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Acute inflammation in the joint: Its control by the sympathetic nervous system and by neuroendocrine systems

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ABSTRACT

Inflammation of tissues is under neural control involving neuroendocrine, sympathetic and central nervous systems. Here we used the acute experimental inflammatory model of bradykinin-induced plasma extravasation (BK-induced PE) of the rat knee joint to investigate the neural and neuroendocrine components controlling this inflammation. 1. BK-induced PE is largely dependent on the sympathetic innervation of the synovium, but not on activity in these neurons and not on release of norepinephrine. 2. BK-induced PE is under the control of the hypothalamo-pituitary–adrenal (HPA) system and the sympatho-adrenal (SA) system, activation of both leading to depression of BK-induced PE. The inhibitory effect of the HPA system is mediated by corticosterone and dependent on the sympathetic innervation of the synovium. The inhibitory effect of the SA system is mediated by epinephrine and β_2-adrenoceptors. 3. BK-induced PE is inhibited during noxious stimulation of somatic or visceral tissues and is mediated by the neuroendocrine systems. The nociceptive–neuroendocrine reflex circuits are (for the SA system) spinal and spino-bulbo-spinal. 4. The nociceptive–neuroendocrine reflex circuits controlling BK-induced PE are under powerful inhibitory control of vagal afferent neurons innervating the defense line (connected to the gut-associated lymphoid tissue) of the gastrointestinal tract. This inhibitory link between the visceral defense line and the central mechanisms controlling inflammatory mechanisms in body tissues serves to co-ordinate protective defensive mechanisms of the body. 5. The circuits of the nociceptive–neuroendocrine reflexes are under control of the forebrain. In this way, the defensive mechanisms of inflammation in the body are co-ordinated, optimized, terminated as appropriate, and adapted to the behavior of the organism.

1. Introduction

Inflammation is characterized by increased blood flow and vascular permeability, attraction of leukocytes and sensitization of primary afferent neurons. While the inflammation provides a protective response against infection and injury, it constitutes a positive feedback cascade that, if left unregulated, can result in tissue injury. For example, while approximately 50% of acute inflammatory arthritis/synovitis is self-limiting, resolving after ~12 months (Inaoui et al., 2004), persistent chronic synovial inflammation leads to joint destruction and the development of rheumatoid arthritis.

The autonomic nervous system regulates physiological systems by integrating afferent inputs from the internal and external environments with neuronal, endocrine and cell-mediated responses to maintain physiological homeostasis (Jänig, 2006). A key role of the autonomic system is the regulation of acute inflammatory responses at local and systemic levels. Multiple integrated mechanisms exist to maintain or to limit the magnitude of inflammation, involving the hypothalamo-pituitary–adrenal and sympatho-adrenal axes (③ and ④ in Fig. 1), afferent nociceptive neurons with unmyelinated (C-) fibers or small diameter myelinated (δ-) fibers (② in Fig. 1), and the sympatho-neural system (① in Fig. 1). These neural and neuroendocrine systems are orchestrated by the brain (spinal cord, brain stem and higher centers; see ⑥ to ⑧ in Fig. 1) and powerfully modulated by processes in the visceral body domain via vagal afferent neurons (⑤ in Fig. 1).

This topical review will summarize an integrated system, involving sympathetic, neuroendocrine, spinal and vagal sensory and central nervous systems, that acts in the control of an acute experimental inflammatory response in the rat knee joint. This close interaction between the nervous system, neuroendocrine and immune systems regulates peripheral inflammatory responses and may provide a link (1) to understand the mechanisms underlying the control of protective inflammatory processes by the brain under physiological conditions and (2) to understand this regulation in inflammatory diseases under pathophysiological conditions, e.g. chronic inflammation. We will use the experimental in vivo model of acute bradykinin-induced plasma extravasation (BK-induced PE) of the synovium in the rat knee joint to dissect out the neural and neuroendocrine components that are involved.

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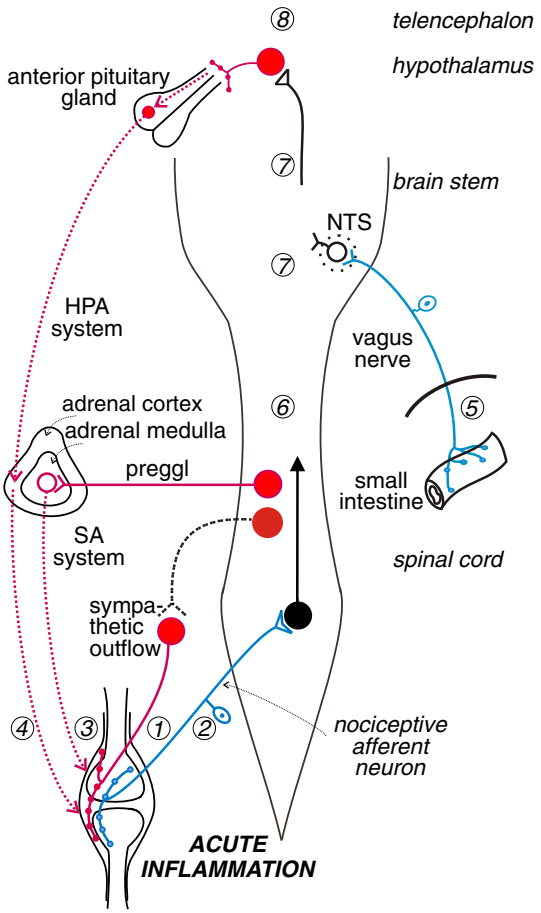

Fig. 1. Neural and neuroendocrine systems involved in bradykinin-induced plasma extrasasation of the synovia (acute knee joint inflammation): ① sympathoneural system; ② peptidergic afferent system; ③ sympathoadrenal (SA) system; ④ hypothalamo-pituitary–adrenal (HPA) system; ⑤ subdiaphragmatic vagal afferent system; ⑥, ⑦ neural circuits in spinal cord, brain stem and hypothalamus; ⑧ telencephalic control.

2. Peripheral mechanisms

2.1. Bradykinin-induced synovial plasma extravasation as a model

The joint synovium is a dynamic environment in which synovial fluid is continuously secreted to maintain normal joint function. Inflammatory stimuli in the synovium increase vascular permeability. This secretion occurs at the venular site of the synovial vascular bed; it is essential for adequate functioning of the joints and finely adjusted to the joint activity. Decreased secretion of synovial fluid leads to damage of joints and finally to arthrosis; increased synovial secretion occurs during synovial inflammation and also leads to a restriction of joint function.

We have used an in vivo model system in the anesthetized rat (pentobarbital, 60 mg/kg intraperitoneally) to study the inflammatory response by measuring vascular permeability in the synovium. Perfusion of the synovia-lined joint cavity with the inflammatory mediator bradykinin produces a dose-dependent enhancement of synovial plasma extravasation by increasing vascular permeability of the post-capillary venules resulting in extravasation of plasma proteins (Fig. 2A). With continuous perfusion of bradykinin through the synovium, a stable level of plasma extravasation can be maintained for hours.

After incision of the skin and connective tissue overlying the anterior aspect of the knee and the saphenous vein, Evans blue dye (50 mg kg^{-1}) is administered intravenously in the saphenous vein. Evans blue dye binds stoichiometrically to serum albumin and does not normally leave the vascular space. It serves as a marker for extravasated plasma proteins. Ten minutes after injection of the dye, a 30-gauge needle is inserted into the cavity of the knee joint for the continuous infusion of fluid (250 μl min^{-1}). After infusion of an initial volume of 100–200 μl of vehicle, a second needle (25-gauge) is inserted into the knee joint, approximately 3 mm from the inflow needle. This second needle serves as an outflow cannula (Fig. 2A). Fluid is withdrawn from the joint through the outflow cannula using a second syringe pump. The fluid is infused and withdrawn at a constant rate of 250 μl min^{-1}. Perfusate samples are collected every 5 min for up to 120 min. Samples are analyzed for the amount of Evans blue dye by spectrophotometric measurement of absorbance at a wavelength of 620 nm. The absorbance at this wavelength is linearly related to the dye concentration (Carr and Wilhelm, 1964) and therefore to the degree of plasma extravasation of the synovium (see ordinate scale in Fig. 2B). After a baseline perfusion period of 15 min with vehicle (saline), plasma extravasation into the knee joint is stimulated by adding bradykinin (160 ng ml^{-1}, i.e., 150 nM) to the perfusion fluid (Miao et al., 1996a). The concentration of bradykinin in various inflamed tissues is in the range of 10^{-8}–3×10^{-7} M (Hargreaves et al., 1993; Swift et al., 1993).

2.2. The involvement of the sympathetic innervation in the control of resting plasma extravasation and bradykinin-induced plasma extravasation

The synovium is innervated by both postganglionic sympathetic fibers and afferent C-fibers. Sympathetic postganglionic fibers constitute between half and two-thirds of the nerve fibers in the synovium (Hildebrand et al., 1991). These postganglionic fibers, which are closely associated with synovial blood vessels (Mapp et al., 1990), are involved in control of blood flow related to the joint including synovium and in control of synovial fluid secretion. Whether the terminals of sympathetic fibers are specifically arranged around the venules of the synovial vasculature is unknown (Eitner and Schaible personal communication). Resting and BK-induced PE are not dependent on the innervation of the joint capsule by unmyelinated afferent fibers (Coderre et al., 1989, see later) but about 60% of BK-induced PE is dependent on the innervation of the synovium by sympathetic post-ganglionic nerve fibers. Both resting and BK-induced PE are significantly reduced 7 to 14 days after surgical sympathectomy (Figs. 2D, and 3) (Miao et al., 1996a; Green et al., 1997).

Transecting the preganglionic axons, to acutely or chronically decentralize the lumbar sympathetic ganglia that contain the cell bodies of the postganglionic neurons to the rat hindlimb, does not significantly change the BK-induced PE in the knee joint capsule (Fig. 2D green). Similarly, acute interruption of the lumbar sympathetic chains during ongoing BK-induced PE does not reduce this plasma extravasation. Furthermore, blockade of conduction of the postganglionic terminals in the synovia by intraarticular co-perfusion of tetrodotoxin does not reduce the resting plasma extravasation and the BK-induced PE. Finally, increased synovial plasma extravasation by intraarticular perfusion of platelet activating factor, which acts directly on the endothelium, does not change after sympathectomy (removal of the paravertebral ganglia 4 or 14 days before the experiments). As expected, activation of the sympathetic postganglionic neurons by electrical stimulation of the lumbar sympathetic chain at frequencies of 0.2 to 5 Hz reduces both resting and BK-induced PE as well as plasma extravasation during infusion of platelet activating factor because the blood flow through the synovium is reduced (Miao et al., 1996a).

Quantitative analysis of the synovial plasma extravasation generated by different concentrations of bradykinin in the perfusate shows that the sympathetically mediated component is particularly large at bradykinin concentrations which have been measured in inflamed tissues (between 10^{-8} and 3×10^{-7} M [black bar in Fig. 3]; Hargreaves et al., 1993; Swift et al., 1993) and almost undetectable at higher (pharmacological) concentrations ($\geq 10^{-6}$ M) as shown by Cambridge and Brain (1995), probably because bradykinin also acts directly on the endothelial cells at these high concentrations and because this direct endothelial