11 **ROLE OF PROSTAGLANDINS IN THE INFLAMMATORY REFLEX: IMPAIRED VAGUS-MEDIATED IMMUNOSUPPRESSION IN MICE DEFICIENT IN MICROSOMAL PROSTAGLANDIN E SYNTHASE-1 (MPGES-1)**

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Introduction The cholinergic anti-inflammatory pathway (ie, inflammatory reflex) comprises an important neuro-immune link whereby inflammation such as arthritis can be tightly controlled by the autonomic nervous system and the vagus nerve (VN). Prostaglandins are known to mediate central effects in neurotransmission, by modulating glial interaction with neurons. Therefore, the authors have investigated the role of prostaglandins, including the major prostaglandin E_2 producing enzyme mPGES-1, in the cholinergic anti-inflammatory pathway.

Material and methods Knock-out mice for the mPGES-1 enzyme (-/-) have been used for the study, with comparison to wild-type (+/+) animals. After VN isolation, the authors injected intraperitoneally lipopolysaccharides (LPS, 2 mg/kg). The authors then electrically stimulated the VN for 5 min. After a recovery of 6 h, mice were killed and blood was collected. Tumour necrosis factor α (TNF α), IL-1 β and other pro-inflammatory cytokines were measured using the meso scale discovery (MSD) instrument. In addition, the authors evaluated the effect of PGE $_2$ on the release of cytokines in vitro, using peripheral blood monuclear cells (PBMC) stimulated by LPS. Supernatants were analysed for TNF α concentration with ELISA.

Results After vagus nerve stimulation (VNS) and analysis of the serum, wild-type animals showed a decrease of the release of TNF α (62.6 $\pm$ 8.5 with VNS vs 90.3 $\pm$ 9.1 pg/ml without VNS; $p<0.05$), IL-1 β (70.5 $\pm$ 11.0 vs 114.0 $\pm$ 15.6 pg/ml; $p<0.05$), IL-12p70 (16,521.9 $\pm$ 2014.6 vs 25,762.4 $\pm$ 2494.6 pg/ml; $p<0.01$) and IFN γ (173.5 $\pm$ 38.7 vs 454.6 $\pm$ 111.9; $p<0.05$). All other cytokines measured with the MSD kit did not differ from the respective controls (ie, IL-2, IL-4, IL-5, IL-10, KC/GRO). Interestingly, VNS had no effect on any of the cytokines measured on serum from the knock-out mice. On in vitro studies, incubation with PGE $_2$ (1 μ M) was shown to inhibit the release of TNF α by PBMC after LPS stimulation from 375.1 $\pm$ 73.7 to 45.5 $\pm$ 22.1 pg/ml ($p<0.01$).

Conclusion Our data indicate that mice deficient in mPGES-1 do not respond to vagus-mediated immunosuppression. These results implicate an involvement of PGE $_2$ in the cholinergic anti-inflammatory pathway and provide support for further investigations regarding the interaction between cholinergic and prostaglandin systems.