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^{1}H-NMR-based metabolomic profiling on serum biochemical profiles after chronic morphine dependence in rats

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Introduction: Opiate abuse lead to the development of tolerance to the depressant effects, upon drug cessation, produces a withdrawal syndrome characterized by motor, autonomic, and affective symptoms (De Vries & Shippenberg, 2002). So, an effective diagnosis and early intervention using reliable biomarker candidates with diagnostic such as serum are needed. The metabolomics have been proven to be a powerful tool for characterizing the pathological states in animals and humans and can present diagnostic information and mechanistic insight into the mental illnesses or neurodegenerative diseases (Bogdanov et al, 2008; Holmes et al, 2006; Paige et al, 2007; Tukiainen et al, 2008). However, the metabolic profiles involved serum in the chronic morphine dependence and tolerance remain to be addressed.

Methods: Rats were given morphine-HCl dose twice per day (08:00 h and 20:00 h) progressively increased from 5 to 40 mg/kg over a period of 14 days. Blood samples from the rats were allowed to clot at 4°C for 60 min. Then all samples were centrifuged (4°C, 3000 rpm, 10 min) to remove any precipitates. And samples were analyzed by 1H NMR.

Results: Firstly, cessation of morphine treatment produced obvious withdrawal signs in rats, including holding the anorexia, quarreling, chattering, holding the abdomen, diarrhea, vomiting. Secondly, the metabolic changes in serum of rats with morphine dependence were explored by using 1H NMR coupled with PLS-DA and OSC analysis. We found that examination of the score contribution plot showed the main signals responsible for separation of the 3 groups in rats were increased concentrations of leucine, glutathione, taurine, glucose, glycine and lysine, and to a lesser extent lipids (LDLs/VLDLs), isoleucine, lactate, NAA, unsaturated lipids and aspartate. When the metabolite levels in withdrawal group compared to the chronic morphine dependence group, serum was characterized by increased levels of lipids (LDLs/VLDLs), isoleucine, NAA, unsaturated lipids and aspartate in rats, and by decreased levels of glutathione in rats.

Conclusions: This study illustrates that the noninvasive approach of metabolic profiling with 1H-NMR spectroscopy can be used not only as a novel diagnostic technique but also as a tool for understanding pathogenesis of morphine dependence. Serum profiling is rapid and minimally invasive, and metabolic biomarkers thus defined have the potential to translate between clinical and laboratory measurements without altering analytical protocols for species differences.

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