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Increased oxytocin levels among abstinent heroin addicts: Association with aggressiveness, psychiatric symptoms and perceived childhood neglect☆

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ABSTRACT

A disruption of the oxytocin system seems to affect a variety of brain functions including emotions, mood and social behavior possibly underlying severe social deficits and susceptibility for substance use and mental health disorders. Early life adversity, such as insecure attachment in childhood, has been suggested to influence oxytocin tone contributing to a condition of neurobiological vulnerability.
Aim of the present study was to investigate oxytocin serum levels in abstinent heroin addicted patients, in comparison with healthy controls, and the possible correlation with co-occurring psychiatric symptoms, aggressiveness and perception of parental neglect. Eighteen (18) abstinent patients, affected by heroin use disorders, and 18 control subjects, who never used drugs or abused alcohol, were included in the study and submitted to 1) collection of a blood sample for oxytocin assay, 2) Symptoms Check List 90 for psychiatric symptoms evaluation 3) Buss Durkee Hostility Inventory to measure aggressiveness 4) Child Experience of Care and Abuse-Questionnaire to retrospectively test the perception of parental neglect. Heroin exposure extent and heroin dosages were also recorded. Oxytocin serum levels were unexpectedly significantly higher among abstinent patients affected by heroin use disorders and positively correlated with psychiatric symptoms, aggressiveness and mother neglect scores. No correlation was evidenced between oxytocin and heroin exposure extent or dosages. Our findings appear to contradict the simplistic view of oxytocin as a pro-social hormone and confirm previous evidence concerning the peptide levels direct association with aggressive behavior and mood disorders. Considering a more complex mechanism, oxytocin would increase the sensitivity to social salience cues related to contextual or inter-individual factors, promoting pro-sociality in "safe" conditions and, in contrast, inducing more defensive and "anti-social" emotions and behaviors when the social cues are interpreted as "unsafe". This latter condition is often characterizing the clinical history of addicted patients.

1. Introduction

Oxytocin, a nine amino acid neuropeptide secreted by the posterior pituitary, has been found to modulate a variety of brain functions including emotions, mood, social and sexual behavior, learning and memory (Gimpl and Fahrenholz, 2001). In addition to improving the psychosocial status, oxytocin has been found to be implicated in mediating mesolimbic dopamine pathways, possibly interfering with the reward mechanism and the susceptibility to addictive behavior (Sarnyai, 2011).

Preliminary findings in experimental animals may indicate the existence of an integrated brain circuit where dopamine and oxytocin interactions mediate the socio-affiliative behaviors. A disruption to these pathways has been suggested possibly to underlie behavioral disorders in patients with severe social deficits and/or drug addiction (Baskerville and Douglas, 2010).

The impairment of the oxytocin system seems to compromise adaptation to social stress, to induce anxiety, to affect social memory and to

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undermine bonding, emotion recognition, empathy, and interpersonal trust (Kirsch, 2015).

In particular, a significant negative association between the blood level of plasma oxytocin and novelty seeking was recently reported among methadone patients (Lin et al., 2015), suggesting that reduced oxytocin levels may underlie the temperamental condition predicting substance use initiation and substance use disorders (Hartman et al., 2013). To this purpose, oxytocin would be involved in shifting the balance between wanting and liking in cortico-striatal loops, with a move from a reactive reward drive (wanting) to a stable appreciation of familiar social aspects ("liking" or "loving") and potentially increasing resilience in the face of stress and addiction (Tops et al., 2014).

In a larger perspective, abnormalities of oxytocin appear to be involved in several neuropsychiatric disorders, including autism, obsessive-compulsive disorder, schizophrenia, post-traumatic stress disorder, alcohol dependence, eating disorders and Prader-Willy syndrome (Marchesi et al., 1997; Marazziti and Catena Dell'osso, 2008; Wojciak et al., 2012). Again, this underlines the possible role of this pituitary peptide in complex mental health conditions related to interpersonal relationships, mood, aggression and behavioral control.

The derangement of the oxytocin system associated to behavioral, psychiatric and substance use disorders has been attributed in previous studies to early life adversity, such as insecure attachment in childhood, neglect and abuse (Ahern and Young, 2009; Mogi et al., 2011). In turn, individual differences in oxytocin levels, reactivity of the system or interactions with other systems have been suggested to influence general resilience, drug effects and the susceptibility to develop problematic drug and alcohol use (Buisman-Pijlman et al., 2014).

To complicate the picture, and make more difficult the interpretation of oxytocin function related to addiction and co-occurring mental health disorders, recent findings have evidenced a positive correlation between oxytocin and impulsiveness, negative emotionality, monotony avoidance and psychic anxiety (Bendix et al., 2015), in contrast with previous data. In line with these results, the links between plasma oxytocin and depression reported in scientific literature appear to be controversial, ranging from negative to positive associations (Mohiyeddini and Opacka-Juffry, 2015). Gender differences may also play a confounding role in the investigation of oxytocin function, with the relationship between oxytocin and depression among men being reported in the opposite direction with respect to women (Massey et al., 2016).

Moreover, in contrast with existing findings, oxytocin levels have been reported higher in bipolar disorder patients, compared to controls, suggesting that oxytocin increased release may be considered a trait marker in bipolar disorder (Turan et al., 2013). Similarly, oxytocin levels were found positively correlated with total score and interpersonal dysfunction dimensional scores of the Schizotypal Personality Questionnaire (Tseng et al., 2014).

Investigating the oxytocin system function in subjects with drug use disorders may also encounter additional problems, considering the possible prolonged action of the drug itself on the neuro-pituitary function. The decrease in oxytocin release was previously reported as a result of μ-opioid receptors activation in neuro-hypophysial terminals (Ortiz-Miranda et al., 2003) and increased firing of oxytocin neurons has been evidenced during morphine withdrawal in pre-clinical studies (Brown et al., 2005). In contrast, long-term opioid withdrawal has been found to be associated with a decrease of oxytocin levels in the hypothalamus of experimental animals and to cause a rebound brain specific upregulation of oxytocin receptors in regions involved in emotionality, including the amygdala and the lateral septum (Zanos et al., 2014). This dysregulation of the oxytocin system was found to be concomitant with the emergence of social deficits, depressive-like behavior and anxiety behavior experienced by opioid abstinent mice, all conditions possibly facilitating the reinstatement of morphine seeking behavior.

Considering the uncertain evidence concerning the possible implications of the peptide in the mechanism underlying addiction, particularly in humans, we decided to investigate the serum levels of oxytocin together with current psychiatric symptoms/aggressive traits, and the retrospective measures of childhood neglect perception, in abstinent heroin dependent patients, in comparison with healthy subjects who never abused psychotropic substances or alcohol.

Aims of the study were 1) to evaluate the possible difference in oxytocin basal levels between abstinent heroin addicts and healthy controls, 2) to measure the possible correlations between oxytocin levels and the exposure to long term opioid receptors stimulation (duration of heroin use disorders), and 3) to evaluate the potential association of oxytocin levels with current mood problems, measures of aggressive behavior, psychiatric symptoms and the perception of childhood adverse experiences. The hypothesis of the study was that oxytocin levels might differ significantly between abstinent subjects affected by drug use disorders and control subjects, as a possible marker of general vulnerability for addiction and co-occurring mental health disorders. In line with this view, we expected that the derangement of oxytocin secretion would be associated with co-occurring psychiatric symptoms and early life adverse experiences, rather than with the duration of addiction clinical history and extent of exposure to heroin.

Eighteen abstinent heroin dependent patients submitted to long term residential treatment in therapeutic community, not exposed to any medication from at least 3 months, have been submitted to blood samples for oxytocin, to psychometric scales for the evaluation of co-occurring psychiatric symptoms (Symptoms Check List 90), measures of aggressiveness (Buss Durkee Hostility Inventory) (BDHI) and adverse childhood experiences, particularly parental neglect (Child Experience of Care and Abuse). Eighteen healthy subjects, who have never used psychotropic drugs or abused alcohol, have been compared with the abstinent heroin dependent patients as controls.

2. Materials and methods

2.1. Subjects

Eighteen (18) male subjects affected by heroin use disorders, aged 21–48 years (34.1 ± 8.0), with a history of heroin dependence of 3–18 years (8.4 ± 4.5), were included in the study. The study design was approved by the local ethics committee and written informed consent was obtained from all participants. They were not paid for their participation and accepted to enter the study as volunteers. They have been using heroin two or three times a day (active principle 5%–10%) from at least 3 years without any abstinence period. The patients met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria for Heroin Dependence.

All the subjects reported cannabis continuous use before starting heroin, and lifetime cocaine use episodes. Previous continuous consumption of other drugs of abuse and psychotropic agents or excessive alcohol intake has been excluded.

The subjects contacted the Addiction Treatment Centres of Biella, Bologna and Parma (Italy) in 2014–2015 for a problematic clinical condition related to drug use. The participants in the study were the first 18 residential treatment patients (inpatients: therapeutic community program) who accepted to take part in the study and completed the procedure, in chronologic order, to be submitted to the experiment after at least 3 months of abstinence from heroin, any other drug and alcohol (4.1 ± 1.1 months).

To obtain the sample of 18 patients, 25 subjects have been initially recruited. Seven subjects (7) were excluded because they were not abstinent for 3 months or did not complete the experimental procedure.

All the subjects accepted to attend a psychosocial rehabilitation program, as inpatients: the inpatients treatment, based on the therapeutic community method, aimed to improve self-control, accountability and interpersonal relationships, providing intensive caregiving and reproducing a "family" climate. The treatment program included also group therapy, cognitive-behavioral therapy and educational interventions