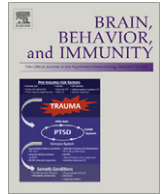




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journal homepage: www.elsevier.com/locate/ybrbiSympathetic inhibition of IL-6, IFN- γ , and KC/CXCL1 and sympathetic stimulation of TGF- β in spleen of early arthritic mice [☆]Rainer H. Straub ^{*}, Luise Rauch, Lena Rauh, Georg Pongratz

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ABSTRACT

Objectives: The connection between sympathetic nerve fibers and immune cells in the spleen is known. In the context of arthritis, the functional meaning of the neuroimmune contact remains unclear. From immunization until disease outbreak, the sympathetic nervous system (SNS) has a proinflammatory influence which is converted into an anti-inflammatory influence after disease outbreak. This study investigated the influence of neuronally released neurotransmitters on IFN- γ , KC (CXCL1), IL-6, and TGF- β in spleen of mice shortly after outbreak of collagen type II-induced arthritis.

Methods: Spleens were removed when animals reached an arthritis score of 3 on a scale of 1–16 (approx. on day 32) in order to generate 0.35 mm-thick spleen slices. Spleen slices were transferred to superfusion microchambers in order to electrically induce release of sympathetic neurotransmitters. By means of this technique, the effect of physiologically released neurotransmitters was investigated on secretion of IFN- γ , KC, IL-6, and TGF- β .

Results: High amounts of IFN- γ , KC, IL-6, and TGF- β were released from superfused spleen, and electrical stimulation markedly inhibited IFN- γ , KC, and IL-6 release but pronouncedly stimulated TGF- β . The adrenergic influence via β -adrenoceptors stimulated release of IL-6 and, particularly, TGF- β . However, catecholamines inhibit release of IL-6 via α 1-adrenergic pathways but without any effect on TGF- β . The co-transmitter adenosine stimulated IL-6 release via A1-adenosine receptors but no influence was recognized on TGF- β .

Conclusion: At disease outbreak, electrically released endogenous neurotransmitters of the SNS inhibit IFN- γ , KC, and IL-6 but β -adrenergically stimulate TGF- β . This creates an anti-inflammatory milieu that might be responsible for the observed dual influence of the SNS on arthritis.

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1. Introduction

In experimental arthritis models, the sympathetic nervous system (SNS) has a proinflammatory influence in the immunization phase and until outbreak of the symptomatic disease (Härle et al., 2005; Levine et al., 1985; Lorton et al., 1999). The proinflammatory support depends on several distinct mechanisms: (1) mobilization of immune cells from systemic stores (Dhabhar and McEwen, 2007), (2) support of plasma extravasation (Miao et al., 1996), (3) remodeling of tissue by inducing matrix metalloproteinases (Speidl et al., 2004; Spiegel et al., 2007), (4) stimulation of nociceptors via α 2-adrenergic and prostaglandin cross-signaling (Chen et al., 1996; Gonzales et al., 1989), and (5) chemoattractant activity of sympathetic neurotransmitters (Straub et al., 2000b). In contrast, in later symptomatic phases of arthritis, there might be

some important anti-inflammatory influences via newly discovered catecholaminergic pathways (Capellino et al., 2010; Härle et al., 2005). Thus, there exists a transition phase between asymptomatic and later symptomatic phases of the disease but contrasting mechanisms still remain largely unexplained.

In order to shed some light on underlying mechanisms, we started to investigate the neuroimmune contact in the spleen of arthritic animals in the early phase of symptomatic collagen type II-induced arthritis (CIA) (Straub et al., 2008). It demonstrated β -adrenergic stimulation and α 1-adrenergic inhibition of splenic interferon- γ (IFN- γ) secretion in the early phase of arthritis (Straub et al., 2008). In these experiments, a superfusion technique was developed to investigate the crosstalk between sympathetic nerve fibers and splenic immune cells (Straub, 2004; Straub et al., 2008). This technique opens an investigative window to scrutinize the local pro- or anti-inflammatory milieu in the spleen of arthritic mice at any desired time point during the course of the disease.

In the recent work, we were interested in further investigating the inflammatory milieu at an early stage of CIA that can affect later chronic stages (programming effect). The focus went from

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