation of impulse-control mechanisms, it would be interesting to measure their anti-craving potential by studying their effect on specific aspects of craving such as compulsivity and loss of control over drug-taking. In this regard, the Obsessive Compulsive Drinking Scale (OCDS) and the Yale–Brown Obsessive Compulsive Scale for heavy drinking (YBOCS-hd), which have been recently developed to measure alcohol-craving, may represent important research tools (Modell et al., 1992a,b; Anton et al., 1995, 1996). These scales, originally developed to score OCD symptoms, can provide important information about obsessionality and compulsivity associated with alcohol abuse.

Lastly, we would speculate that craving could be viewed as the result of a two-stage phenomenon. The first step is the pre-conscious process of salience attribution to an external stimulus that may become attractive and 'wanted'. The second step consists in the emission of goal-directed behaviour aimed at obtaining the stimulus. We could imagine that 5-HT drugs, owing to their possible action on the impulse-control mechanisms, may presumably influence craving at this second stage.

It is possible that a better anti-craving action could be achieved if 5-HT drugs are associated to agents (i.e., DA or opioid antagonists) acting at a motivational level (first stage). For example, in the case of alcohol abuse it may be interesting to evaluate whether the anti-alcohol effect of the opioid antagonist naltrexone could be improved by co-administration of an SSRI (Volpicelli et al., 1992; Jaffe et al., 1996; O'Malley, 1996; O'Malley et al., 1996). In this regard, it has recently been observed that a better drinking outcome occurs in alcoholics receiving combined therapy with sertraline and naltrexone, compared to subjects treated only with naltrexone (Farren, 1998).

Despite the importance of craving in the addictive processes, not much is known about the neurochemical basis of this phenomenon. This lack of information has severely limited the possibility of developing effective anti-craving treatments. More studies are therefore needed to clarify the potential anti-craving effects of new treatments.

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