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Brief Report

Decreased Whole Blood RNA Expression of Cathelicidin in HIV-Infected Heroin Users in Bandung, Indonesia

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Abstract

The antimicrobial peptide cathelicidin is critical in killing pathogens by innate immune cells, including *Mycobacterium tuberculosis* and *Candida albicans*. These pathogens often cause infections in opioid users, a risk that is greatly increased with concurrent human immunodeficiency virus (HIV) infection. Therefore, we examined the association between opioid use and cathelicidin in HIV-infected subjects from Bandung, Indonesia. The following three groups of HIV-infected individuals were included: (i) Active drug users: used heroin in the last 30 days; (ii) Methadone clients: received methadone maintenance therapy in the last 30 days; and (iii) Controls: never used opioids or did not use opioids in the year preceding inclusion. In addition to interviews, blood samples were taken to examine the RNA expression of cathelicidin. We found that the RNA expression of cathelicidin was significantly decreased ($p = 0.007$) in heroin users, compared with controls. Opioids are associated with immunosuppression, and cathelicidin could be an important factor in this association. However, more research is needed to examine the direct effects of decreased cathelicidin levels.

Introduction

Injecting drug use is a global health problem and studies have shown that injecting drug users are more susceptible to infections, which are the major cause of hospitalization and morbidity (22). On average, one in five injecting drug users is infected with the human immunodeficiency virus (HIV), among whom tuberculosis is a prevalent illness (27). The increased incidence of HIV and blood-borne diseases is caused by high risk behavior, such as using dirty needles and unsafe sex. In addition, the elevated risk of other infections, such as tuberculosis, is associated with increased exposure to pathogens and is usually attributed to social determinants, such as use of tobacco and alcohol, homelessness, and incarceration (6,16). Biological aspects related to drug use may also play a role, as opioids have immunosuppressive effects (24,25). Opioids can affect the innate and adaptive immune response, either directly by binding opioid receptors on immune cells or indirectly by modulating the hypothalamo-pituitary-adrenal axis (1), which deregulates the production of immunosuppressive hormones.

Chronic opioid use is associated with diminished vitamin D, which is at least partly due to the overall behavior of addicted individuals (13). In addition, HIV infection is known to cause nutritional deficiencies, such as a diminished vitamin D (10,20). Vitamin D deficiency has been linked to a wide range of diseases (28), and it is able to modulate the innate immune response by upregulation of antimicrobial peptides (AMPs) (30). Cathelicidins are a large family of AMPs and the only human cathelicidin LL-37/hCAP-18 is regulated by the biologically active form of vitamin D: ($1,25(OH)_2D_3$) (7,30). Cathelicidin targets inflammatory pathways, and it forms an important link between the innate and adaptive immune system. It can modulate the innate immunity, activate different cell types, induce chemotaxis, and support cytokine secretion (17,32).

Previous studies have shown a strong relationship between the expression of cathelicidin and the occurrence of infections. In cathelicidin knockout mice, infections of cornea, gastrointestinal tract, and skin are frequently seen (11,12,18). In addition, humans who suffer from cathelicidin deficiency are more susceptible to periodontal diseases (21), respiratory tract infections (14,15), and candidiasis (8). Interestingly, these infections are very common among drug users, especially among those infected with HIV. Therefore, we hypothesize that the expression of cathelicidin is downregulated in opioid

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