Role of Serotonin in Cue Exposure-Induced Craving in an Inpatient Sample of Egyptian Addicts

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Abstract

Craving is one of the phenomena that attracted the attention of all researchers working in the field of substance use disorder due to its impact on abstinence and recovery. In this study we examined whether plasma level of (serotonin) 5-HT was altered during substance abuse and whether this measure would be related to craving. We also explored whether alterations in 5-HT activity differ between types of cue exposure (auditory and visual) in substance dependent patients during craving**.** Plasma measurements of 5-HT and assessments of craving were performed longitudinally in 10 Egyptian opium-dependent patients who were hospitalized for detoxification, at baseline, after answering craving questionnaire assessing the different craving inducing situations; and after exposing them to a video that is full of cues. These measures were compared with 5-HT levels obtained from equal number of matched controls. Baseline serotonin level for these patients had a mean of 39.31(± 49.23), which is highly significantly ($P<0.01$) lower than that for the healthy controls who had a mean of 194.1 (±10.65) with a significantly ($P<0.05$) sharp rise after completing the craving questionnaire to reach a mean of 113.85 (± 144.49). However, after watching a craving inducing film it reached a mean of 64.15 (± 80.15), yet this rise was not significantly different from baseline ($P>0.05$). Using student t-test for comparing those taking heroin intravenous to those using other modes of opium administration, it was found that there is a highly significant difference on comparing the serotonin levels after applying the questionnaire ($P=0.003$).It can be concluded that craving can be induced by auditory as well as visual cues; both are associated with changes in serotonin levels which is more evident with auditory cues. This proved that craving has biological basis: more studies are needed to clarify the picture as regards the different neurotransmitters involved and the role of pharmacotherapy in controlling these phenomena.

Introduction

Craving is a commonly used term to describe an intense desire for a substance or behaviour ***(Lingford-Hughes et al, 2006).*** It has been increasingly recognized to contribute to continued abuse and is believed to play an important role in relapse ***(Petrakis et al., 1999, Volkow et al, 2006)***, The main *Psychological* models of drug craving are classified broadly into three categories: (1) phenomenological models; based on clinical observation and description; these have been influential in classification systems of addictive disorders and in the development of pharmacological therapies; (2) conditioning models: based on conditioning theory; these have been influential in the development of cue exposure treatments; (3) cognitive theories; based on cognitive social learning theory: these have been influential in the development of cognitive therapies of addiction. It is concluded that no one specific theory provides a complete explanation of the phenomenon of craving ***(Drummond, 2001).*** However, its

underlying neurobiology is still not fully characterized.

Serotonin, the chemical 5-hydroxytryptamine (5-HT), is derived from the amino acid tryptophan and plays an important role in a wide range of physiological states, such as sexual behavior, intestinal functions, and affective states. As a chemical, serotonin has been launched to celebrity status in the past two decades because of its known involvement in depression, anxiety, and obsessive-compulsive disorders. Moreover, numerous data in both animals and humans have shown that the serotonergic system in the brain plays a key role in self-control behavior as a low serotonergic tone is well known to be frequently associated with impulsivity, auto-and hetero-aggressive behavior ***(Hamon, 2002).*** In substance abuse, acute administration of alcohol is known to stimulate 5-HT turnover, while chronic alcohol intake is reported to decrease 5-HT synthesis and release ***(Tollefson, 1989***). Reduced central 5-HT has been implicated in mediating alcohol preference in animals ***(LeMarquand et al., 1994).*** On the other hand, Cocaine use causes an initial increase in dopamine and serotonin neurotransmission that is largely responsible for the pleasurable and reinforcing effects of the drug. Dysregulation of these neurotransmitters during withdrawal plays an important role in craving. Recent research has focused on the use of dopamine and serotonin antagonists early in recovery to reduce cocaine craving ***(Smelson et al, 2004).***

Evidence supporting the effects of substance abuse on 5-HT function in humans is less consistent. Possible reasons may be the variation with dose, length of exposure or abstinence, heterogeneity of the clinical population, treatment with selective serotonin reuptake inhibitors and craving states ***(Naranjo and Knoke, 2001).***

A major methodological issue in studying peripheral levels of 5-HT and its relationship to central mechanisms, such as craving**,** is that it is unclear whether plasma 5-HT levels reflect corresponding changes in human brain. Certain metabolic differences are present between periphery and the brain in humans that may need to be considered during interpretation of data ***(Linnoila et al., 1986).*** Human studies have found similarities between the uptake, storage and release of 5-HT in neurons and blood platelets ***(Da Prada et al., 1988).***

In this study we tried to demonstrate the effect of cue exposure in different modalities in abstinent substance use disorder (dependence type) patients and if this can affect their serotonin blood levels. Since repeated central measurements of neurotransmitters in humans are expensive, invasive and technically difficult, we examined plasma 5-HT levels.

Methods:

Sampling:

The sample consisted of 10 opioid-dependent patients diagnosed according to DSM-IV criteria (American Psychiatric Association, 1994) who were hospitalized for detoxification; and an equal number of age and gender matched healthy volunteers, who served as the control population. The opioid-dependent subjects were recruited from a university affiliated inpatient addiction unit in Cairo, Egypt (ethically we can not expose patients to cues and let them go to see whether or not they are going to relapse, so we carried this research on

inpatients to avoid exposing them to relapse).

Procedure:

The study protocol was approved by the Staff committee of the hospital. All subjects gave written informed consent to proceed in the study. Opioid-dependent individuals who completed the study underwent a full psychiatric, medical interview and routine laboratory investigations for blood sugar, liver and kidney functions, in addition to screening for HIV as a part of the admission procedure of the addiction unit. Individuals with major depression, bipolar disorders or psychotic disorders, serious medical disorders and current illicit drug misuse, were excluded from the study.

Patients and controls then completed a craving questionnaire which represented the auditory cues. The questionnaire was prepared by using a multi-item scale in substance misusers. It included 8 variables, which were categorized as representing the high risk situations, moods or thoughts related to substance use that can induce craving if one imagines that he experiences. The questionnaire required 15 min to be complete. It was tested on 100 Egyptian patients and was found to have a Kappa coefficient of 0.92 which stands for excellent validity. Second, patients were exposed to a video that is full of cues related to substance abuse followed by measuring craving using visual analog scale. Serum serotonin level was obtained at baseline and after each step. However, on studying the effect of craving on baseline serotonin level, we decided to consider each patient's baseline as his own control.

Laboratory techniques

Thirty millilitres of venous blood were collected in glass tubes from subjects and controls. Blood samples were collected in the morning and transported to the laboratory on ice within 2 hours. For 5-HT assay, a good blood sampling technique, adequate platelet stabilization in the test tubes and rapid processing after collection reduced the possibility of platelet aggregation and activation that may stimulate 5-HT release and inflate the measured values (Beck *et al.*, 1993).

5-HTwas assayed using ELISA technique.

Statistical analysis

Data were analysed using SPSS for Windows. Release 11.0.1 (2001)

Data were summarized as frequencies and means. Comparing serotonin levels at different points of the study was done using Wilcoxon signed rank test since data proved to have a non-parametric distribution. To study the association between any of the craving high-risk situation and the changes in the serotonin level was done using ANOVA.

Results

We examined 10 opioid-dependent individuals (8males and 2 females). Their age ranged between 17-35 years with mean (25.6±6.13). They were more likely to be single 60%, 30% unemployed. No individuals proved positive for HIV. 90% had a history of opium as their main drug of dependence. Six of them were taking heroin i.v., while the remaining three were taking synthetic opiates. The duration of their drug dependence ranged from 3 up to 16 years (mean = 10.30 ± 4.83 years). The number of relapses experienced by these patients

ranged from one relapse till 8 relapses. They were all receiving treatment for the past one month in the form of carbamazepine (600 mg/day), chlorpromazine (300 mg/day), flouxetine (60 mg/day). Using Shapiro-Wilk test, sample proved to be non-normal in distribution.

The mean baseline 5HT level for the healthy control group was (m.194.1 ± 10.65 std.). Regarding that of patients, it was (m. 39.31 ± 49.23 std.). Using Mann- Whitney test, there has been a highly significant difference between baseline means being lower within the patient group ($P < 0.01$) despite receiving SSRI. Within the patient group, there has been a sharp rise after completing the craving questionnaire to reach a mean of 113.85 (± 144.49 std.). However, after watching a craving inducing film it dropped to reach a mean of 64.15 (± 80.15 std.). It is worth mentioning that all the patients reported very high craving on visual analog scale (8-10).

Comparing baseline serotonin levels with that after applying the craving questionnaire as well as to that following exposure to the craving-inducing film using Wilcoxon signed rank test, it was found that there is a significant difference on comparing the serotonin level after applying the questionnaire to the baseline serotonin level ($Z= -2.325$,$P= 0.02$) but not after watching the craving-inducing film to baseline 5 HT ($Z= -1.7$, $P=0.08$), however, there was a statistically significant difference between the serotonin levels after film and after craving questionnaire ($Z= -2.23$, $P=0.02$) as shown in table 1. There was no significant ($P>0.05$) on comparing males and females using Mann-Whitney test.

Using oneway ANOVA for comparing those taking heroin i.v. to those using other modes of administration (oral, sniffing), it was found that there is non significant difference on comparing the serotonin levels after applying the questionnaire as well as to that after watching the film ($P>0.05$).

There was a significant correlation ($P= 0.01$) between serotonin level after questionnaire and the number of relapses, while there was no such correlation between number of relapses and 5-HT level after the craving-inducing film. Regarding correlation between the duration of substance dependence and 5-HT level, there was a significant correlation ($P= 0.04$) with baseline serotonin level, while there was no such correlation with 5-HT level after the questionnaire or the film (table 2).

Regarding the confidence of the patients to control craving in the different situations tested by the craving questionnaire, results show that the situations that can be considered as high-risk situations were: physical discomfort (39.6±15.83), followed by pleasant times with others (41.6±22.33), and social pressure to use (42.6±20.46). Table (3)

Using ANOVA to study the possible role of each situation in relapse in our sample, it was found that physical discomfort, urges/temptations as well as testing personal control were highly significantly associated with relapse ($P=0.007$, $P=0.007$, and $P=0.009$ respectively). However, unpleasant emotions was only significantly associated with relapse ($P=0.013$). None was related to the duration of substance dependence.

Also when studying the association between any of the craving high-risk situation with the changes in the serotonin level after applying the questionnaire as well as that after exposure to the craving-inducing film,

it was found that having a high confidence to control physical discomfort was highly significantly associated with higher levels of serotonin after both applying the questionnaire and exposure to the craving-inducing film (P=0.001 and P=0.01 respectively). It is worth mentioning that none of the high-risk situations had any association with baseline serotonin level.

Table (1): Comparison between various levels of serotonin in different situations within patients:

Baseline 5 HT	5 HT after questionnaire	5 HT after film	Wilcoxon (Z)	P
39.31 ± 49.23	113.85 ± 144.49	-	-2.33	0.02*
39.31 ± 49.23	-	64.15 ± 80.15	-1.7	0.08
-	113.85 ± 144.49	64.15 ± 80.15	-2.23	0.02*

Significance: P<0.05

Table (2): Correlation between various 5 HT levels and clinical variables:

		Duration of abuse	Number of relapses
Baseline 5HT	r	-0.653	0.36
	p	0.04*	0.31
5 HT after questionnaire	r	0.611	0.76
	p	0.06	0.01*
5 HT after film	r	0.53	0.55
	p	0.12	0.1

Significance: P<0.05

Table (3): Confidence to Control Craving in the Different Situations Tested by the Craving Questionnaire

situations	**minimum**	**maximum**	**mean**	**Std.**
unpleasant emotions	16	76	51.0	22.02
physical discomfort	16	72	39.6	15.83
conflicts with others	20	76	49.2	18.77
pleasant emotions	16	76	47.4	21.58
urges/temptations	16	88	49.6	23.19
social pressure to use	12	74	42.6	20.46
testing personal control	24	84	51.6	23.88
pleasant times with others	12	72	41.6	22.33

Discussion

5HT and substance dependence:

This study showed that 5-HT levels were significantly lower in substance dependent patients compared to healthy controls. This finding is in accordance with previous research which suggests lowered 5 HT levels in substance dependence and considered it an etiological factor in the disorder. For example, ***Leyton et al. (2001)*** found that low 5-HT synthesis capacity in corticostriatal pathways may contribute to the development of impulsive behavior in persons with borderline personality disorder which is a common comorbid condition with substance dependence. An alternative explanation was presented by ***Deakin (2003)*** who hypothesed that projections of the anterior group of raphe 5HT cells (dorsal raphe nucleus) oppose the action of dopamine and mediate avoidance of threats and that impaired function sensitizes the dopamine system resulting in impulsivity and drug addiction. This also gets along with the finding that lowering of serotonin by rapid tryptophan depletion increases impulsiveness and decreases discrimination in normal individuals ***(Walderhaug, 2002).*** Conversely, other studies found that serotonin produced an inhibitory effect on drug intake (i.e., if you increased the serotonergic component, you make the drugs less attractive. However, now that we have better pharmacologic tools for studying serotonin neurotransmission we're finding a much more complicated picture. ***(Parsons, 2003).*** Interestingly, it was found that repeated administration of addictive drugs actually induces a decrease in the brain serotoninergic tone; thereby producing loss of self-control which characterizes drug craving in dependent subjects ***(Hamon, 2002).***

In a recent study testing effect of different drugs on delay aversion behavior (an aversion to waiting for rewards) in rats which positively correlates with aggression, substance abuse and persistence during extinction of conditioned responses suggesting a possible shared pharmacology, the results show that D(3)-receptor agonist 7-OH-DPAT slightly decreased choice for the large reward. Flesinoxan, 5-HT(1A)-receptor agonist, disrupted task execution by lowering choice for the large reward even at a delay of 0 s. Eltoprazine, 5HT(1A/1B)-receptor agonist, slightly increased choice for the large reward, but the 5-HT(1B)-antagonist GR127935 had no effect. Administration of D-cycloserine NMDA-receptor agonist, also had no effect on choice behavior. The data suggest the dopamine D(3)-receptor and the 5-HT(1B)-receptor are interesting targets for treating delay aversion impulsivity. These targets were correctly predicted by the positive correlation between delay aversion and aggressive behavior and the intimate links between delay aversion and substance abuse disorders ***(van den Bergh et al, 2006).*** Indeed, extensive neurobiological studies showed that the changes in central serotoninergic neurotransmission caused by cocaine and other addictive drugs are in fact opposite to those produced by drugs which enhance serotoninergic neurotransmission such as selective serotonin reuptake inhibitor. Accordingly, the latter effect very probably accounts for the capacity of these antidepressants to promote autoinhibition, and reduce both craving and consumption of drugs ***(Hamon, 2002).***

(5-HT) and craving:

In an attempt to localize areas of the brain responsible for craving and drug seeking behavior, scientists have been carrying a variety of research. Positron emission tomography was used to map regional cerebral blood flow (CBF) in 21 detoxified patients with alcohol dependence during exposure to alcoholic and non-alcoholic beverages. During the alcohol condition compared with the control condition, significantly increased CBF was found in the ventral putamen. Additionally, activated areas included insula, dorsolateral prefrontal cortex and cerebellum. Cerebral blood flow increase in these regions was related to self-reports of craving assessed in the alcoholic patients. It was thus concluded that cue-induced alcohol craving was associated with activation of brain regions particularly involved in brain reward mechanisms, memory and attentional processes ***(Olbritch et al, 2006).*** Another study measured brain activity in cocaine addicts and healthy subjects by functional magnetic resonance imaging (fMRI) while the subjects watched videotapes designed to elicit happy feelings, sad feelings, or the desire to use cocaine. The subjects indicated the onset of drug craving or emotional response, allowing comparison of groups before and after such feelings. Patients showed low activation of sensory areas during initial viewing of all videotapes, suggesting generalized alteration in neuroresponsiveness. Also cocaine cues lead to abnormally high cingulate and low frontal lobe activation in cocaine addicts. Addicts also show more general abnormalities in affect-related brain activation ***(Wexler et al, 2001).*** The development of novel pharmacological agents for the treatment of psychostimulant use disorders is an important research imperative. One potential target system that has been largely overlooked is the serotonin (5-HT) neurotransmitter system. In this study, we attempted to study 5HT levels and found a statistically significant difference between baseline 5HT and level after exposure to either visual or auditory cues with the patients reporting craving. Our results can be explained by preclinical studies that indicate that 5-HT2A R antagonists and/or 5-HT2C R agonists (presynaptic receptor) may effectively reduce craving and/or relapse, and likewise, enhance abstinence, while 5-HT2C R agonists may also effectively reduce cocaine intake in active cocaine users ***(Bubar & Cunningham 2006).*** Also our findings can be explained in light of Parsons conclusion who stated that when ethanol, cannabinoids, opioids, or psychostimulants are taken into body, serotonin levels in the brain are elevated significantly thereby playing a role in the motivation to continue taking drugs and that this may account for affective disorders similar to depression and anxiety often seen during withdrawal ***(Bardi, 2003).*** Interestingly, Parsons and his colleagues have subsequently found that serotonin-1B receptors enhance the reinforcing effects of amphetamine, alcohol, and opiates, and this effect does not seem to depend on route of consumption of the drug ***(Bardi, 2003)***. This goes with our finding of non significant difference in serotonin levels concidering route of opium intake.

It is worth mentioning that despite the agreement on the level of craving experienced subjectively on exposure to the craving-inducing film, yet it was found that serotonin increased markedly following applying the questionnaire than following

exposure to the craving-inducing film. This might be explained by the fact that when the patient is responding to the questionnaire, he/she is asked to think how they would be confident in response to these emotions, thoughts, or situation, this coincides with increased serotonin to face the craving thus multiple cognitive processes are involved for example memory, attention as well as activation of the reward system on a personalized level. However, as the film is not associated with expected response from the patient, so this actually represents what happens to the patient when suddenly developing craving and the elevation after the questionnaire might represent the neurobiological response in an attempt from the body to face craving and avoid relapse. Our results are not in agreement with a previous study comparing the effects of visual and auditory stimulation with that of cocaine (0, 5, 10, 20mg/kg; i.p.) on the extracellular serotonin (5-HT) activity in the occipital and temporal cortices in relation to behavior. Visual stimulation increased 5-HT in the occipital, but not temporal cortex, parallel to an increase in locomotion. Auditory stimulation decreased 5-HT in the auditory, but not occipital cortex, thus, showing a double dissociated 5-HT response. These data suggest that a locally restricted 5-HT response to sensory stimulation may gate behavioral activity sense-modality selectively. Cocaine affected 5-HT in the occipital cortex and behavioral activity in the same direction as visual stimulation, but in an amplified and prolonged way. In the temporal cortex cocaine also caused an increase in 5-HT. The findings demonstrate common effects of visual stimulation and cocaine on 5-HT activity in the occipital cortex in relation to locomotor activity ***(Maller et al, 2007).*** This study, thereby, suggests a stronger influence of visual cues than auditory cues in craving, an issue that needs further elaboration.

Serotonin over time of drug abuse

So, the balance between the facilitory and inhibitory mechanisms can be altered by long-term drug use. It was suggested that reduction in central serotonin leads to altered neuromodulation of the cortical and subcortical regions (e.g., orbitofrontal cortex, striatum and anterior temporal structures) that mediate important aspects of associative learning whereby exteroceptive stimuli acquire altered incentive motivational value. The brain serotonergic system plays a central role in the regulation of impulse-control mechanisms, and 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 (**Ciccocioppo, 1999**). This explains the significant negative correlation found between baseline serum serotonin levels and duration of drug abuse rather than number of relapses which in some cases may be frequent but over a short period of time. Conversely, a significant positive correlation existed between serotonin level after exposure to auditory cues and number of relapses which may emphasize the strong role of the upsurge of 5 HT level during cue exposure and craving and consequently relapse.

Recommendations

The challenging components of drug addictions, including counteradaptation, sensitization, abstinence, craving and relapse need further neurobiological exploration and understanding, which may be done through

the use of advanced imaging and genetic techniques.

Hopefully, future studies will dissect out the influence of different serotonin receptor subtypes as well as different neurotransmitters involved in craving.

The studies focusing on understanding the mechanism of craving and relapse will set the groundwork for developing new therapeutics for drug addiction. As, on this basis, it can be suggested that the combination of selected serotonin receptor ligands with substance having the capacity to reduce the reinforcing appetitive properties of drugs of abuse (such as opioid receptor antagonist as naltrexone) might be a novel therapeutic approach of withdrawal in addicted subjects ***(Hamon, 2002)***

Limitations of the study

This study has put into consideration, the bias that can occur due to the differences in clinical heterogeneity of substance dependence by taking each patient as his/her own control.

Although, this study is the first to study the effect of craving from the neurobiological perspective in an Egyptian sample of substance use disorder patients, yet it had several limitations: First, the small sample size; Second, females in particular were underrepresented in that sample; Third, the results were obtained from an inpatient sample in a University hospital which represents a special subpopulation of substance use disorders with the most severe form of the disorder, so these results can't be generalized to the population of substance use disorder patients as a whole. Lastly, as subjects were inpatient they had no access to drugs (i.e., no drug expectancy which is a very important determinant of drug craving), this might have limited the severity of craving despite the fact that clinically being inpatient did not stop it altogether.

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دور مادة السيروتونين في اللهفة الناتجة عن الإدمان في الإشارات السمعية و البصرية في عينة مصرية من مرضي الإدمان في الكحول الداخلية

تعد اللهفة واحدة من الظواهر التي جذبت الباحثين في مجال سوء استخدام العقاقير للدراسة و ذلك لدورها الهام في العلاج و الإقلاع عن هذه العقاقير. أختبر الباحثون ما إذا كان مستوى مادة السيروتونين يختلف في حالات سوء استخدام العقاقير و هل يمكن أن توجد علاقة بين مستوى المادة و اللهفة. كذلك هل يختلف مستوى المادة باختلاف نوعية الإشارات (سمعية أو بصرية) في المدمن أثناء حالة اللهفة. منهج البحث: تم اخذ عينات دم متتالية من عشرة حالات لإدمان الأفيون من نزلاء مركز الطب النفسي بكلية الطب جامعة عين شمس أولا عند بدء الدراسة، ثم بعد ملء استبيان اللهفة الذي يحدد المواقف المثيرة اللهفة لدي المريض ثم بعد عرض شريط مسجل مرئي ملئ بالإشارات المرئية و تم مقارنة مستوي مادة السيروتونين في الحالات مع مستوي المادة في عينة مرجعية متماثلة من عشر أشخاص أصحاء. و قد أثبت التحليل الاحصائى للبيانات أنه من الممكن حفز اللهفة بإشارات بصرية و سمعية وكلاهما يحدث معه تغير بمستوي مادة السيروتونين.