Phase-dependent alterations in blood orexin-A levels in methamphetamine users

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Background
Orexin is a neuropeptide that regulate reward circuits and motivated behaviors. Existing literature have revealed increased orexin expression during acute substance withdrawal and decreased expression after long-time abstinence. However, evidence of alteration of orexin expression in people who use methamphetamine (METH) is scant and exploration of this issue could further our understanding of the underlying neurobiological mechanism of METH addiction.

Aims & Objectives
We hypothesized that orexin-A level initially increases after acute exposure to METH but decreases after a long period of abstinence. To test the hypothesis, we designed two studies to explore the changes of serum orexin-A levels among people who use METH during acute and subacute withdrawal separately.

Methods
In study 1, a total of 35 participants with recent abstinence of METH (less than 3 week) and 36 healthy controls were enrolled. Fasting serum orexin levels were measured by enzyme-immunoassay method, and then compared the difference of the orexin levels between METH users and healthy controls. In study 2, 60 METH users were enrolled and divided into 2 groups: (1) acute withdrawal (AW) group (N=20), with the last taken METH within 7 days, and (2) subacute withdrawal (SAW) group (N=40), with the last taken of METH within the preceding 1-2 months. Levels of serum orexin-A in AW group and SAW group at baseline (T1) and 2-week follow up (T2) were measured and compared.

Results
In study 1, METH users had significantly increased orexin levels compared with controls (1.67 ± 0.41 ng/ml v.s 1.45 ± 0.25 ng/ml, P=0.007). In study 2, orexin levels decreased significantly in the SAW group (0.58 ± 0.13 ng/ml v.s 0.50 ± 0.14 ng/ml, p=0.004) but not in the AW group during the 2-week follow up period.

Discussion & Conclusion
In these two studies, we found a significant increased serum orexin level among recent abstinent METH users compared with controls. Furthermore, we found a significant reduction of orexin levels in METH users enduring subacute withdrawal. These findings collectively indicated phase dependent alterations of orexin expression during METH withdrawal. Modulation of orexin system might be a promising target of treating METH use disorder.