Acute induction of psoriasis-like skin inflammation disturbes vascular tone and provokes a rapid blood pressure response in mice

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Background: Psoriasis is the most common chronic skin disease worldwide. Furthermore, it is an independent cardiovascular risk factor. Several genetic and inducible murine models reproduce specific aspects of the human disease. In mice genetically overexpressing IL-17A in keratinocytes or dendritic cells, we coulod show both aspects of the disease: cutaneous hallmarks and the vascular phenotype. The most popular inducible model consists of topical application of Imiquimod (IMQ), a Toll-like receptor 7/8 agonist. In this model, cardiovascular aspects have not been studied yet. Therefore, we examined vascular and hemodynamic effects in this most popular murine psoriasis model.

Methods: C57BL/6J mice were treated with 5% IMQ or sham cream. During treatment, we measured bodyweight, skin thickness and skin water loss. After 10 days, aortic relaxation studies were performed. For assessment of vascular inflammation, inflammatory cell infiltration into the aortic tissue was investigated by flow cytometric analysis. To record physical activity, blood pressure and heart rate, carotid catheters were implanted two weeks before treatment with IMQ. Blood pressure and heart rate were continuously recorded by receiver platforms.

Results: IMQ treatment resulted in severe skin inflammation and induced a skin barrier defect resulting in a 7-fold increase of transcutaneous water loss (from 11±6 ml/m^{2}h to 77±30 ml/m^{2}h). Physical activity decreased more than 50% after d1 of treatment and normalized at d7. Telemetric recording revealed a reflex tachycardia at 1d of IMQ-application (from 492±21 bpm to 524±20 bpm) followed by a significant reduction of heart rate for the next two days (456±18bpm). Systolic blood pressure showed a similar trend: after a fast increase (from 120±13 mmHg to 127±18 mmHg), blood pressure dropped below baseline at d2/3 with a subsequent recovery. We could display a highly significant positive correlation between blood pressure and heart rate during the treatment (R=0.6; $p \leq 0.0001$). Aortas from animals after 10d of IMQ-treatment showed an increased infiltration of CD45+ and CD11b+ inflammatory cells but no change of responsiveness to endothelium dependent and independent vasodilators in organ chamber studies.

Conclusion: Skin treatment with IMQ had severe implications on the hemodynamic system: After an initial peak of heart rate and blood pressure, mice showed significantly lower values for two days with a subsequent full recovery. Moreover, bodyweight and physical activity were significantly altered during treatment. Our data indicate that skin inflammation and inflammatory skin barrier disruption by IMQ forces a compensatory whole-body response. 10 days of IMQ-treatment resulted in vascular inflammation without mediating vascular dysfunction. In summary, we could reveal that IMQ-induced psoriasis, as the most popular murine psoriasis model worldwide, has extensive effects on the cardiovascular system.

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