News Release

Title

Xanthine oxidase inhibition by febuxostat attenuates stress-induced hyperuricemia, glucose dysmetabolism, and prothrombotic state in mice

Key Points

- ○ Two-week daily restraint stress evoked lipolysis-induced low-grade inflammation in lean murine visceral adipose tissue (VAT), resulting in reduced insulin sensitivity and induction of plasminogen activator inhibitor-1 and tissue factor in VAT.
- ○ Restraint stress upregulated expression and activity of xanthine oxidoreductase (XOR), and accumulation of reactive oxygen species (ROS) in VAT, liver, and intestine, resulting in an increase in serum uric acid levels.
- ○ Treatment with febuxostat, a potent XOR inhibitor, suppressed stress-induced ROS production and VAT inflammation, resulting in improvement of serum UA levels, insulin sensitivity, and prothrombotic tendency.
- ○ Our results suggest that stress perturbs glucose and UA metabolism, and promotes prothrombotic status, and that XOR inhibition by febuxostat might be a potential therapy for stress-related disorders.

Summary

Graduate student Maimaiti Yisireyili, Professor Toyoaki Murohara (Department of Cardiology, Nagoya University Graduate School of Medicine, Dean Kenji Kadomatsu), Professor Tadashi Matsushita (Departments of Clinical Laboratory and Blood Transfusion, Nagoya University Hospital, Director; Naoki Ishiguro), Professor Toshimitsu Niwa (Shubun University, President), and Kyosuke Takeshita (Department of Clinical Laboratory, Nagoya University Hospital, Department of Cardiology, Nagoya University Graduate School of Medicine)found that mental stress activates xanthine oxidoreductase (XOR) in visceral adipose tissue (VAT), liver and intestine to increase serum uric acid levels in a murine restraint stress model. In the present study, 2-week intermittent restraint stress induced simultaneous increase in plasma uric acid levels and ROS generation downstream of XOR activation in VAT, liver and intestine. The stress-induced ROS generation augmented NOX subunits and reduced antioxidant enzyme activities in VAT. In addition, stress induced lipolysis and adipose tissue inflammation, decreased insulin sensitivity, and prothrombotic state, confirming the results of previous studies. Thus, febuxostat suppressed stress-induced lipolysis, adipose inflammation and ROS production, resulting in restoration of glucose and uric acid metabolism, and reduced thrombotic tendency.

Research Background

Chronic stress is closely linked to the metabolic syndrome, diabetes, hyperuricemia and thromboembolism, but the mechanisms remain elusive. We reported recently that stress targets visceral adipose tissue (VAT), inducing lipolysis, low-grade inflammation with production of inflammatory adipokines, metabolic derangements such as insulin resistance, and prothrombotic state.

Research Results

In the present study, we hypothesized the involvement of VAT xanthine oxidoreductase (XOR), a source of reactive oxygen species (ROS) and uric acid (UA) in the above processes. Restraint stress in mice resulted in upregulation of XOR and xanthine oxidase activity, accumulation of ROS in VAT as well as liver and intestine, increase in serum UA levels, upregulation of NADPH oxidase subunits and downregulation of antioxidant enzymes. Immunohistochemistry and RT-PCR analysis also showed that restraint stress induced VAT monocyte accumulation and proinflammatory adipokine production, resulting in reduced insulin sensitivity and induction of plasminogen activator inhibitor-1 and tissue factor in VAT. Treatment with febuxostat, a potent XO inhibitor, suppressed stress-induced ROS production and VAT inflammation, resulting in improvement of serum UA levels, insulin sensitivity, and prothrombotic tendency.

Research Summary and Future Perspective

Our findings suggest that febuxostat inhibits stress-induced XOR activation to suppress VAT inflammation, and rectifies disorders of uric acid and glucose metabolism, and prothrombotic state. XOR inhibition by febuxostat might be a potential therapy for stress-related disorders.

Publication

Maimaiti Yisireyili, Motoharu Hayashi, Hongxian Wu, Yasuhiro Uchida, Koji Yamamoto, Ryosuke Kikuchi, Mohammad Shoaib Hamrah, Takayuki Nakayama, Xian Wu Cheng, Tadashi Matsushita, Shigeo Nakamura, Toshimitsu Niwa, Toyoaki Murohara, and Kyosuke Takeshita "Xanthine oxidase inhibition by febuxostat attenuates stress-induced hyperuricemia, glucose dysmetabolism, and prothrombotic state in mice"
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Japanese ver.

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