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Short communication

Resveratrol intake enhances indoleamine-2,3-dioxygenase activity in humans

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ABSTRACT

Background: Resveratrol is a polyphenol compound found in various nutrients that was shown to have immunomodulatory, anti-cancerogenic, and cardioprotective effects. The regulation of indoleamine-2,3-dioxygenase (IDO), the rate-limiting enzyme in inflammatory tryptophan metabolism, has been proposed to be involved in resveratrol's biological effects. These observations, however, rely on *in vitro* findings and animal studies. Therefore, we assessed the impact of resveratrol on tryptophan metabolism after oral intake in humans.

Methods: Healthy volunteers were orally administrated 5 g resveratrol (n = 8) or placebo (n = 2) in a pilot study. IDO activity was determined by analyzing plasma levels of tryptophan and kynurenine. Determination of the immune activation marker neopterin was included in the analysis.

Results: Resveratrol administration significantly reduced tryptophan levels 2.5 h ($p < 0.001$) and 5 h ($p < 0.001$) after treatment. Kynurenine levels were slightly, but not significantly, elevated 2.5 h after the intervention, which resulted in an 1.33- and 1.30-fold increase of the kynurenine to tryptophan ratio at 2.5 h ($p < 0.01$) and 5 h ($p < 0.01$), respectively. Neopterin levels were not affected by resveratrol administration.

Conclusion: This is the first evidence of a modulatory effect of orally administered resveratrol on tryptophan metabolism in humans. Since IDO has been shown to play a crucial role in immunity, cancer development and regulation of vascular tone, the modulation of this enzyme might be involved in resveratrol's diverse biological effects.

Introduction

Resveratrol (3,4′,5-trihydroxystilbene) is a polyphenol found in various nutrients such as peanuts, mulberries, and red wine. The substance has been attributed to have wide-ranging biological effects, including immune modulation [1,2], cancer inhibition [3] and cardioprotection [4]. A major molecular target of resveratrol is indoleamine-2,3-dioxygenase (IDO), the rate limiting enzyme in inflammatory tryptophan metabolism [5,6]. Activation of IDO enhances breakdown of tryptophan to kynurenine, which depletes the essential amino acid tryptophan, inhibits protein synthesis, and causes accumulation of bioactive kynurenine downstream products [7]. During infection, nutrient deprivation due to IDO activity decreases microbial growth and, in turn, also inhibits T-cell proliferation and activation [8]. Thus, the enzyme is known to exhibit potent immune-modulatory functions, and impairment of its activity was shown to impact on the course of several inflammatory conditions, such as transplant rejection [9–11] and autoimmunity [12–15]. Additionally, IDO activity has been implicated to have opposing effects in oncogenic processes as it inhibits early tumor formation through tryptophan depletion whereas its tolerogenic effects on immune cells might impair tumor surveillance [6,8,16,17]. Similar to a potentially detrimental influence on immunological cancer surveillance, IDO activity was found to be down-regulated in HIV-infected dendritic cells [18], thus enabling immune-evasion by the virus [19]. Apart from its influence on immune cells, recent findings have identified IDO and kynurenine as crucial regulators of vascular tone [20]. Furthermore, the enzyme was identified to play an important role in the development of neuropsychiatric disorders, since the depletion of tryptophan results in lower serotonin levels and the downstream metabolites of kynurenine are neuroactive [21].

The vast implications of IDO in the modulation of immunity highlight its potential as a therapeutic target for immunoregulatory treatments. Although resveratrol has been reported to modulate

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Table 1
Demographic characteristics of study population. All characteristics with the exception of sex were self-reported. Plus–minus values are means ± SD.

	Resveratrol ($n = 8$)	Placebo ($n = 2$)
Male sex (%)	100	100
Age (yr)	23.88 ± 1.62	23; 25
Ethnicity (%Caucasian)	100	100
Body mass index (kg/m^2)	22.89 ± 1.79	20.56; 22.64

IDO activity, these observations have relied on *in vitro* findings or animal models. Therefore, we investigated the impact of orally administered resveratrol on IDO activity in humans. In addition, its potential effect on neopterin levels was assessed, as neopterin is reliable biomarker for IFN-γ-mediated immune activation [22].

Methods

Study population

A detailed description of inclusion criteria and participant characterization was published elsewhere [2]. In brief, inclusion criteria were male sex, age between 18 and 45, no clinically relevant finding at physical examination, hematology, clinical chemistry and urine analysis, non-smoker (for at least 1 month), no regular alcohol consumption (defined as alcoholic beverage ≥1 daily), negative result at urine drug screening and the ability to communicate with the investigators. Demographic characteristics of the study population are described in Table 1. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and it was approved by the appropriate Ethical Committee. All subjects agreed to participation by written informed consent.

Study design and endpoints

The study was a randomized, open-label, parallel-group, single-dose pilot trial. The subjects were allocated into 2 groups (resveratrol intervention, n = 8; placebo, n = 2). In the intervention group, 5 g resveratrol (Terraternal, Santa Clara, CA, USA) was administered orally in the morning after overnight fasting. All subjects received a standardized diet lacking polyphenols during the study period of 48 h. The resveratrol dose was selected based on safety observations of previous clinical trials conducted in humans [23].

The primary endpoints of the study were previously published pharmacokinetic parameters [2], and secondary endpoints were specific markers of immune cell function.

Blood sampling and bioanalytical methods

Blood samples were collected via venipuncture at baseline (BL), 2.5 h, 5 h, 7.5 h, 10 h, 24 h and 48 h after resveratrol intake. The

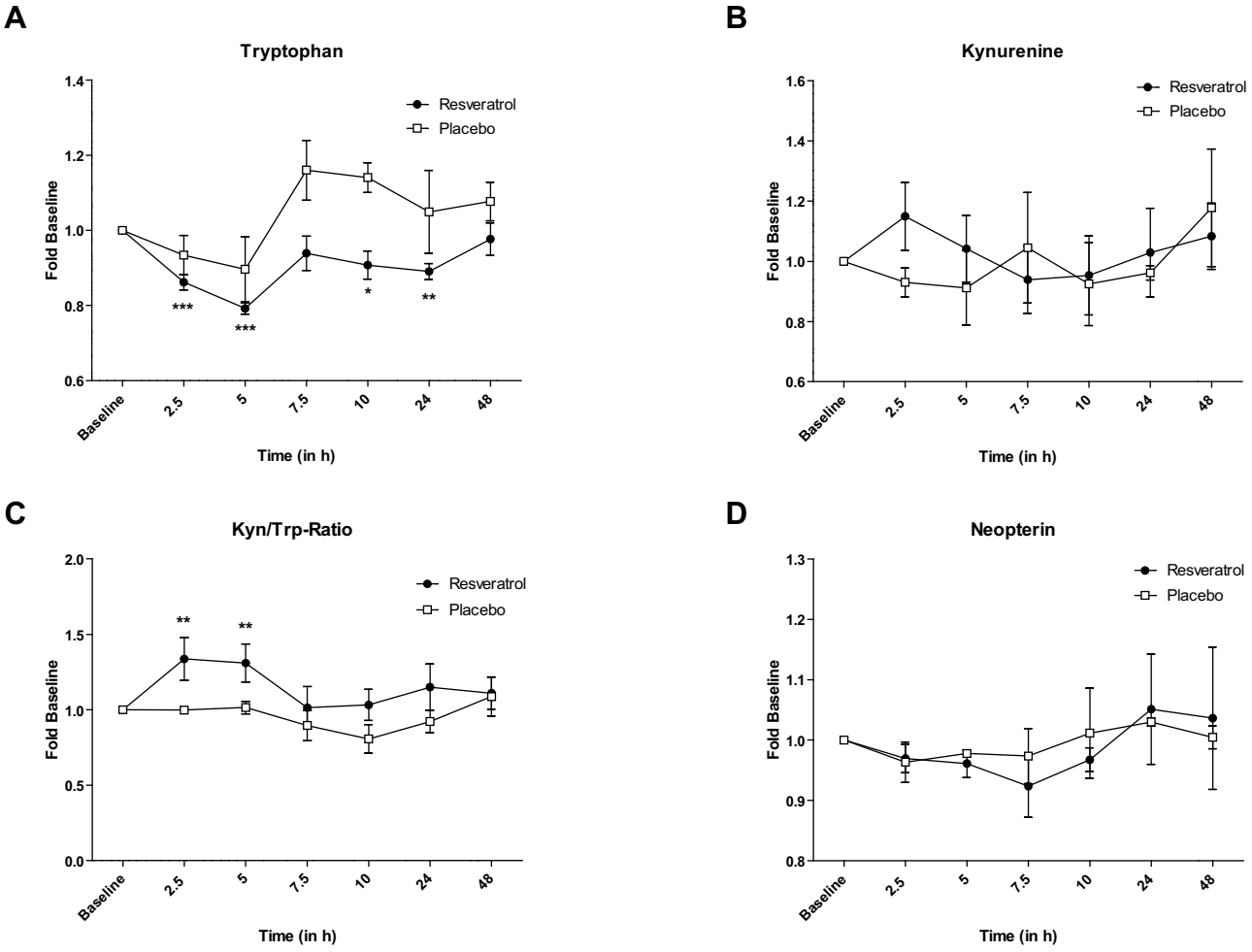

Fig. 1. Resveratrol enhances IDO activity. 5 g of resveratrol were administered orally to 8 healthy male individuals, 2 individuals received placebo. Blood samples were obtained at indicated time points and plasma levels of tryptophan, kynurenine and neopterin were measured as indicated in the materials and methods section. Results are expressed as mean ± SEM. *Significance of the treatment group compared to baseline levels, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, calculated by paired *t*-test.