Orexin A in men with heroin use disorder undergoing methadone maintenance treatment

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A R T I C L E   I N F O

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A B S T R A C T

Orexins have played a role in reward-seeking and addiction-related behavior. There are few reports in the literature on serum levels of orexins in patients with heroin use disorder (HUD) undergoing methadone maintenance treatment (MMT). The aim of this study was to investigate the serum levels of orexin A in HUD patients undergoing MMT. Fifty male HUD patients undergoing MMT and 25 healthy males were enrolled for this study. Serum orexin A were measured with assay kits. Using analysis of covariance (ANCOVA) with body mass index (BMI) adjustments, the serum levels of orexin A in HUD men undergoing MMT were found to be significantly higher than in healthy controls. In conclusion, our results suggest that MMT might increase orexin A levels in HUD patients.

1. Introduction

Heroin addiction might be related to a dysfunction in the dopamine neurotransmitter system (Nutt et al., 2015). Orexins regulate the reward-seeking pathway, including the nucleus accumbens (NAc) and ventral tegmental area (VTA) (Sakurai, 2014a; Wise and Rompre, 1989). Orexins might be associated with opioid addition (Aston-Jones et al., 2009; Harris et al., 2005; Harris et al., 2007; Richardson and Aston-Jones, 2012). Methadone maintenance treatment (MMT) is an effective harm-reduction treatment for heroin use disorder (HUD); MMT decreases mortality and improves the quality of life of heroin-dependent patients (D’Aunno et al., 2014; Pierce et al., 2016). However, there are few reports of orexins in HUD patients undergoing MMT.

The neuropeptides orexin A and orexin B (hypocretin-1 and hypocretin-2) are produced from neurons in the lateral and dorsomedial hypothalamus and perifornical area (de Lecea et al., 1998; Peyron et al., 1998; Sakurai et al., 1998). Orexins and orexin neurons are related to reward-seeking and addiction (Baimel et al., 2015; James et al., 2017b). Orexins also regulate various behaviors, including feeding (Sweet et al., 1999), arousal (Alexandre et al., 2013; Chrobok et al., 2017), stress (Bonnivion et al., 2015; Grafe et al., 2017; Li et al., 2014), depression/anxiety (Azogui and Plamondon, 2017; Connor et al., 2017; James et al., 2017a) and pain (Razavi and Hosseinzadeh, 2017). The effects of orexin A and orexin B are mediated via activation of two G protein-coupled receptors, known as orexin receptor 1 (OX1R) and 2 (OX2R) (Alexander et al., 2013; de Lecea et al., 1998; Marcus et al., 2001; Sakurai et al., 1998). OX1R has a higher affinity for orexin A than orexin B, and OX2R has similar affinities for both orexin A and orexin B (Lu et al., 2000; Trivedi et al., 1998; Xu et al., 2013). Therefore, orexin A acts at OX1R and OX2R, and orexin B acts mainly at OX2R (Chieffo et al., 2017). Dysfunction of the dopamine neurotransmitter system is involved in drug addiction. Orexin neurons affect most dopamine neurons in the ventral tegmental area (VTA) (Muschamp et al., 2014). Orexin A is involved in drug-seeking, including drugs such as morphine and cocaine (Harris et al., 2005; Harris et al., 2007). Orexin A might play important roles in drug addiction (Bayerlein et al., 2011; Bernstein et al., 2017; Espana et al., 2011; Farahinanesh et al., 2017; Zarepour et al., 2014; Ziolkowski et al., 2016). Orexin A also regulates feeding behaviors (Dube et al., 1999; Haynes et al., 1999) and modulates dopaminergic, GABAergic, glutamatergic and cholinergic neurons (Arrigoni et al., 2010; Balcita-Pedicino and Sesack, 2007; Fadel and Frederick-Duus, 2008).

The aims of this study were to investigate the serum levels of orexin A in HUD patients undergoing MMT compared to healthy controls.

2. Methods

2.1. Patients and study design

Fifty HUD male patients undergoing MMT at Kaohsiung Chang Gung Memorial Hospital were enrolled. Inclusion criteria were as follows: (1) a diagnosis of heroin dependence based on the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition); (2) males, aged from 20 to 65 years; (3) no history of psychotic, bipolar,
major depressive, anxiety, or substance use disorder except heroin or nicotine use disorder; (4) seronegative for human immunodeficiency virus (HIV); (5) stable physical condition. We collected data including serum orexin A, body mass index (BMI: kg/m²) and age. The diagnosis of HUD for all the participants was performed by a single board-certified psychiatrist. In addition, all patients underwent blood drawing during the no-heroin withdrawal period.

Twenty-five healthy males were recruited. They were excluded if they had any mental disorder or medical disease. All of the healthy males were free of medication.

All participants signed informed consent after explanation of the study procedures and aims. The study was performed at Kaohsiung Chang Gung Memorial Hospital in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the Institutional Review Board of the hospital (IRB number: 105-4595C).

2.2. Laboratory data

We collected 15-ml blood samples from a forearm vein. The samples were drawn from all participants in a fasting state (fasting for at least 8 h). The blood was allowed to clot at room temperature for 30 min, and the serum samples were immediately separated by centrifugation at 3000g for 10 min. The samples were stored at −80 °C (for 1–3 months) for further analysis and in aliquots to avoid repeated freeze/thaw cycles. Commercially available assay kits were used to perform the assays (enzyme-linked immunosorbent assay: ELISA) for orexin A (MyBioSource, San Diego, USA). All analyses were performed by a senior operator and at the same laboratory.

2.3. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD). Data analysis was performed using analysis of covariance (ANCOVA) with BMI adjustment to evaluate the differences in orexin A between patients and healthy subjects. A p value of less than 0.05 was used to indicate statistical significance. These analyses were performed using SPSS for Windows, version 18.

3. Results

We consecutively recruited 50 HUD male patients undergoing MMT and 25 healthy men. Table 1 shows the demographic data of the HUD patients undergoing MMT (the average dose of methadone was 65.0 ± 26.3 mg per day, the average length of treatment was 47.6 ± 40.0 months, the average number of times for the patients receiving MMT program was 2.1 ± 1.3, and the average age of the patients was 44.8 ± 6.2 years). Table 2 shows the orexin A of HUD patients and healthy controls. The intra-assay and inter-assay coefficient of variation of orexin A was 5.17% and 5.05%, respectively. The duration of MMT means the beginning day of the patient receiving MMT to the day of patient underwent a blood drawing of this study. The duration of MMT is defined as the period from the first day the patient received MMT to the day the patient underwent a blood drawing in this study. The “number of times undergoing the MMT program” refers to how many times the patient underwent the MMT program that was provided by the government at Kaohsiung Chang Gung Memorial Hospital. Undergoing the MMT program is Taiwan policy for HUD patients. If patients do not obey the MMT program rules, they are expelled, but if they want to receive MMT again, they can re-enter the MMT program (participating in the previous MMT program counted as one time; re-entering the MMT program also counted as one time.). Using ANCOVA with BMI adjustment, serum levels of orexin A were significantly higher in HUD patients undergoing MMT than in the healthy subjects (F_{1,75} = 7.287; p = 0.009).

4. Discussion

The most important finding in this study was that HUD men undergoing MMT had significantly higher serum levels of orexin A than the healthy men. To the best of our knowledge, this is the first study investigating serum orexin A levels in HUD patients undergoing MMT. OxIr was found in the ventral tegmental area (VTA), stria terminalis bed nucleus, prefrontal and infralimbic cortex, hippocampus, amygdala, laterodorsal tegmental nucleus/pedunculopontine nucleus, anterior hypothalamus, dorsal raphe and locus coeruleus (Lu et al., 2000; Trivedi et al., 1998). Lateral hypothalamic orexin neurons may drive reward-seeking behavior by exciting VTA OxIr (Esparza et al., 2011; Espana et al., 2010; Richardson and Aston-Jones, 2012). Orexin A could act as OxIr in the VTA to excite VTA dopamine neurons, and then VTA would release dopamine (Baime et al., 2017). In an animal study, addictive drugs targeted the mesocorticlimbic dopamine system originating from the VTA and increased dopamine concentrations in the nucleus accumbens (NAc) (Di Chiara and Imperato, 1988). Morphine might activate the mesolimbic dopamine pathway to affect VTA orexin-neurons, which drives the reward effect (Narita et al., 2006). Orexin A but not orexin B can cross the blood-brain barrier (Kastin and Akersrrom, 1999). During the opiate withdrawal period, opiate addicts had lower median orexin levels than healthy controls (Zhang et al., 2013). In an animal study, heroin increased orexin mRNA levels in the hypothalamus (Zhou et al., 2015), and morphine significantly elevated the orexin A released from the lateral hypothalamic area (Guo et al., 2016). Our data were consistent with those of previous animal studies, in that MMT increased serum orexin A levels in HUD patients. Body weight could influence orexin A levels (Sakurai, 2014b). Therefore, our data were adjusted with BMI. Taken together, our results suggested that MMT might increase orexin A levels in HUD patients.

Our study has several limitations. First, it is still unclear that peripheral orexin A levels can directly reflect central orexin A levels. Second, our study did not have female groups; all patients were male. In an animal study, methadone effects on orexin mRNA levels differed

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 50, male)</th>
<th>Controls (n = 25, male)</th>
<th>ANCOVA adjustment BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>44.8 ± 6.2</td>
<td>46.3 ± 6.2</td>
<td></td>
</tr>
<tr>
<td>Age of the first time heroin use, years</td>
<td>25.5 ± 6.0</td>
<td>25.0 ± 3.5</td>
<td>24.7 ± 3.2</td>
</tr>
<tr>
<td>Methadone dosage in recent one month (mg/day)</td>
<td>65.0 ± 26.3</td>
<td>25.0 ± 3.5</td>
<td>24.7 ± 3.2</td>
</tr>
<tr>
<td>Duration of MMT, months</td>
<td>47.6 ± 40.0</td>
<td>47.6 ± 40.0</td>
<td>47.6 ± 40.0</td>
</tr>
<tr>
<td>Times for receiving MMT program</td>
<td>2.1 ± 1.3</td>
<td>2.1 ± 1.3</td>
<td>2.1 ± 1.3</td>
</tr>
<tr>
<td>Employed</td>
<td>50 (100%)</td>
<td>50 (100%)</td>
<td>50 (100%)</td>
</tr>
<tr>
<td>Smoker</td>
<td>50 (100%)</td>
<td>50 (100%)</td>
<td>50 (100%)</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>44 (88%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HBsAb</td>
<td>25 (50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBs-Ag</td>
<td>6 (12%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Plus-minus values are given as mean ± standard deviation. Abbreviation: HUD = heroin use disorder; BMI = body mass index. *p < 0.05. *F_{1,75} = 7.287; p = 0.009.
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