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Review Article

Plasma Urate and Neurodegenerative Disease

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Abstract

Diminished levels of urate have been linked to oxidative stress in birds and mammals. Urate, a major antioxidant that lowers reactive oxygen/nitrogen species (ROS/RNS), ameliorates these effects. Recent studies have proposed that an increased permeability in the intestine due to some insult can induce inflammation in peripheral organs such as the brain. Allopurinol, a relatively toxic purine analogue that serves as a xanthine oxidase inhibitor, reduces urate levels which can subsequently induce an inflammation state in the intestine. Recent studies have implicated that the intestinal permeability can be with linked with CNS dysfunction, which include Parkinson's, Alzheimer's, autism, schizophrenia, multiple sclerosis, depression, anxiety, and post-traumatic stress disorder. However, the relationship between reduced urate, the immune system and the pathogenesis of the intestine, the liver or the brain has not been well characterized in avians. The elevated body temperatures of birds may accentuate the pathogenesis of complications induced by allopurinol and so may be a model for future studies investigating neurodegenerative disease progression.

INTRODUCTION

Urate is synthesized the liver, intestines and the vascular endothelium as a product of an exogenous pool of purines [1]. Urate can also be produced endogenously by damaged, dying or dead cells; where nucleic acids, adenine, and guanine, are degraded into urate to act as damage-associated molecular patterns [1], [2]. This biomolecule conventionally generates concerns due to acute and chronic inflammatory arthritis, gout, and other metabolic diseases [1], [3]. However, it is also thought to have a dual role and serve by inducing a type 2 immune response [1], [2], [4]. The inhibition of urate production can elucidate the protective potential by observing how lowered urate concentrations alter immunological function in several organs [5], [6]. Several studies have indicated how the intestinal environment can exert profound effects on the liver and central nervous system through the regulation of the microbiota and the intestinal barrier function [7]. This gut-brain connection is becoming a model of immune activity with a fundamental contribution towards neurodegenerative disorders [7]. These studies indicate that inflammation in the intestine appears to be particularly relevant in the disease pathogenesis. Studies have shown that urate serves as a potent scavenger of singlet oxygen, peroxyl radicals and hydroxyl radicals [6]. Elevated urate concentrations in the circulation helps to protect cells by scavenging these free radicals which then prolongs the organism's life [6], [8]. Living systems have adapted to regulate free radicals by developing pathways to inactivate these reactive species such as oxygen and nitrogen, which induce tissue injury [6], [9]. Allopurinol, a toxic purine analog, serves as a xanthine oxidase inhibitor which reduces urate concentrations; which can induce a type I inflammation state in the intestine and brain of birds [3]. Changes in the compositions of the bacterial populations in the intestines have also been widely associated with an array of conditions that can cause neurological and developmental disorders such as multiple sclerosis, autism, depression, schizophrenia, and Parkinson's disease [4], [7]. Shifts in intestinal microbiota can alter concentrations of growth factors and signaling proteins in the brain, which contributes to inflammation and functional changes in the neurological remodeling [5]. Among the roles for gut bacteria are the conversion of primary bile acids produced by the liver to secondary bile acids which then are absorbed through the intestinal epithelium [7]. Moreover, bile acids can also act as potent signaling molecules that regulate a variety of processes related to both the nervous and immune systems. A detailed look into the effects of allopurinol on the early recognition and effector response by the immune system in the intestines could elucidate how these responses affect the liver and brain [4], [7]. Metabolites generated from intestinal microbes such as those described here have also been reported to alter host gene expression in the brain, providing ways for the microbiota to influence the activity of the CNS [4], [7]. Thus, the administration of allopurinol can potentially evoke strong type 1 immune reactions via IL-6 by altering the intestinal environment and induce effects that ultimately alter CNS function.

The Immune System and The Urate Paradox

A vast amount literature shows an elevated level of urate is strongly associated with inflammatory diseases such as hypertension, cardiovascular and cerebrovascular events [2], [3], [10]. While urate accounts for over half of the free radical scavenging activity in blood [8], it can also reduce the oxidative

stress implicated in several neurodegenerative diseases. Antioxidant activities of urate can quench superoxide and singlet oxygen and protecting oxidation of vitamin C through the chelation of iron [6], [11]. These qualities make urate an attractive CNS antioxidant because neurons are remarkably susceptible to oxidative stress. In multiple sclerosis, free radicals can contribute to the inflammation and demyelination of axons [10], [12]. Thus, preventing oxidative damage may delay onset and improve the prognosis of CNS disorders [10]. The ratio of reactive species over antioxidants determine the shift from their advantageous function to detrimental effects [11]. The major source of these reactive species that become detrimental are dependent on cell type, duration of oxidant production, reactive species produced, and the localization of their source [6]. The oxidant-antioxidant paradox can be further investigated by the analyzing how decreased blood urate can alter various genes associated with inflammation [4], [6], [10].

Urate's Systemic Effects

Immune cells can engage in direct communication with these dying cells as well as with neurons. The extent of the functional impact of neuroimmune synapses is not known. However, activated immune cells can modulate neuronal activity via neurotransmitters and cytokines [4]. Proinflammatory cytokines and activated immune cells in the circulation also access the brain when the blood brain barrier is compromised [2]. Systemic inflammation associated with increased BBB permeability can be considered a precursor to neurodegenerative diseases [13]. Extensive evidence has reported linking molecules associated with inflammatory conditions, which include cytokines, reactive oxygen species, matrix metalloproteases, and mediators of angiogenesis with blood brain barrier disruption [2], [13]. Additionally, a positive feedback loop involving IL-6 in conjunction with neuroimmune reflex circuits has been implicated in increasing permeability such that peripheral T cells gain access to the CNS [7]. Leaks in the blood brain barrier can significantly alter immune responses to CNS antigens and compromise CNS protection against potentially harmful substances [7], [13].

The systemic effects of intestinal inflammation may be further augmented by increases in intestinal permeability via some insult to the gut [7]. Acute tissue injury may occur with a severe infection generated by an intestinal pathogen, which causes temporary defects in the intestinal epithelial barrier [2]. These low-grade insults induce more selective increases in paracellular permeability through regulation of tight junctions. Intestinal microbes also regulate expression of barrier promoting tight junction proteins [7]. While many proinflammatory cytokines secreted by activated immune cells, which include TNF, IL-1β, and IL-6, allow for tight junctions to increase barrier permeability in order to facilitate recruitment of immune cells and other molecules [2], [14], [15], [16], [17], [18]. However, a side effect of this response permits microbes to leak from the intestine into the peritoneal cavity and from there into the blood, which then triggers a systemic proinflammatory immune responses [7].

Typically, the immune challenge is rapidly cleared, proinflammatory responses terminate, and gut barrier function is restored [7]. However, unique features of the intestine allow for persistent inflammation and barrier dysfunction [7]. Sustained permeability of the intestinal barrier can have harmful effects on numerous body systems. Many microbial components can trigger "leaky gut syndrome" and lead to conditions like Irritable bowel syndrome (IBS) and metabolic syndrome. Moreover, recent studies have implicated that intestinal permeability can be with linked with CNS dysfunction, which include Parkinson's, Alzheimer's, autism, schizophrenia, multiple sclerosis, depression, anxiety, and post-traumatic stress disorder [7]. Proinflammatory responses in the brain can alter CNS function and CNS immune responses can have serious and enduring consequences. If inflammation becomes chronic, proinflammatory cytokines and oxidative stress that are linked to neuron death, and neuroinflammation should be investigated as a key factor in numerous neurodegenerative diseases.

DISCUSSION & CONCLUSION

Typically, the immune challenge is rapidly cleared, proinflammatory responses terminate, and gut barrier function is restored [7]. However, unique features of the intestine allow for persistent inflammation and barrier dysfunction [7]. Sustained permeability of the intestinal barrier can have harmful effects on numerous body systems. Many microbial components can trigger "leaky gut syndrome" and lead to conditions like Irritable bowel syndrome (IBS) and metabolic syndrome. Moreover, recent studies have implicated that intestinal permeability can be with linked with CNS dysfunction, which include Parkinson's, Alzheimer's, autism, schizophrenia, multiple sclerosis, depression, anxiety, and post-traumatic stress disorder [7]. Proinflammatory responses in the brain can alter CNS function and CNS immune responses can have serious and enduring consequences. If inflammation becomes chronic, proinflammatory cytokines and oxidative stress that are linked to neuron death, and neuroinflammation should be investigated as a key factor in numerous neurodegenerative diseases. Further, the elevated body temperatures of birds may accentuate the pathogenesis of complications induced by allopurinol and so may be a model for future studies investigating neurodegenerative disease progression.

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