Cerebrospinal fluid oxytocin correlated with peripheral ALT and AST in Chinese female subjects

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Abstract

OBJECTIVE: Oxytocin (OT) is primarily synthesized in the paraventricular nucleus of the hypothalamus and supraoptic nucleus of the hypothalamus in the central nervous system and exhibits a wide spectrum of central and peripheral activities. OT is involved in lipid metabolism and glucose homeostasis and plays a protective role against liver damage.

METHODS: In this study, we investigated whether CSF OT levels correlates with peripheral glucose, lipid profiles, and/or liver enzymes in Chinese subjects. Sixty-nine subjects (n=36 males; n=33 females) who were recruited from Beijing Jishuitan Hospital participated in the study. Their levels of CSF OT and peripheral parameters were assayed by radioimmunoassay and continuous monitoring assay, respectively.

RESULTS: There was no significant difference in CSF OT levels between males (53.09±6.88 nmol/mL) and females (52.34±6.87 nmol/mL), and no correlation found between CSF OT levels and peripheral glucose and lipid profiles. Significant negative correlation was observed between CSF OT levels and peripheral ALT and AST concentration in females but not in males.

CONCLUSION: Our results support the physiological role of neuropeptides acting on brain sites to regulate liver enzymes, and shed new light on the brain-liver interaction.
INTRODUCTION

The brain and liver are two metabolically active organs that are under constant threat of disease. Abnormal levels of triglycerides and cholesterol combined with increased blood glucose cause damage to the liver and the brain that worsen with time. The interaction between the central nervous system (CNS) and the liver is important to understand, as it modulates mechanisms at work throughout all tissues in the body. Delineating the mechanism of brain interaction with the liver may provide insight into effective preventative or therapeutic measures for all body tissues.

Oxytocin (OT), a neurohypophysial nonapeptide, was named after the “quick birth” characterized by its uterotropic activity. OT exhibits a wide spectrum of central and peripheral activities and has been researched quite extensively (Ludwig 1998; Bergquist & Ludwig 2008). The neuronal pathways giving rise to oxytocin in the cerebrospinal fluid (CSF) and the periphery are anatomically and functionally separate in primates, and the release of oxytocin into the CSF of lactating monkeys is disassociated from release into peripheral circulation (Amico et al. 1990). OT is primarily synthesized in the paraventricular hypothalamus (PVH) in the CNS (Ludwig 1998), then released from magnocellular and parvocellular neurons and into the circulating CSF via somatodendritic mechanism (Knobloch & Grinevich 2014). The PVH is a critical brain region known to control feeding and energy balance (Balthasar et al. 2005; Madden & Morrison 2009) where OT is involved in nutrient metabolism (e.g., lipid metabolism and glucose homeostasis) by increasing glycogenesis and glycolysis (Deblon et al. 2011). OT knockout mice show a selectively enhanced intake of carbohydrates instead of fats (Miedlar et al. 2007); other animal studies have demonstrated that high-dose intracerebroventricular OT injection reduces food intake in a dose-dependent manner (Arletti et al. 1989). OT has been shown to increase heart rate, body temperature, and oxygen consumption in animal studies, as well (Zhang & Cai 2011; Zhang et al. 2011; Yoshida et al. 2009). Peripheral OT infusion affects lipid metabolism and central OT infusion induces lipolysis and fatty acid β-oxidation (Deblon et al. 2011). Food intake has been shown to facilitate OT release in humans and animals (Ohlsson et al. 2002; Verbalis et al. 1986), as it appears that among the hypothalamic OT neurons involved in the control of food intake, those projecting from the PVN to the nucleus tractus solitarii are the most important in terms of mediating the effects of leptin. Lack of OT, in fact, causes rodents to develop obesity.

The liver plays a unique role in nutrient metabolism, including lipid metabolism and glucose metabolism. In healthy individuals, when blood glucose falls and glucagon increases, the liver disintegrates glycogen or synthesizes glucose through gluconeogenesis in order to maintain circulating glucose levels (Barthel & Schmoll 2003). Alanine transaminase (ALT) and aspartate aminotransferase (AST) are enzymes mainly found in liver cells that are commonly monitored as liver damage markers in blood biochemistry assays and are also known to play a role in metabolism. ALT functions in gluconeogenesis and helps catalyze a group of aminos from alanine to alpha-ketoglutarate, making pyruvate and glutamate (Le Couteur et al. 2010).

Studies have confirmed that there is a relationship between OT and liver metabolism or function. In experimental Ischemia-Reperfusion models, OT repressed neutrophil infiltration, controlled the activation of proinflammatory mediators, and played a protective role against remote liver damage (Tas Hekimoglu et al. 2013). A study on the effects of OT on Nili Ravi buffalo revealed significantly higher levels of glucose, total cholesterol, LDL-C, triglycerides, total proteins, C-reactive protein, ALT, and AST in OT-injected lactating buffaloes compared to a control group, demonstrating that OT has a key role in increasing metabolic parameters and hormones to optimize production (Iqbal et al. 2015). Increase in serum cholesterol and triglyceride level due to OT injection results in increased ALT and AST levels, because high cholesterol and LDL-C is a contributing factor for the development of hepatic lipodosis, thus disturbing normal function of the liver (Iqbal et al. 2015). Further, increased peripheral utilization of tissue proteins and increasing cholesterol level may be caused by increased synthetic activity in the liver resulting in the development of fatty liver. Consequently, serum AST and ALT activities are increased during lactation (Greenfield et al. 2000; Iqbal et al. 2013).

As CSF is in direct contact with the CNS and is a reservoir of potential biomarkers reflecting brain biochemistry, any changes in the biochemical composition of brain parenchyma should be predominantly reflected in the CSF. In this study, we explored the central regulating function of OT by investigating the physiological relationship between CSF OT and peripheral glucose, lipid profile, and liver enzymes (including ALT and AST) in healthy Chinese individuals.

MATERIALS AND METHODS

Subjects

Sixty-nine (n=36 males; n=33 females) subjects participated in this study. All study participants were scheduled for spinal anesthesia at Beijing Jishuitan Hospital for lower extremity injuries, unrelated to endocrine diseases, caused by ligament damage or bone fracture below the knee. Participants who had no history of drug abuse or dependence (including alcohol or nicotine)
according to self-report and confirmed by his or her
next of kin were included based on Mini-International
Neuropsychiatric Interview, Chinese version, criteria.
Participants had no family history of psychiatric dis-
orders or neurological diseases, nor systemic or CNS
disease. All of the participants were healthy Chinese
individuals between the ages of 17 to 67 years. This
study was approved by the Institutional Review Board
of Beijing Jishuitan Hospital, and all subjects (or their
guardians) provided informed written consent prior to
participating.

CSF and peripheral blood collection
Lumbar punctures were performed by a licensed anes-
thesist. After spinal anesthesia and before surgery
began, a spinal needle was inserted into the L3/L4 or
L4/L5 interspace and a 5 mL CSF sample was obtained
from each participant, which was then placed in
fractions of 0.5 mL polypropylene tubes and frozen
immediately at –80 °C pending analysis. Five mL
peripheral blood was also obtained from each subject
for serum collection at the same time as the CSF draw.

OT levels in CSF and metabolic
parameters in peripheral blood
CSF OT levels were quantified using a commercial
radioimmunoassay system (Phoenix Pharmaceuticals,
Belmont, CA, USA) according to the manufacturer's
instructions. Ten percent of each CSF sample (0.5 mL)
was assayed in duplicate. Biochemical indexes including
ALT, AST, glucose, HDL, LDL, cholesterol, triglyceride,
APOA1, and APOB were determined using Hitachi
705/717 instrumentation after blood was drawn.

Statistical analysis
Statistical analysis was performed using Pearson cor-
relations for CSF OT levels with peripheral metabolic
parameter concentrations; p<0.05 was considered sta-
tistically significant. All analyses were performed with
GraphPad InStat v6.01 (GraphPad Software, Inc. USA)
or SPSS 19.0 software (Statistical Package for Social
Studies, Chicago, IL, USA).

RESULTS
Cerebrospinal fluid OT levels are not
very variable between individuals
Sixty-nine (males: 36, females: 33, age: 30.87±9.26
years) subjects participated in this study. All partici-
pants’ OT levels were assayed and results respectively
analyzed by gender (Table 1). The Q-Q plot for CSF
OT levels is shown in Figure 1, where the levels showed
no considerable inter-individual variation ranging
from 37.75 to 72.5 pg/mL. No difference in OT levels
between genders was observed. Metabolic parameters,
ALT, and AST concentrations were tested in all partici-
pants and in the two respective gender groups as listed
in Table 1.

### CSF OT correlates with ALT and AST in females
As shown in Table 2, CSF OT levels did not correlate
to serum glucose, total, LDL, or HDL cholesterol, nor
TG, APOA1, or APOB in any subject or either gender.
Significant associations were only observed between
OT levels and ALT and AST concentrations in females.
Pearson correlation results revealed that OT levels
were negatively correlated with ALT concentration
(r=–0.361, p=0.030) and AST concentration (r=–0.363,
p=0.030) in females.

DISCUSSION
In this study, we investigated the physiological relation-
ship between CSF OT and peripheral glucose, lipid
profiles, and liver enzymes in healthy Chinese individ-
uals. The most notable finding was that CSF OT level

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Subjects (69)</th>
<th>Males (n=36)</th>
<th>Females (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>30.87±9.26</td>
<td>29.27±8.53</td>
<td>32.60±9.83</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.07±0.42</td>
<td>5.13±0.41</td>
<td>5.02±0.42</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.30±0.28</td>
<td>1.20±0.20</td>
<td>1.41±0.33</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>2.46±0.51</td>
<td>2.51±0.56</td>
<td>2.39±0.46</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.62±0.82</td>
<td>4.72±0.82</td>
<td>4.51±0.83</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.41±0.83</td>
<td>1.78±0.92</td>
<td>1.02±0.48</td>
</tr>
<tr>
<td>APOA1 (g/L)</td>
<td>1.50±0.19</td>
<td>1.48±0.14</td>
<td>1.52±0.23</td>
</tr>
<tr>
<td>APOB (g/L)</td>
<td>0.87±0.21</td>
<td>0.93±0.22</td>
<td>0.81±0.18</td>
</tr>
<tr>
<td>ALT (IU/mL)</td>
<td>16.56±1.04</td>
<td>20.51±1.58</td>
<td>13.21±1.08</td>
</tr>
<tr>
<td>AST (IU/mL)</td>
<td>17.47±0.71</td>
<td>20.06±1.01</td>
<td>14.88±0.67</td>
</tr>
<tr>
<td>CSF OT (nmol/mL)</td>
<td>52.73±6.83</td>
<td>53.09±6.88</td>
<td>52.34±6.87</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation.

Tab. 1. Demographic data for all participants.

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Subjects (69)</th>
<th>Males (n=36)</th>
<th>Females (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLU</td>
<td>0.166</td>
<td>0.172</td>
<td>0.046</td>
</tr>
<tr>
<td>HDL</td>
<td>−0.025</td>
<td>0.841</td>
<td>−0.045</td>
</tr>
<tr>
<td>LDL</td>
<td>−0.055</td>
<td>0.656</td>
<td>−0.049</td>
</tr>
<tr>
<td>CHO</td>
<td>0.027</td>
<td>0.829</td>
<td>0.000</td>
</tr>
<tr>
<td>TG</td>
<td>0.025</td>
<td>0.843</td>
<td>−0.005</td>
</tr>
<tr>
<td>APOA1</td>
<td>−0.031</td>
<td>0.803</td>
<td>−0.062</td>
</tr>
<tr>
<td>APOB</td>
<td>−0.035</td>
<td>0.777</td>
<td>0.013</td>
</tr>
<tr>
<td>ALT</td>
<td>−0.217</td>
<td>0.092</td>
<td>−0.069</td>
</tr>
<tr>
<td>AST</td>
<td>−0.162</td>
<td>0.198</td>
<td>−0.016</td>
</tr>
</tbody>
</table>

Comparisons between CSF OT levels and parameters and indexes were made using the Pearson correlation. *p<0.05.
The liver is the most important metabolic organ of the body, and is involved in regulating blood glucose, breaking down fat compounds and lipids, and degrading harmful substances and drugs. In clinic, liver function is generally assessed according to levels of ALT and AST, the most sensitive liver enzymes widely used as an indicator of liver injury (Ceriotti et al. 2010). In this study, we found CSF OT level was negatively correlated with peripheral ALT and AST concentrations in female Chinese individuals, but not in males. It is possible that females are more sensitive or prone to liver damage than males, resulting in decreased OT release in the brain. ALT and AST also plays a role in the process metabolism that converts food into energy, and ALT functions as a key enzyme in gluconeogenesis (Le Couteur et al. 2010). This might illuminate the relationship between CSF OT and blood ALT levels on the basis of this study’s results. Simulating the VMH by CSF OT may influence the liver glucose metabolism to promote β-oxidation of fatty acid, the feedback of which may inhibit the gluconeogenesis catalyzed by ALT in healthy individuals – this phenomenon may explain our observation that CSF OT levels are negatively correlated with peripheral ALT concentration. There are different blood glucose kinetics between males and females (Horton et al. 2006), which might explain the observation that CSF OT levels in males were not correlated with peripheral ALT concentration.

OT has been reported to be involved in lipid metabolism and glucose homeostasis. Central OT infusion causes body weight loss in diet-induced obese mice (Deblon et al. 2011), for example, and lack of OT causes obesity in rodents, as the hypothalamic OT neurons are involved in the control of food intake. In this study, we did not find any association between CSF OT and peripheral glucose or lipid profiles, nor any correlation between CSF OT and age either males or females. Parker et al. (Parker et al. 2010) found that CSF OT concentrations are significantly positively correlated with adult female age. But when lactating and non-lactating adult female groups were considered separately, the correlation between CSF OT levels and age was most evident is negatively correlated with peripheral ALT and AST concentrations in Chinese females. No correlation was found between CSF OT and peripheral glucose or lipid profiles.
in lactating rather than non-lactating adult females. In the present study, only non-lactating females were recruited, which may explain the differences between our findings and Parker’s.

There were several limitations in the present study. First, our sample size was relatively small (especially once separated to two groups by gender), so we did not divide groups into different BMI categories. Second, four subjects were under 18 years old (2 females, 2 females) and the age range of the participants was rather large, which likely influenced the results as several of the assessed variables may change with age. Third, we did not measure plasma OT concentrations. Several previous studies have indicated that plasma OT concentration significantly positively predicts CSF OT concentration due to the relationship between peripheral OT concentration and central activity (Carson et al. 2015).

Notwithstanding these limitations, this study represents the first report that CSF OT level is correlated with peripheral ALT and AST concentrations in healthy Chinese females. As such, CSF OT may play a role in regulating ALT and AST levels; this association may be important in terms of the modulating mechanisms of liver enzymes. The findings presented here further support the physiological role of neuropeptides acting on brain sites to regulate liver enzymes, and provides new insight into the brain-liver interaction.

ACKNOWLEDGEMENTS

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Conflict of interest: The authors declare there is no conflict of interest.

REFERENCE


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