Effects of Ketamine and Cannabinoids on Antimicrobial Peptide Expression and Infection Susceptibility: An *In Vitro* and Animal Study

Executive summary

Background: The abuse of ketamine and cannabis has generated serious health concerns worldwide. Studies have shown that ketamine abuse is associated with the syndrome of cystitis. The nature and mechanism of immunomodulation induced by ketamine and cannabis abuse, however, remains obscure, in particular, in aggravating *Staphylococcus aureus* (S. aureus, MRSA) associated pneumonia infection. Thus, there is a need to explore the underlying mechanisms by which ketamine and cannabis mediate immunomodulation in relation to susceptibility to respiratory infection in humans.

Objectives: To determine the effects of ketamine and cannabinoid on increasing *Staphylococcus aureus* lung infection *in vitro* and *in vivo* and investigate the molecular mechanisms by which ketamine and cannabinoid increase susceptibility to *S. aureus* colonization in the lungs.

Methods: This experiment first explored and verified the effects of ketamine and cannabinoid abuse on *S. aureus* lung infection through *in vitro* cell experiments and *in vivo* mouse pneumonia models, and then uncovered the underlying molecular mechanism.

Results: Ketamine and cannabinoid (AEA and CP 55, 940) treatment significantly increased *S. aureus* adhesion and invasion ability in human lung epithelial cell lines *in vitro*. Importantly, ketamine injection significantly deteriorated *S. aureus* colonization and infection in the intranasal pneumonia model via upregulating fibronectin 1 (FN1) and integrin αV gene (ITGAV) expression in the lung *in vivo* and *in vitro*.

Conclusion: Ketamine high doses usage increased the *S. aureus* pulmonary infection levels (both adhesion and invasion) *in vivo* and *in vitro*, and ketamine increased *S. aureus* adhesion infection in the lungs by upregulating FN1 and ITGAV expression. Cannabinoids increased the *S. aureus* invasion infection in human epithelial cells.

Clinical Impact: By clarifying the relationship between ketamine and cannabinoid abuse and pulmonary infection and the possible mechanism, we will promote the general awareness of different sectors of the community about the previously unknown harms of drugs with a view to encouraging and enabling them to play a more active role in drug prevention, early

identification and intervention.