Published in final edited form as:

Neuropharmacology. 2011 September ; 61(3): 421–432. doi:10.1016/j.neuropharm.2011.03.022.

Contributions of Serotonin in Addiction Vulnerability

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Abstract

The serotonin (5-hydroxytryptamine; 5-HT) system has long been associated with mood and its dysregulation implicated in the pathophysiology of mood and anxiety disorders. While modulation of 5-HT neurotransmission by drugs of abuse is also recognized, its role in drug addiction and vulnerability to drug relapse is a more recent focus of investigation. First, we review preclinical data supporting the serotonergic raphe nuclei and their forebrain projections as targets of drugs of abuse, with emphasis on the effects of psychostimulants, opioids and ethanol. Next, we examine the role of 5-HT receptors in impulsivity, a core behavior that contributes to the vulnerability to addiction and relapse. Finally, we discuss evidence for serotonergic dysregulation in comorbid mood and addictive disorders and suggest novel serotonergic targets for the treatment of addiction and the prevention of drug relapse.

Keywords

5-hydroxytryptamine; impulsivity; relapse; 5-HT₂ receptor; substance abuse

1. Introduction

The trajectory from drug use to addiction begins against a background of vulnerability based upon genetic and environmental factors. As this disease progresses, atypical neuronal plasticity may occur within key brain circuits, which contributes to the development and maintenance of addiction. While the dopaminergic and glutamatergic circuits have definitive roles in the neuroplasticity underlying addiction, important advances in understanding serotonergic mechanisms in addictive processes have been made in recent years. In addition, there is growing evidence that dysregulation of the serotonin system by long-term exposure to drugs of abuse may underlie the high rate of comorbidity of affective disorders (e.g., depression) with drug dependence. Rather than reviewing data that demonstrate how manipulations of 5-HT function impact addiction and the actions of drugs of abuse, this review will instead focus on the impact of long-term drug use on 5-HT function which in turn affects behaviors related to drug seeking.

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First, we will review preclinical anatomical, neurochemical and neurophysiological data indicating that the 5-HT raphe nuclei and their forebrain projections are targets of drugs of abuse, highlighting the effects of psychostimulants, opioids and ethanol. Next, we will examine the role of 5-HT receptors in impulsivity, a core behavior that contributes to the vulnerability to addiction and relapse. Finally, we will examine the clinical evidence for serotonergic dysregulation in addiction and suggest novel serotonergic targets for the treatment of addiction and the prevention of drug relapse.

2. Modulation of serotonin neurotransmission by drugs of abuse

The 5-HT system is modulated by all of the major classes of drugs of abuse but in the current review we will limit our discussion to psychostimulants, opioids and ethanol. Furthermore, serotonergic neurotransmission changes across the addiction cycle from initial to chronic drug exposure, the development of dependence, withdrawal, abstinence and relapse.

2.1 Psychostimulants

The psychostimulant effects of cocaine, amphetamine and its derivatives have been linked primarily to their elevation of dopamine in the synapse and activation of dopamine receptors. However, these non-selective compounds also have significant effects on other monoamines including 5-HT (see Muller et al., 2007 for review). Mice with genetic deletion of the dopamine transporter respond to the rewarding properties of cocaine as evidenced by self-administration (Rocha et al., 1998) and conditioned place-preference models (Sora et al., 1998), indicating that non-dopaminergic mechanisms may also contribute to psychostimulant effects. Double dopamine/5-HT transporter knockouts fail to show cocaine place-preference (Sora et al., 2001), indicating a role for 5-HT as well as dopamine in psychostimulant reward.

Acutely, non-contingent or self-administered cocaine inhibits monoamine reuptake, elevating extracellular monoamines including 5-HT in a dose-dependent manner in a number of brain regions including nucleus accumbens (NAc), ventral tegmental area, dorsal raphe nucleus (DRN), hippocampus, striatum and cortex (Parsons and Justice, 1993; Bradberry et al., 1993; Chen and Reith, 1994; Parsons et al., 1995; Parsons et al., 1996; Cunningham et al., 1996; Andrews and Lucki, 2001; Broderick et al., 2004; Muller et al., 2004; Muller et al., 2007; Kurling-Kailanto et al., 2010). Acute cocaine also inhibits firing of serotonergic DRN neurons due in part to the stimulation of inhibitory autoreceptors by elevated synaptic 5-HT (Pitts and Marwah, 1987; Cunningham and Lakoski, 1988; Lum and Piercey, 1988; Pan and Williams, 1989; Cunningham and Lakoski, 1990) and also by recruitment of inhibitory “long-loop” meso-habenular circuits (Paris and Cunningham, 1994). The elevation of extracellular 5-HT in response to acute cocaine becomes sensitized following chronic cocaine exposure (Parsons and Justice, 1993), an effect accompanied by increased activity of the 5-HT synthesizing enzyme tryptophan hydroxylase in the raphe nucleus (Vrana et al., 1993). During withdrawal from cocaine, 5-HT levels in the nucleus accumbens are inhibited (Parsons et al., 1995; Parsons et al., 1996; Broderick et al., 2004). Amphetamine and methamphetamine produce similar acute stimulatory effects on forebrain 5-HT levels (see Muller et al., 2007 for review) and subsequent autoreceptor-mediated inhibition of raphe firing (Rebec et al., 1982) but these effects are attenuated with repeated administration (in contrast to the sensitization seen with chronic cocaine) (Heidenreich et al., 1987; Parsons and Justice, 1993; Kuczenski et al., 1995; Segal and Kuczenski, 1997a; Segal and Kuczenski, 1997b).

The methylenedioxy-substituted amphetamine derivatives including (+)-3,4-methylenedioxymethamphetamine (MDMA; Ecstasy) have particularly prominent effects on

5-HT neurotransmission including potent 5-HT-specific neurotoxicity, as compared to other psychostimulants. Neurotoxic effects of MDMA are expressed in a number of ways including reduced forebrain 5-HT content, 5-HT axonal degeneration and loss of 5-HT terminals (Green et al., 2003; Yamamoto et al., 2010; Steinkellner et al., 2011). Like other psychostimulants, MDMA elevates the release of monoamines in the synapse via actions at their respective transporters but does so with significantly greater potency for 5-HT than for dopamine transporters (Steele et al., 1987; Battaglia et al., 1988; Rothman and Baumann, 2003). MDMA has dual actions at the 5-HT transporter, blocking 5-HT uptake and inducing non-exocytotic release of 5-HT through reverse transport (Steinkellner et al., 2011). As a consequence, acute MDMA administration elevates extracellular levels of 5-HT in the DRN *in vitro* (Sprouse et al., 1989; Sprouse et al., 1990; Bradberry et al., 1990; Bradberry et al., 1991; Baumann et al., 2004; Baumann et al., 2005; Renoir et al., 2008) and in the brain *in vivo* in a number of regions including the nucleus accumbens (White et al., 1994; Kankaanpää et al., 1998; Baumann et al., 2004; Baumann et al., 2005; O'Shea et al., 2005; Kurling et al., 2008; Baumann et al., 2008b), striatum (Gough et al., 1991; Gudelsky and Nash, 1996; Sabol and Seiden, 1998; Gough et al., 2002; O'Shea et al., 2005; Freezer et al., 2005; Stanley et al., 2007; Baumann et al., 2008b), hippocampus (Gartside et al., 1997; Esteban et al., 2001; Mehan et al., 2002), substantia nigra (Yamamoto et al., 1995; Hewton et al., 2007) and frontal cortex (Gudelsky and Nash, 1996; Gartside et al., 1997; Baumann et al., 2008b). This acute 5-HT stimulatory effect of MDMA then adapts upon subsequent exposures (Rodsiri et al., 2011). Acute elevations of 5-HT release in the raphe nuclei act on 5-HT_{1A} autoreceptors to suppress neuronal activity *in vitro* (Sprouse et al., 1989; Sprouse et al., 1990; Bradberry et al., 1990; Bradberry et al., 1991; Renoir et al., 2008) and *in vivo* (Gartside et al., 1997). Chronic MDMA administration has a number of longer term consequences. While 5-HT concentrations in brain tissue are depleted (Shankaran and Gudelsky, 1999; Matuszewich et al., 2002; Baumann et al., 2008a), extracellular levels of 5-HT and basal neuronal activity of 5-HT neurons are largely unaffected by chronic MDMA treatment (Gartside et al., 1996; Shankaran and Gudelsky, 1999; Reveron et al., 2010). In contrast, 5-HT neurotransmission deficits are consistently revealed when the system is challenged. For example, non-contingent chronic or “binge-like” administration of MDMA or self-administered MDMA produces blunted responses of 5-HT release to acute challenge with MDMA or other 5-HT releasers (Series et al., 1994; Shankaran and Gudelsky, 1999; Galineau et al., 2005; Baumann et al., 2008a; Reveron et al., 2010) as well as blunted responses to stressors (Matuszewich et al., 2002) and altered responses to 5-HT_{1A} stimulation (Piper et al., 2006; Renoir et al., 2008). Therefore, MDMA-induced compensatory mechanisms normalize 5-HT neurotransmission under basal conditions but not under conditions of pharmacological or environmental challenge, an additional expression of 5-HT-specific MDMA neurotoxicity. This form of compensation from surviving neuronal terminals to maintain basal functioning has also been observed in the 5-HT system following treatment with other 5-HT-specific neurotoxins (Kirby et al., 1995).

2.2 Opioids

Both endogenous opioids (Martin-Schild et al., 1999; Neal, Jr. et al., 1999) and all of the opioid receptor subtypes including μ , δ , κ (Mansour et al., 1995; Kalyuzhny et al., 1996; Kalyuzhny and Wessendorf, 1997; Kalyuzhny and Wessendorf, 1998) are located in the DRN and median raphe nuclei (MRN) as well as in the surrounding periaqueductal gray (PAG). μ -receptors, the primary site of action of abused opioid compounds, are present at moderate levels in the DRN, MRN and PAG (Mansour et al., 1994).

The literature describing opioid effects on 5-HT neurotransmission contains conflicting findings. Some early studies suggested that morphine enhances 5-HT synthesis, release and metabolism in several brain regions (Smialowska and Bal, 1984; Spampinato et al., 1985;

Rivot et al., 1989) but others have found an inhibitory effect of morphine on the firing rate of 5-HT cells in the raphe nuclei (Haigler, 1978; Alojado et al., 1994). Opioid-5-HT interactions are complex in part because different receptor subtypes mediate distinct effects on 5-HT. For example, in the DRN but not the MRN, μ - and δ -opioid receptor stimulation elevates extracellular levels of 5-HT (Tao and Auerbach, 2002b). In contrast, κ -receptor stimulation decreases extracellular levels of 5-HT in both raphe nuclei (Tao and Auerbach, 2002b). This effect may be indirect as κ -receptor stimulation has been shown to inhibit excitatory glutamatergic afferents to 5-HT DRN neurons (Pinnock, 1992).

The picture of opioid effects on 5-HT neurotransmission is further complicated when acute administration is compared to chronic, and when the 5-HT system is examined during conditions of opioid withdrawal. For example, under conditions of acute administration, opioids including morphine depolarize 5-HT DRN neurons (Jolas and Aghajanian, 1997) and elevate extracellular levels of 5-HT in the DRN as well as those areas of the forebrain that are innervated at least in part by 5-HT fibers from the DRN (i.e. NAc, amygdala, frontal cortex, striatum, thalamus, hypothalamus, ventral hippocampus) (Tao and Auerbach, 1995). This acute effect of morphine is mediated primarily by the inhibitory actions of μ -receptors (see Duggan and North, 1983; Tao and Auerbach, 2002b). Therefore, the net excitatory effect of morphine on 5-HT release appears to be indirect, mediated by morphine inhibition of local GABA neurons in the raphe that synapse on 5-HT cells (Jolas and Aghajanian, 1997; Tao and Auerbach, 2002a).

However, the effect of opioids on 5-HT neurotransmission changes when opioid administration is chronic or sustained. For example, though initial injections of morphine elicit elevations in 5-HT levels in the DRN, after one week of daily administration, those injections elicit a much reduced or absent 5-HT response (Tao et al., 1998). This adaptation appears to occur at the level of GABAergic afferents to 5-HT DRN neurons. When brain slices are prepared from subjects previously exposed to chronic morphine, the dose-response curve for μ -receptor-mediated suppression of GABA synaptic activity in 5-HT DRN neurons is shifted to the right, indicating tolerance to the effect of μ -receptor activation (Jolas et al., 2000). When chronic opioids are discontinued and withdrawal precipitated by opiate antagonist administration, 5-HT DRN levels are significantly reduced (Tao et al., 1998). In brain slices from morphine-withdrawn subjects, the firing rate of 5-HT DRN cells is also reduced (Jolas et al., 2000). This reduction of firing rate during withdrawal appears also to be indirectly mediated by an increase of GABA synaptic activity at 5-HT DRN neurons, indicating an increase in presynaptic GABA release (Jolas et al., 2000). In summary, the 5-HT system can be stimulated or inhibited by morphine, depending on the conditions of administration: acute, chronic or withdrawal. Morphine's effects also appear to be indirect, mediated primarily by μ -receptors located on local GABA afferents to the DRN.

2.3 Ethanol

Both non-contingent and self-administered ethanol have been shown to consistently elevate 5-HT levels in multiple brain regions including NAc (Yoshimoto et al., 1992a; Weiss et al., 1996; Szumlinski et al., 2007), VTA (Yan et al., 1996), amygdala (Yoshimoto et al., 2000; McBride, 2002) and hippocampus (Bare et al., 1998; Thielen et al., 2002). This effect also appears to be strengthened in alcohol-preferring rat strains compared to their non-preferring counterparts (Portas et al., 1994; Selim and Bradberry, 1996). The mechanism for this acute ethanol effect on extracellular 5-HT is not clear. However, it is thought to reflect an increase in 5-HT release rather than a decrease in 5-HT uptake as ethanol stimulation of extracellular 5-HT is not accompanied by reductions in its metabolite, 5-hydroxyindoleacetic acid (Yoshimoto et al., 1992b), as would be expected with reuptake inhibition and consequent reductions in 5-HT metabolism. Furthermore, in synaptosomes, ethanol stimulates rather than inhibits 5-HT uptake (Alexi and Azmitia, 1991). Reverse dialysis of ethanol in the

nucleus accumbens also mimics the effect of systemic ethanol administration, increasing extracellular 5-HT (Yoshimoto et al., 1992a) in support of the hypothesis that ethanol stimulates 5-HT release through direct actions on 5-HT terminals or indirectly through other circuits that regulate terminal 5-HT release (Thielen et al., 2002). Interestingly, electrophysiology studies have demonstrated ethanol-induced reductions in DRN neuronal activity (Chu, 1984; Verbank et al., 1990; Pistis et al., 1997). These findings may be explained by the fact that ethanol may stimulate 5-HT release in terminal fields that have recurrent collaterals which activate inhibitory autoreceptors in the raphe, suppressing neuronal firing (Wang and Aghajanian, 1977). However, ethanol's effects in the NAc (Szumlinski et al., 2007) and hippocampus (Bare et al., 1998) are diminished and basal 5-HT levels in NAc are significantly reduced in chronically ethanol treated subjects (Thielen et al., 2004) and during withdrawal (Weiss et al., 1996). Following withdrawal from chronic ethanol, reduced accumbal 5-HT can be restored by re-exposure of the subjects to ethanol (Weiss et al., 1996).

In summary (see Table 1), these three drug classes, though distinct in their primary mechanism of action, can initiate the cycle of addiction and all regulate the 5-HT system in a similar manner. Psychostimulants, opioids and ethanol all acutely stimulate extracellular 5-HT in a number of brain regions but suppress 5-HT output during withdrawal. Hypoactivity of the 5-HT system may contribute to dysphoric mood states reported as part of the withdrawal syndrome (Koob, 2000; Weiss et al., 2001; Koob and Volkow, 2010) and may trigger drug-seeking and vulnerability to relapse as a means of 'self-medication' and restoration of homeostasis within the 5-HT system (Markou et al., 1998). Indeed, previous studies have shown that 5-HT depletion increases cocaine-seeking in some animal models (see Walsh and Cunningham, 1997 for review), particularly those models in which drug seeking is tested in the presence of cocaine (i.e. self-administration under a progressive ratio schedule (Loh and Roberts, 1990; Roberts et al., 1994) and cocaine-primed reinstatement (Tran-Nguyen et al., 2001)).

3. Serotonin, impulsivity, and addiction: insight from animal models

Both clinical and preclinical studies suggest that a relationship exists between addiction and a lack of impulse control. Specifically, high levels of impulsivity may be considered a risk factor for developing substance use disorder, and can contribute to various aspects of the addiction cycle (Jentsch and Taylor, 1999; Perry and Carroll, 2008; de Wit, 2009; Winstanley et al., 2010). For example, a link between substance abuse and disorders encompassing high levels of impulsivity, such as attention deficit hyperactivity disorder (ADHD), has recently been established, as treatment of impulsivity symptoms in comorbid ADHD and substance abuse patients reduces relapse (Wilson and Levin, 2005). Furthermore, substance abuse patients who benefited from pharmacological treatment of alcohol abuse also showed associated decreases in levels of impulsive behavior (Rubio et al., 2009). Additionally, increased levels of impulsivity were positively correlated with the severity of substance abuse in cocaine-dependent individuals, and those with the highest impulsive tendencies were also less likely to remain in treatment for substance abuse (Moeller et al., 2001). Consequently, high levels of impulsivity may be used to reliably predict the willingness of patients to drop out of treatment. Perhaps unsurprisingly, similar brain regions and neurotransmitter systems—such as the orbitofrontal cortex (OFC) and the dopaminergic system—are involved in both addiction and impulsivity (ex. Volkow et al., 1992). As previously mentioned, the serotonergic system plays a role in addiction, and evidence supports a strong role for 5-HT in modulating certain aspects of impulsivity. Hence, a deeper understanding of impulsivity, and the relationship between impulsivity and addiction, may aid in developing more effective treatment strategies for patients with substance abuse disorder.

Preclinical animal models of both impulsivity and addiction have the ability to provide researchers with valuable information in this regard (Potenza, 2009). Animal models allow researchers to systematically manipulate brain function at different levels by performing experiments that are not possible using human subjects. Results from these studies can then be translated into understanding the human condition. Thus, preclinical studies have the ability to significantly improve our understanding of addiction, as well as a range of psychiatric disorders in which impulse control deficits are observed, contributing to the development of effective treatments.

Impulsivity can be considered as an umbrella term, encompassing a range of different and dissociable impulsive behaviors. Using self-report questionnaires, such as the Barratt Impulsiveness Scale (Barratt, 1994), clinical researchers have divided impulsivity into multiple components (see Evenden, 1999 for review). The most commonly modelled features of impulsivity in preclinical studies are the cognitive or decision-making aspect of impulsivity (impulsive choice) and motor impulsivity (impulsive action) (Winstanley et al., 2006b; Pattij and Vanderschuren, 2008). Numerous laboratory-based tests have been developed in order to quantitatively measure these impulsive traits, and the most widely adopted models will be further discussed in relation to 5-HT (especially the 5-HT₂ receptors) and addiction.

3.1 Tests of Impulsive Choice

A frequently used test of impulsive choice in both human and laboratory animal studies is the delay discounting task (Ainslie, 1975; Evenden and Ryan, 1996). Here, impulsive choice is defined as a preference for smaller immediate over larger delayed rewards—even though it is highly advantageous in the long-term to choose the larger delayed reward option. This preference is thought to reflect intolerance to delay-of-gratification. Although many different types of delay discounting tasks have been developed for clinical and preclinical research, comparisons between human and animal studies can still be drawn, as devaluing rewards that occur later in time is a highly conserved behavioral trait (Ainslie, 1975).

In humans, the rate of delay discounting is often measured by questionnaires, where the delay to a hypothetical large reward would occur over days, months, or years, but is not actually experienced (ex. Rachlin et al., 1991). In contrast, the delay to the large reward in animal models of delay discounting is small enough to allow for multiple trials within a single testing session and real, consumable rewards are used. However, minimal differences were found between the performance of human subjects on a delay discounting task, regardless of whether hypothetical or real money rewards were used (Johnson and Bickel, 2002). Researchers have recently developed a delay discounting task using real monetary rewards, where the delay to the larger reward is actually experienced during the laboratory session (Reynolds and Schiffbauer, 2004; Reynolds et al., 2006). However, discounting rates are considerably steeper than would be expected by the questionnaire assessments; potentially because the larger reward is actually quite small (US \$0.30) and whether or not the subject would receive the large reward on any given trial is probabilistic. Another delay discounting task involving real-time delays in humans has also been developed, where participants are rewarded by viewing an erotic image for either a long (large reward) or short (small reward) time period (Prevost et al., 2010). These variations in task design may be important factors in the amount of discounting observed, and care should be taken to compare like with like.

The development of multiple animal models of delay discounting adds further complexity to understanding the neural mechanisms of impulsive choice (see Winstanley, 2009 for review). For example, in one rodent delay discounting task, testing takes place in an operant chamber, where the animal has multiple opportunities to choose either a small immediate

reward or a larger delayed reward, and the delay to the large reward is systematically increased throughout the duration of the daily testing session (ex. Evenden and Ryan, 1996). However, in another paradigm, animals are tested using a t-maze apparatus: choice of one arm results in a fixed delay to a larger reward and the animal has fewer choice opportunities per session (Bizot et al., 1999; Rudebeck et al., 2006). Furthermore, whether or not cues are present during the delay-to-reward period may also influence the animals' choice of the large reward, possibly by altering the way in which certain brain regions, such as the OFC, are recruited during the decision-making process (Floresco et al., 2008; Zeeb et al., 2010). Due to these variations in task design across different studies, the type of model used must be considered when comparing results between studies.

3.2 Tests of Impulsive Action

Impulsive action can be defined as the inability to withhold a prepotent motor response. Similar to models of impulsive choice, many widely adopted tests of impulsive action have been developed for use in both human and animal studies. In human research, a subjects' attentional capacity and level of impulsive action can be measured using the continuous performance task (CPT, Beck et al., 1956). A rodent analogue of this task—the five choice serial reaction-time task (5CSRT, Carli et al., 1983)—has been successfully used to investigate the neurobiological basis of these processes. Additional models of impulsive action are also available for use in human, non-human primate, and rodent studies, such as the stop-signal reaction time task (SSRTT) and go/no-go tasks (Iversen and Mishkin, 1970; Terman and Terman, 1973; Logan et al., 1984; Eagle and Robbins, 2003). Although these various models have provided researchers with a large breadth of knowledge regarding the neurochemical and neurobiological basis of impulsive action, the following discussion will focus on studies using the 5CSRT. Not only has the 5CSRT been extensively characterized from a pharmacological perspective (Robbins, 2002), it is also the only test of motor impulsivity, to date, which has been used to explore the relationship between high levels of impulsivity and substance abuse.

4. Relationship between impulsive action and addiction

Using the self-administration model of addiction, animal studies have looked at whether rates of impulsivity recorded prior to drug administration affects subsequent drug intake. High levels of motor impulsivity, as assessed using the 5CSRT, have the ability to predict whether or not rats will relapse in the extinction-reinstatement model of drug-seeking (Economidou et al., 2009). These highly impulsive rats also show a quicker escalation of cocaine self-administration (Dalley et al., 2007; Perry et al., 2008). Furthermore, high levels of impulsive action, as assessed using the 5CSRT, provides researchers with the ability to predict whether drug intake will develop into a compulsive, addictive-like behavior (Belin et al., 2008). These results parallel a human study, where high levels of impulsivity in individuals with cocaine-dependency reliably predicted the degree of substance abuse and the willingness of patients to continue receiving treatment for substance abuse (Moeller et al., 2001). However, the ability for high levels of impulsive action to predict the onset of drug dependency may be substance specific. For example, using an animal model of heroin self-administration, levels of impulsive responding measured using the 5CSRT was unable to predict the development of addictive tendencies (McNamara et al., 2010). Therefore, high levels of impulsive action may only be able to determine the likelihood of developing an addiction in relation to stimulants, but not opiates (McNamara et al., 2010).

Although the aforementioned studies observed the important relationship between high baseline levels of impulsivity and the onset of drug dependency, these studies did not examine how impulsivity is altered by drug intake. In order to address this issue, animals can be trained to self-administer drugs of abuse and the animals' level of impulsivity can be

observed. One training schedule utilized is to train rats on the 5CSRT, then cycle between self-administration sessions and withdrawal periods, where animals are tested on the 5CSRT only during the withdrawal period. In this case, animals trained to self-administer either cocaine, heroin, amphetamine, methamphetamine, or MDMA show only minor, if any, alterations in impulsive responding on the 5CSRT (Dalley et al., 2005a; Dalley et al., 2005b; Dalley et al., 2007).

In contrast, animals that receive daily training sessions on the 5CSRT in the mornings, while receiving cocaine self-administration sessions in the evenings exhibit a different pattern of behavior (Winstanley et al., 2009). Results from this study revealed that, although self-administration of cocaine initially increased impulsivity, animals soon developed a tolerance to these effects. However, during withdrawal, the level of impulsive responding again increased, suggesting that increased rates of impulsivity during withdrawal could contribute to the willingness to relapse (Winstanley et al., 2009). Thus, the levels of impulsivity associated with the withdrawal period may partially depend upon the rate and frequency of substance abuse, and thus, the type of addict (ex. one who uses frequently versus one who cycles through multiple binge and withdrawal periods) (Winstanley et al., 2009). Unfortunately, animals were not separated into high and low impulsive groups beforehand in any of these self-administration studies, so it is unknown if the baseline level of impulsivity is also a factor in the amount of impulsive action observed during the withdrawal period. Future studies should be aimed at addressing these issues.

Results from these studies suggest that alleviating abnormally high rates of impulsivity—either before or subsequent to drug intake—may prevent the subject from developing an addiction or relapsing during withdrawal. Studies on rodents using *in vivo* microdialysis within the medial prefrontal cortex, an area highly implicated in both addiction and impulsivity, found a positive correlation between levels of impulsive action and 5-HT release (Dalley et al., 2002; Steketee, 2003; Van den Oever et al., 2010). Such data suggest that decreasing activity within the serotonergic system may be a possible mechanism for alleviating impulsivity symptoms. However, widespread, permanent lesions to the serotonergic system—accomplished by an intracerebroventricular (ICV) infusion of the selective serotonergic neurotoxin 5,7-dihydroxytryptamine (5,7-DHT)—increased impulsive responding in rats on the 5CSRT (Harrison et al., 1997). Similarly, increased impulsivity was observed in subjects performing a go/no-go task following acute dietary tryptophan depletion, which results in transient, but significant, decreases in global 5-HT levels (Crean et al., 2002).

One possible explanation for these paradoxical findings is that the serotonin system is notoriously complex, with more than 14 different receptor subtypes currently identified, including both pre- and postsynaptic receptors which can have excitatory and/or inhibitory effects (Barnes and Sharp, 1999). Therefore, targeting specific 5-HT receptors may prove to be a more fruitful approach for development of effective pharmacotherapies, rather than using non-selective agents which appear to have limited effects on impulsive behavior in humans (ex. Chamberlain et al., 2006; Wingen et al., 2007; Drueke et al., 2010).

As many of the 5-HT receptors are distributed throughout the entire central (and peripheral) nervous system (Barnes and Sharp, 1999), it is possible that manipulations of 5-HT receptor activity within specific brain regions may affect impulsive action differentially as compared to widespread alterations. Interestingly, infusion of ketanserin (a mixed 5-HT_{2A/2C} antagonist) into the medial prefrontal cortex decreases impulsivity on the 5CSRT, similar to the effect of this drug when given systemically (Passetti et al., 2003). In contrast, infusion of ketanserin into the OFC does not affect impulsive action (Hadamitzky and Koch, 2009). Likewise, intra-cortical infusion of a mixed 5-HT_{2A/2C} agonist into the OFC does not affect

this form of impulsivity, yet infusion of this drug into both the OFC and basolateral amygdala increases impulsive action on the 5CSRT (Hadamitzky and Koch, 2009). Unfortunately, due to the non-selective nature of these drugs, it is unclear whether these effects are caused by altering activity at either the 5-HT_{2A} or 5-HT_{2C} receptors.

However, infusion of either a selective 5-HT_{2A} antagonist or a 5-HT_{2C} agonist into either the infralimbic or prelimbic cortices did not affect impulsive action on the 5CSRT (Robinson et al., 2008). Interestingly, infusion of these compounds into the nucleus accumbens had opposing effects on impulsivity—the 5-HT_{2A} antagonist decreased impulsive action while the 5-HT_{2C} agonist increased impulsive action (Robinson et al., 2008). Moreover, although the amount of 5-HT within the medial prefrontal cortex is correlated with the level of impulsivity (Dalley et al., 2002), direct infusion of the serotonin neurotoxin 5,7-DHT into the medial prefrontal cortex did not affect the rate of impulsive action observed on the 5CSRT (Fletcher et al., 2009). In summary, there is relatively little consistency in the literature as to the consequence of activating different 5-HT receptors in selective brain regions. Although global alterations and direct targeting of specific brain regions can sometimes have similar effects on impulsive action, further research into how impulsive action is affected by increasing or decreasing the activity of 5-HT within these brain regions.

One issue which may contribute to the discrepancies between studies noted above is that ligand binding at different 5-HT receptors can have very different effects on the target cell (Bockaert et al., 2006). This may be important when considering that systemic drug studies indicate that the 5-HT_{2A} and 5-HT_{2C} receptors have opposing effects in relation to impulsive action. In rats, an acute systemic injection of a 5-HT_{2A} antagonist or a 5-HT_{2C} agonist decreases impulsive responding on the 5CSRT, whereas a 5-HT_{2C} antagonist can increase this form of impulsivity (Higgins et al., 2003; Winstanley et al., 2003a; Winstanley et al., 2004b; Navarra et al., 2008). Unfortunately, the effect of a 5-HT_{2A} agonist has yet to be determined due to the lack of availability of a selective pharmacological product. However, it could be hypothesized that a 5-HT_{2A} agonist would increase motor impulsivity. Interestingly, a mixed 5-HT_{2A/2C} agonist increased impulsive action (Koskinen et al., 2000; but see Fletcher et al., 2007), whereas a mixed 5-HT_{2A/2C} antagonist decreased impulsive action (Passetti et al., 2003). However, the non-selective nature of these compounds makes it difficult to draw any mechanistic conclusions.

Together, the results from these studies suggest that blockade of the 5-HT_{2A} receptors or stimulation of the 5-HT_{2C} receptors during withdrawal, especially in highly impulsive individuals, may prevent relapse. Unfortunately, there is currently no direct evidence to support this claim, as the levels of impulsivity and relapse to drug-seeking and have yet to be empirically determined in conjunction with concurrent treatment with serotonergic pharmacological agents. However, administration of a 5-HT_{2A} antagonist or 5-HT_{2C} agonist significantly attenuated reinstatement of cocaine-seeking in animals that had previously self-administered cocaine, whereas the opposite was observed following an acute dose of a 5-HT_{2C} antagonist (Fletcher et al., 2002; Fletcher et al., 2008b; Nic Dhonnchadha et al., 2009). Additionally, stimulation of 5-HT_{2C} receptors within the medial prefrontal cortex decreased cocaine-seeking behavior following withdrawal in a rodent model of addiction (Pentkowski et al., 2010). Hence, the 5-HT_{2A} and 5-HT_{2C} receptor subtypes may be effective targets for development of therapeutic agents to treat motor impulsivity symptoms associated with substance abuse in order to prevent relapse.

5. Relationship between impulsive choice and addiction

Similar to studies involving tests of impulsive action, a relationship between impulsive choice and addiction also exists. In human studies, decision-making deficits on a delay discounting task are observed in patients who continually use drugs, such as cocaine, heroin, or nicotine (Bickel et al., 1999; Kirby et al., 1999; Mitchell, 1999; Petry et al., 2002; Coffey et al., 2003). In support of these findings, animals tested on an operant-based delay discounting task while receiving chronic daily doses of cocaine show a transient, but significant, increased preference for the smaller immediate reward (Paine et al., 2003). Research using animal models have also shown that high basal levels of impulsive choice on a delay discounting task contributes to the severity of substance abuse, as animals that were more impulsive were also more likely to self-administer cocaine—and did so at a faster rate—compared to less impulsive rats (Perry et al., 2005). Furthermore, an increased locomotor response to cocaine is predictive of increased preference for the smaller immediate reward (Stanis et al., 2008). Additionally, mice that prefer alcohol also show a steeper rate of delay discounting compared to low alcohol-preferring mice (Oberlin and Grahame, 2009).

In vivo microdialysis experiments have shown that 5-HT release within the medial prefrontal cortex, but not the OFC, occurs while animals are performing a delay discounting task (Winstanley et al., 2006a). These results imply that 5-HT must be released in order for animals to properly make delay discounting judgments. In support of this hypothesis, acute dietary tryptophan depletion in humans resulted in an increased choice of the smaller immediate reward on a modified delay discounting task (Schweighofer et al., 2008). In this task, the delay to a large monetary reward (20 yen) was actually experienced during the task, however subjects were only rewarded with the real amount following completion of the entire session (i.e. subjects were not immediately rewarded on a trial-by-trial basis). In support of these findings, rats that were treated acutely (3 days) with para-Chlorophenylalanine (pCPA), a 5-HT synthesis inhibitor, also showed an increased preference for the smaller immediate reward on a t-maze delay discounting task (Bizot et al., 1999).

In a rodent delay-based decision making task, where an adjusting-delay procedure was used (where the delay to a large reward is variable for any given trial and directly dependent upon the subjects' previous choice), animals with forebrain lesions of the serotonergic system were more impulsive, choosing the smaller immediate reward more often than sham control subjects (Wogar et al., 1993). However, these effects were only present when there was little difference between the small and large rewards (small: 1 sucrose pellet versus large: 2 sucrose pellets; Wogar et al., 1993). In contrast, forebrain lesions of the 5-HT system did not alter the rate of delay discounting observed when animals were tested on another operant-based delay discounting task (Winstanley et al., 2003b). In the task used by Winstanley and colleagues (2003b), the delay to the large reward increased within each testing session and the difference between the large (4 sucrose pellets) and small (1 sucrose pellet) rewards was greater than those used in the study by Wogar et al. (1993). However, when animals were tested on a t-maze delay discounting task where the difference between the large (10 sucrose pellets) and small (2 sucrose pellets) rewards were even larger than those used by Winstanley and colleagues (2003b), infusion of 5,7-DHT into the DRN caused rats to be more impulsive (Bizot et al., 1999).

Together, these studies suggest that there are differences between acute and chronic depletions of 5-HT, which may be partially dependent upon the type of delay discounting paradigm used. Additionally, differences in task design also resulted in opposing effects even when permanent forebrain depletions of the 5-HT system were performed

[accomplished by either direct infusion of 5,7-DHT into the DRN and MRN (Wogar et al., 1993), just the DRN (Bizot et al., 1999), or ICV infusions (Winstanley et al., 2003b)].

Observing contrasting effects of 5-HT lesions on impulsive choice and impulsive action may be somewhat surprising, considering that both types of impulsivity have the ability to predict the severity of drug abuse and may contribute to relapse in both human and animal studies (de Wit and Richards, 2004; Perry et al., 2005; Dallery and Raiff, 2007; Diergaarde et al., 2008; Perry and Carroll, 2008; Economidou et al., 2009). However, quantitative measures of impulsive choice and action do not appear to be correlated with each other (humans: Crean et al., 2002; rats: Winstanley et al., 2004a). Furthermore, distinct cortical and sub-cortical brain regions may be differentially involved in modulating these behaviors (Dalley et al., 2008; Pattij and Vanderschuren, 2008).

As with studies involving the 5CSRT, direct targeting of specific receptor subtypes may be critical in understanding the relationship between serotonin, addiction, and impulsive choice. However, fewer studies have been conducted to address this issue, and many have not used truly selective compounds. For example, an acute dose of a mixed 5-HT_{2A/2C} antagonist (ketanserin) did not affect performance on a delay discounting task performed in either an operant or t-maze apparatus (Talpos et al., 2006; Hadamitzky et al., 2009). However, given that the 5-HT_{2A} and 5-HT_{2C} receptors have opposing effects on the 5CSRT, this may not be hugely surprising. An acute dose of a mixed 5-HT_{2A/2C} agonist increased choice of the smaller immediate reward in the t-maze paradigm (Hadamitzky et al., 2009), unfortunately the non-selective nature of this compound hinders the interpretation of these data.

Further insight into the relationship between 5-HT and impulsive choice may also be gained by observing the effects of regional manipulations of 5-HT. However, to date, this avenue of research has not been extensively explored. In sum, although the effects of different 5-HT receptor subtypes have yet to be fully characterized in relation to impulsive choice, 5-HT does appear to play a role in delay discounting.

6. Possible role of 5-HT in other models of decision-making

Although delay discounting is one of the most commonly used measure of impulsive choice in both clinical and preclinical research, other behavioral tasks may also provide insight into the relationship between addiction and impulsivity. In humans, a strong relationship exists between pathological gambling and substance abuse. Patients with pathological gambling experience cravings, 'highs', and withdrawal states, similar to those experienced by addicts (see Potenza, 2008 for review). As such, pathological gambling can be considered as a behavioral addiction (Potenza, 2008). A well-studied laboratory test of gambling behavior is the Iowa Gambling Task (IGT, Bechara et al., 1994). Pathological gamblers and patients with substance abuse choose disadvantageously on this task, selecting more often from decks of cards associated with larger reward in the short-term, but also greater long-term loss (Bechara et al., 2001; Goudriaan et al., 2005; Goudriaan et al., 2006).

In humans, altered serotonergic functioning is present in pathological gamblers as peripheral measures of 5-HT are decreased in these patients (Nordin and Sjodin, 2006). In contrast, pathological gamblers also have a decreased amount of the 5-HT reuptake transporter, also measured peripherally (Marazziti et al., 2008). Although it is unclear how these peripheral levels relate to the activity of 5-HT within the brain, treatment of pathological gambling with selective 5-HT reuptake inhibitors (SSRIs) is beneficial in some cases (Hollander and Rosen, 2000). These results may imply that pathological gamblers have decreased levels of 5-HT both peripherally and centrally. Additionally, patients with pathological gambling may exhibit an increased sensitivity to 5-HT stimulation, possibly mediated by post-synaptic receptors (Meltzer and Maes, 1995; Pallanti et al., 2006). As 5-HT is known to influence

both impulsive action and choice, it may be hypothesized that alterations in serotonin functioning also contribute to the maladaptive decision-making observed in pathological gamblers. Unfortunately, it has not yet been directly tested whether or not manipulation of the 5-HT system in pathological gamblers impairs or improves performance on the IGT.

In order to provide greater insight into this type of gambling-related decision making, animal models of 'gambling' have recently been developed (van den Bos et al., 2006; Rivalan et al., 2009; Zeeb et al., 2009). In rats, manipulation of the 5-HT system has the ability to alter decision-making on these rodent gambling tasks. In one study, female 5-HT transporter knock-out rats showed impairments in decision-making processes on a maze rodent gambling task (Homberg et al., 2008). In humans, activity of the 5-HT transporter can be assessed by observing the genotype of the 5-HT transporter-linked polymorphic region (5-HTTLPR). Subjects homozygous for the short allele of the 5-HTTLPR have decreased levels of the 5-HT transporter which results in a less efficient 5-HT system (Lesch et al., 1996). Consistent with the findings in rats, subjects homozygous for the short allele showed impairments on the IGT (Homberg et al., 2008; He et al., 2010; but see Stoltenberg and Vandever, 2010). In another study, acute injection of a 5-HT_{1A} agonist impaired performance on an operant-based rodent gambling task (Zeeb et al., 2009). Although 5-HT does appear to modulate this type of gambling-related decision making in both humans and animals, further research is required in order to fully understand the role of 5-HT in relation to pathological gambling and addiction.

7. Future directions and translational implications

The 5-HT system has long been implicated in mood and its dysregulation in affective disorders. Some of the clearest evidence for this association is the clinical effectiveness of serotonin-selective reuptake inhibitors in the treatment of a wide range of affective and anxiety disorders (see Nemeroff, 1998). Drug addiction and withdrawal states also have affective behavioral components; the positive hedonic property of the drug and the negative, aversive state produced during withdrawal. Receptors which mediate these drug effects (e.g. dopamine and opioid receptors) as well as endogenous opioids are present at high concentrations in a variety of limbic brain regions known to process emotional information, stress responses and reward such as the prefrontal cortex, amygdala and NAc (Mansour et al., 1995). These brain regions all receive significant serotonergic input from the raphe nuclei, particularly the DRN (Vertes, 1991). The serotonin system is therefore anatomically positioned to mediate some of the affective responses to drugs of abuse that may contribute to their compulsive use and to high rates of drug relapse in former addicts.

A related phenomenon is the high rate of comorbidity of clinical depression with drug dependence (Woody et al., 1975; Rounsaville et al., 1982; Brooner et al., 1997; Pani et al., 1997; Mason et al., 1998; Palomo et al., 2007). This comorbidity may reflect a common neurobiological substrate for the two disorders (Paterson and Markou, 2007). It is possible that drug dependence leads to dysregulation of the 5-HT system, a critical factor in the etiology of major depressive disorder. Another hypothesis, the "self-medication" hypothesis of drug dependence, states that an underlying depressive disorder leaves subjects vulnerable to the effect of drugs of abuse. These subjects will seek and then become dependent upon drugs in order to "treat" or reverse the neurobiological abnormalities underlying their depressed state (Markou et al., 1998). As preclinical data described above indicate that many of the drugs of abuse have acute stimulatory effects on 5-HT neurotransmission, subjects may engage in drug-seeking and relapse during periods of serotonergic hypofunction, as seen during withdrawal.

Current data further suggest that 5-HT—particularly via 5-HT_{2A} and 5-HT_{2C} receptors—have an important role in mediating impulsive action and, to a lesser degree, impulsive choice. Preclinical research has shown that modulating activity at these receptors may prevent relapse following withdrawal, and may also decrease the amount of drug intake (see above). Targeting the 5-HT system may therefore prove to be an effective strategy in developing treatments for substance abuse (see Fletcher et al., 2008a for review in relation to nicotine addiction), partially due to its importance in regulating impulsivity. Furthermore, abnormally high levels of either impulsive choice or action may also be a potential risk factor for the development of an addictive phenotype. It should be noted that other behavioral measures, besides impulsivity, may also contribute to an increased vulnerability, such as novelty seeking and poor executive function (Kalechstein et al., 2008; Carroll et al., 2009; Winstanley et al., 2010). Furthermore, as quantitative levels of impulsive action and choice do not generally correlate, other predispositions and their interactions with impulsivity should also be considered when determining the most effective treatment option for each individual.

Additionally, further research should be aimed at determining the role specific 5-HT receptor subtypes other than the 5-HT_{2A} and 5-HT_{2C} receptors in impulsivity and addiction. Although the discussion of all other receptor subtypes is beyond the scope of this review, the 5-HT_{1A} receptor may be of particular importance. For instance, systemic administration of a 5-HT_{1A} receptor agonist increases both impulsive action and impulsive choice (Carli and Samanin, 2000; Winstanley et al., 2005; Van den Bergh et al., 2006; but see Winstanley et al. (2003a)). Interestingly, systemic administration of a 5-HT_{1A} agonist impairs decision-making on a rodent gambling task, which appears to be due to the activity of postsynaptic 5-HT_{1A} receptors (Zeeb et al., 2009; Zeeb FD, Fletcher PJ, Winstanley CA, unpublished observations). Additionally, antagonism of the 5-HT_{1A} receptors may alleviate some of the behavioral symptoms associated with nicotine withdrawal (Rasmussen et al., 1997; Rasmussen et al., 2000), and this receptor also has an established role in psychostimulant addiction (Muller et al., 2007). Therefore, drugs which target the 5-HT_{1A} receptor may be potentially beneficial in the treatment of addiction and impulsivity-associated behaviors.

8. Summary

Clearly, the 5-HT system plays a large role in the neurochemical effects of several drugs of abuse, which may contribute to the development and maintenance of an addiction. Furthermore, 5-HT is involved in modulating different aspects of impulsivity. Abnormal levels of impulsivity have been shown to be a risk factor for compulsive drug use, as well as contributing to relapse following withdrawal. Therefore, effective pharmacological manipulation of the serotonergic system may contribute to successful recovery from the repeating cycle of addiction by alleviating some of the neurochemical abnormalities associated with drugs of abuse, which may in turn affect the quantitative levels of impulsivity. Although many other neurotransmitters also contribute to drug addiction and impulsivity is not the only vulnerability factor to consider, the 5-HT system should not be overlooked when developing effective pharmacotherapies for substance abuse. Insight from preclinical models suggests that targeting specific 5-HT receptors—such as the 5-HT_{2A} and 5-HT_{2C} subtypes—may prove to be effective. However, further work will be needed to better characterize the mechanisms by which 5-HT influences impulsivity and the role of this important neurotransmitter in mediating both the relapse to drug-seeking and the maintenance of addiction.

Acknowledgments

This work was supported by NIH grant DA 20126 (LGK) and an operating grant awarded to CAW from the Canadian Institutes for Health Research (CIHR). CAW also receives salary support through the Michael Smith

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Table 1
Summary of drug effects on 5-HT neurotransmission

All five drugs/drug classes represented stimulate extracellular levels of 5-HT via 5-HT uptake inhibition or 5-HT releasing actions (psychostimulants, ethanol) or indirectly via GABAergic disinhibition (opioids). Acutely elevated 5-HT levels inhibit 5-HT neuronal activity by actions at inhibitory 5-HT_{1A} autoreceptors (psychostimulants, ethanol) whereas acute opioids stimulate neuronal activity via GABAergic disinhibition. Following chronic administration, cocaine effects become sensitized whereas amphetamine, MDMA and opioid effects adapt and ethanol's effects become inhibitory. Withdrawal from these drugs/drug classes are generally characterized by reduced extracellular 5-HT levels.

DRUG	ACUTE	CHRONIC	WITHDRAWAL
Cocaine	↑ extracellular 5-HT and ↓ 5-HT neuronal activity via inhibitory 5-HT _{1A} autoreceptor activation	Sensitization of 5-HT response	↓ extracellular 5-HT
Amphetamine	↑ extracellular 5-HT and ↓ 5-HT neuronal activity via inhibitory 5-HT _{1A} autoreceptor activation	Adaptation of 5-HT response	
MDMA	↑ extracellular 5-HT and ↓ 5-HT neuronal activity via inhibitory 5-HT _{1A} autoreceptor activation	Adaptation of 5-HT response	
Opioids	↑ extracellular 5-HT and ↑ 5-HT neuronal activity via GABAergic disinhibition	Adaptation of 5-HT response	↓ extracellular 5-HT
Ethanol	↑ extracellular 5-HT and ↓ 5-HT neuronal activity via inhibitory 5-HT _{1A} autoreceptor activation	↓ extracellular 5-HT	↓ extracellular 5-HT