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Disturbed Tryptophan Metabolism in Cardiovascular Disease

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Abstract

Atherosclerosis (AS), a major pathologic consequence of obesity, is the main etiological factor of cardiovascular disease (CVD), which is the most common cause of death in the western world. A systemic chronic low grade immune-mediated inflammation (scLGI) is substantially implicated in AS and its consequences. In particular, pro-inflammatory cytokines play a major role, with Th1-type cytokine interferon- γ (IFN- γ) being a key mediator. Among various other molecular and cellular effects, IFN- γ activates the enzyme indoleamine 2,3-dioxygenase (IDO) in monocyte-derived macrophages, dendritic, and other cells, which, in turn, decreases serum levels of the essential amino acid tryptophan (TRP). Thus, people with CVD often have increased serum kynurenine to tryptophan ratios (KYN/TRP), a result of an increased TRP breakdown. Importantly, increased KYN/TRP is associated with a higher likelihood of fatal cardiovascular events. A scLGI with increased production of the proinflammatory adipokine leptin, in combination with IFN- γ and interleukin-6 (IL-6), represents another central link between obesity, AS, and CVD. Leptin has also been shown to contribute to Th1-type immunity shifting, with abdominal fat being thus a direct contributor to KYN/TRP ratio. However, TRP is not only an important source for protein production but also for the generation of one of the most important neurotransmitters, 5-hydroxytryptamine (serotonin), by the tetrahydrobiopterin-dependent TRP 5-hydroxylase. In prolonged states of scLGI, availability of free serum TRP is strongly diminished, affecting serotonin synthesis, particularly in the brain. Additionally, accumulation of neurotoxic KYN metabolites such as quinolinic acid produced by microglia, can contribute to the development of depression via NMDA glutamatergic stimulation. Depression had been reported to be associated with CVD endpoints, but it most likely represents only a secondary loop connecting

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CONFLICT OF INTEREST

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excess adipose tissue, scLGI and cardiovascular morbidity and mortality. Accelerated catabolism of TRP is further involved in the pathogenesis of the anemia of scLGI. The pro-inflammatory cytokine IFN- γ suppresses growth and differentiation of erythroid progenitor cells, and the depletion of TRP limits protein synthesis and thus hemoglobin production, and, through reduction in oxygen supply, may contribute to ischemic vascular disease. In this review we discuss the impact of TRP breakdown and the related complex mechanisms on the prognosis and individual course of CVD. Measurement of TRP, KYN concentrations, and calculation of the KYN/TRYP ratio will contribute to a better understanding of the interplay between inflammation, metabolic syndrome, mood disturbance, and anemia, all previously described as significant predictors of an unfavorable outcome in patients with CVD. The review leads to a novel framework for successful therapeutic modification of several cardinal pathophysiological processes leading to adverse cardiovascular outcome.

Keywords

Anemia; cardiovascular disease; chronic immune activation syndrome; mood alteration; tryptophan breakdown

TRYPTOPHAN METABOLISM, ANEMIA, CHRONIC INFLAMMATION, AND CARDIOVASCULAR DISEASE

Pro-inflammatory cytokines like IFN- γ and TNF- α suppress the growth and differentiation of erythroid progenitor cells [61]. Patients with anemia of chronic inflammation had decreased TRP plasma levels positively correlated with a drop in hemoglobin [62]. Thus, IFN- γ induced TRP deprivation may play a central role in the cytokine induced suppression of hematopoieses seen in patients with chronic systemic inflammation. With respect to scLGI in patients in coronary artery disease, anemia is probably “a player” rather than a “bystander” because it worsens the oxygenation of the myocardial tissue already reduced by the mechanical process of coronary obstruction [63]. Additionally, the tachycardia of anemia increases the myocardial oxygen demand. This paves the way for a higher probability of fatal outcomes. Taken together, scLGI, anemia and immune (T-cell) dysfunction, based on an insufficient TRP supply due to IDO activation, may have a robust effect on mortality in CVD patients.

TRYPTOPHAN METABOLISM, AGING, IMMUNE FUNCTION, AND CARDIOVASCULAR RISK

Systemic chronic low grade immune-mediated inflammation in aging induces alterations in two enzymatic pathways, the IDO and the guanosine-triphosphate-cyclohydrolase-1 (GTP-CH1) pathways, both involved in the biosynthesis of monoamines [64] and potential neuropsychiatric symptoms. KYN/TRP was found significantly higher in nonagenarians compared with controls [65]. In a similar way elevated neopterin levels have been described in nonagenarians and being associated with a shorter residual life span [66]. Further, IDO activity predicted subsequent mortality in nonagenarians [65]. As an important regulatory mechanism in the immune system, increased IDO activity downregulates T cell functions.

As aging of the immune system has been previously associated with a decline in T cell function [67], it seems justified to consider increased IDO activity as an important mechanism involved in the decline of T cell responses in immunosenescence [65]. Thus, accelerated TRP catabolism could be a modifiable step on this causal pathway. As T-cells play an important role in the process of progression of CVD towards MI, a suppressed T cell function is expected to be beneficial rather than detrimental to the incidence of coronary events, conceptually supported by the low MI rates in subjects > 85 years. On the other hand, IDO may have a detrimental role in early AS, particularly in young female adults [68]. In these subjects, IDO activity correlated significantly with several risk factors for AS, i.e. with LDL-cholesterol, BMI, and inversely with HDL-C and triglyceride. Thus, IDO may be involved in the immune regulation of AS in a gender and age dependent way.

TRYPTOPHAN METABOLISM AND GENETIC LINKAGE TO IFN- γ CODING GENES

Raitala *et al.* reported that the TRP catabolism appears to be genetically moderated by the IFN- γ gene and may thus be operative in disease conditions associated with certain IFN- γ gene polymorphisms [69]. Specifically, interferon- γ +874(T/A) genotypes are known to have an effect on IFN- γ production. The high producer T allele was associated with an increased IDO activity (i.e. elevated KYN/TRP) in females. Hence, it would be worthwhile to investigate if the previously reported IDO associated increased AS risk factors seen in young females [68] are associated with the IFN- γ risk alleles [69].

THERAPEUTIC CONSIDERATIONS

To achieve a normalization of the TRP metabolism would be an important goal for the treatment of related symptoms in patients suffering from CVD. For instance, administration of the IDO-inhibitor 1-methyl tryptophan [70] may represent a relevant pharmacological approach to be considered for future investigation. However, IDO is well known for its immunosuppressive properties, and inhibiting it may prove detrimental, as it may boost proinflammatory mechanisms. Likewise, an elevated KYN/TRP ratio might represent a natural response of the human immune system to counteract inflammation. Also anti-inflammatory drugs such as aspirin and salicylic acid [71] but also statins [72] may affect the IDO mediated pathways. Specifically, Atorvastatin suppresses INF- γ -induced neopterin formation and TRP depletion in human peripheral blood mononuclear cells and in monocytic cell lines [72]. Moreover, immunosuppressants like rapamycin [73] counteract IDO induction during the pro-inflammatory response *in vitro*. The same is true for several natural compounds with anti-inflammatory properties and with immunosuppressant capacity *in vitro*, e.g., resveratrol [74]. Finally, melatonin seems to have cardioprotective properties via its direct free radical scavenger and its indirect antioxidant activity [75].

CONCLUDING REMARKS

Within this review we generated substantial evidence that the Th1-type cytokine IFN- γ causes increased IDO activity which ultimately decreases serum levels of the essential amino acid TRP. As a scLGI with activation of certain T-cell subsets (Th1, less Th2) [76] is

usually present in patients with CVD, these subjects have an increased IDO activation leading to an increased TRP breakdown with an increased KYN/TRP ratio. Importantly, elevated KYN and KYN/TRP indicate a higher likelihood of cardiovascular fatalities. As shown in our recently published observations [77], increased production of the proinflammatory adipokine leptin in combination with interleukin-6 (IL-6), represents another link between obesity and early occurrence of mediators of AS. Leptin has also been shown to upregulate Th1-type immunity, and increased abdominal fat, an important source of leptin, leads to increased KYN/TRP [16].

In prolonged states of scLGI, availability of free serum TRP is persistently diminished, and thus, serotonergic functions are affected. Accumulation of neuroactive KYN metabolites such as quinolinic acid is neurotoxic and may contribute to mood dysregulation, previously implicated in increased likelihood of myocardial infarction. However, the data reviewed in this article suggest that mood disorders appear to more likely be a consequence of scLGI and an epiphenomenon rather than a mediating step of cardiovascular events.

More importantly for CVD, accelerated catabolism of TRP is centrally involved in the pathogenesis of the anemia of scLGI. IFN- γ suppresses erythroid progenitor cells, and the depletion of TRP decreases hemoglobin production. Anemia caused by scLGI and increased TRP breakdown add to the detrimental effects of pre-existent reduced vascular reserves.

Measurement of TRP, KYN concentrations, and calculation of the KYN/TRYP ratio are important predictors of an unfavourable outcome in patients with CVD. It will be important to investigate if these parameters can provide a basis for more successful and precise biologically grounded therapeutic protocols to further reduce cardiovascular morbidity and mortality.

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Fig. 1.

Tryptophan metabolism. Tryptophan 5-hydroxylase (T5H) catabolizes the synthesis of 5-hydroxytryptamin (serotonin); tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO) initiate the formation of kynurenine.

Fig. 2.

The Th1 cytokine interferon- γ (IFN- γ) is released during the innate and adaptive immune response. It induces the enzyme indoleamine 2,3-dioxygenase (IDO) in macrophages, dendritic and other cells.

Fig. 3. The complex involvement of TRP metabolism in serotonin availability, mood alterations, T-cell mediated inflammation and clinical endpoints of CVD.