

News Release

Title

Angiotensin receptor blocker irbesartan reduces stress-induced intestinal inflammation via AT1a signaling and ACE2-dependent mechanism in mice.

Key Points

- Two-week daily restraint stress activated the classical renin-angiotensin system (RAS) to evoke intestinal inflammation in mice.
- Stress altered tryptophan metabolism and the composition of gut microbiota in the downstream of the RAS activation and decrease in an intestinal amino acid transporter, ACE2 / B⁰AT-1.
- Irbesartan, an angiotensin receptor blocker, inhibited the RAS activation and restored ACE2 expression to suppress stress-induced intestinal inflammation.
- The RAS is a potent target of stress-induced intestinal inflammation in a murine model of irritable bowel syndrome.

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) and Kyosuke Takeshita (Department of Clinical Laboratory, Nagoya University Hospital, Department of Cardiology, Nagoya University Graduate School of Medicine) found that mental stress activates the classical renin-angiotensin system (RAS) in intestine to evoke intestinal inflammation and perturbation in brain-gut axis in mice.

In the present study, 2-week intermittent restraint stress induced colon inflammation with higher histological damage scores, increased expression of Nox4, TLR-4 and IL1- β , accumulation of reactive oxygen species (ROS), and activation of the ACE-angiotensin II-AT1 receptor axis. Stress also downregulated intestinal amino acid transporter, ACE2/B⁰AT-1, and activity of intestinal mammalian target of rapamycin (mTOR) and p70 S6 kinase (p70S6K), resulting in decrease in α -defensins, changes in intestinal microbial contents, and perturbation of tryptophan metabolism with activation of the kynurenine pathway. Administration of irbesartan inhibited activation of stress-induced AT1 pathway to reduce intestinal ROS accumulation and inflammation, restored expression of ACE2/B⁰AT-1, activity of mTOR and p70S6K, dysbiosis and tryptophan metabolism. Our results suggest that AT1 is a potentially suitable therapeutic target in stress-induced intestinal inflammation, and that irbesartan could be beneficially suitable for the treatment of stressed patients with irritable bowel syndrome.

Research Background

Stress is associated with pathophysiology of both irritable bowel syndrome (IBS) and hypertension. Angiotensin receptor blockers (ARB) have anti-inflammatory properties via inhibition

of angiotensin II (Ang II)/Ang II type I receptor axis (AT1). Inhibition of the classical RAS pathway is also involved in upregulation of angiotensin converting enzyme-2 (ACE2), which activates the Ang-(1-7) /Mas pathway to counteract inflammatory signaling and acts as a partner of the amino acid transporter, B⁰AT-1, to absorb tryptophan for regulation of microbiota-gut-brain axis.

Research Results

In this study, we determined the effects of ARB irbesartan on stress-induced intestinal inflammation. C57BL/6J mice were subjected to 2-week intermittent restraint stress. They were orally treated during the stress with either vehicle, 3 or 10 mg/kg/day irbesartan. Restraint stress resulted in colon inflammation with higher histological damage scores, increased expression of Nox4, TLR-4 and IL1- β , accumulation of reactive oxygen species (ROS), and activation of the ACE-angiotensin II-AT1 receptor axis. Stress also downregulated intestinal amino acid transporter, ACE2/B⁰AT-1, and activity of intestinal mammalian target of rapamycin (mTOR) and p70 S6 kinase (p70S6K), resulting in decrease in α -defensins, changes in intestinal microbial contents, and perturbation of tryptophan metabolism with activation of the kynurenine pathway. Administration of irbesartan inhibited activation of stress-induced AT1 pathway to reduce intestinal ROS accumulation and inflammation, restored expression of ACE2/B⁰AT-1, activity of mTOR and p70S6K, dysbiosis and tryptophan metabolism.

Research Summary and Future Perspective

Our results suggest that AT1 is a potentially suitable therapeutic target in stress-induced intestinal inflammation, and that irbesartan could be beneficially suitable for the treatment of stressed patients with IBS.

Publication

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