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COMMENT

Can we obtain a reliable marker that shows the hypoxic burden in patients with sleep disordered breathing?

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Sleep disordered breathing (SDB) is widely prevailed in Japan and all over the world [1, 2]. SDB has two main problems on human body; one of which would be sleepiness leading to impairment of daily activity and productivity, and another would be unfavorable physical and mechanical influence especially on the cardiovascular system and various metabolism processes [3]. The treatment of sleepiness caused by SDB would be relatively straightforward because the degree of sleepiness and its improvement after treatment would be relatively easily detected by various ways; questionnaire like the Epworth sleepiness scale or change in complaint of the patient itself. On the other hand, the evaluation of the range and the degree of negative physical impact of the SDB is not so simple because the influence might be brought about through various pathways; activation of sympathetic nervous system, elevation of blood pressure, change in intrathoracic pressure and/or substantial hypoxia [4]. Among them, hypoxia would be the one of most influential factors because it triggers an increase in sympathetic nervous activity resulting in elevation of blood pressure and heart rate, increase of inflammatory agents such as hypoxia-inducible factor and nuclear factor-κB or various cytokines leading to endothelial dysfunction and ultimately atherosclerosis [5], or increase in the activity of xanthine oxidoreductase (XOR) [6]. In a daily clinical setting, physicians can easily know the degree of desaturation in a patient by the data from pulse oximeter. On the other hand, it would not be easy to estimate the degree of the real negative impact of hypoxia because to know actual degree of resultant sympathetic nervous system excitation, nocturnal precise blood pressure changes, changes of intrathoracic pressure and metabolic changes by hypoxia in daily clinical setting is very difficult. Recent randomized control trials failed to establish the favorable influence of continuous positive airway pressure (CPAP) treatment in the patients with SDB even with cardiovascular or cerebrovascular diseases [7, 8]. One of the reasons of the difficulty to prove the treatment effect in such trials might have been that SDB patients who had suffered serious negative impact from hypoxia were not properly evaluated and chosen. It has been known that hypoxia directly affects purine metabolism, which is playing a central role in energy production and nucleotide metabolism. Hypoxia suppresses transition of adenosine monophosphate (AMP) to adenosine diphosphate (ADP) and eventually to adenosine triphosphate (ATP) [9] (Fig. 1). Actually, increase of adenosine by after hypoxia has been already reported in SDB patients [10]. In this process, hypoxia enhances the activity of XOR, resulting in acceleration of the process from hypoxanthine to xanthine and to uric acid and enhanced XOR also produces reactive oxygen species (ROS) [11] (Fig. 1). Increased ROS by hypoxia produces various oxidative stress markers like 8-hydroxyl-2'-deoxyguanosine (8-OHdG) (Fig. 1), but hypoxia and other oxidative stress affect other metabolic systems and produce ROS and oxidative stress markers all over a body.

There are several candidates for metabolic marker that we can use as an indicator of insult on the purine metabolism by hypoxia in daily clinical setting; serum uric acid, uric acid secretion, 8-OHdS, XOR activity and adenosine. So far, the results of the change in serum uric acid after hypoxia is not consistent, probably because the uric acid excretion is known also to increase by hypoxia [9] and there is backward cascade called salvage pathway which might also affect serum uric acid level and uric acid excretion [12]. The article of Shimizu et al. in Hypertension Research

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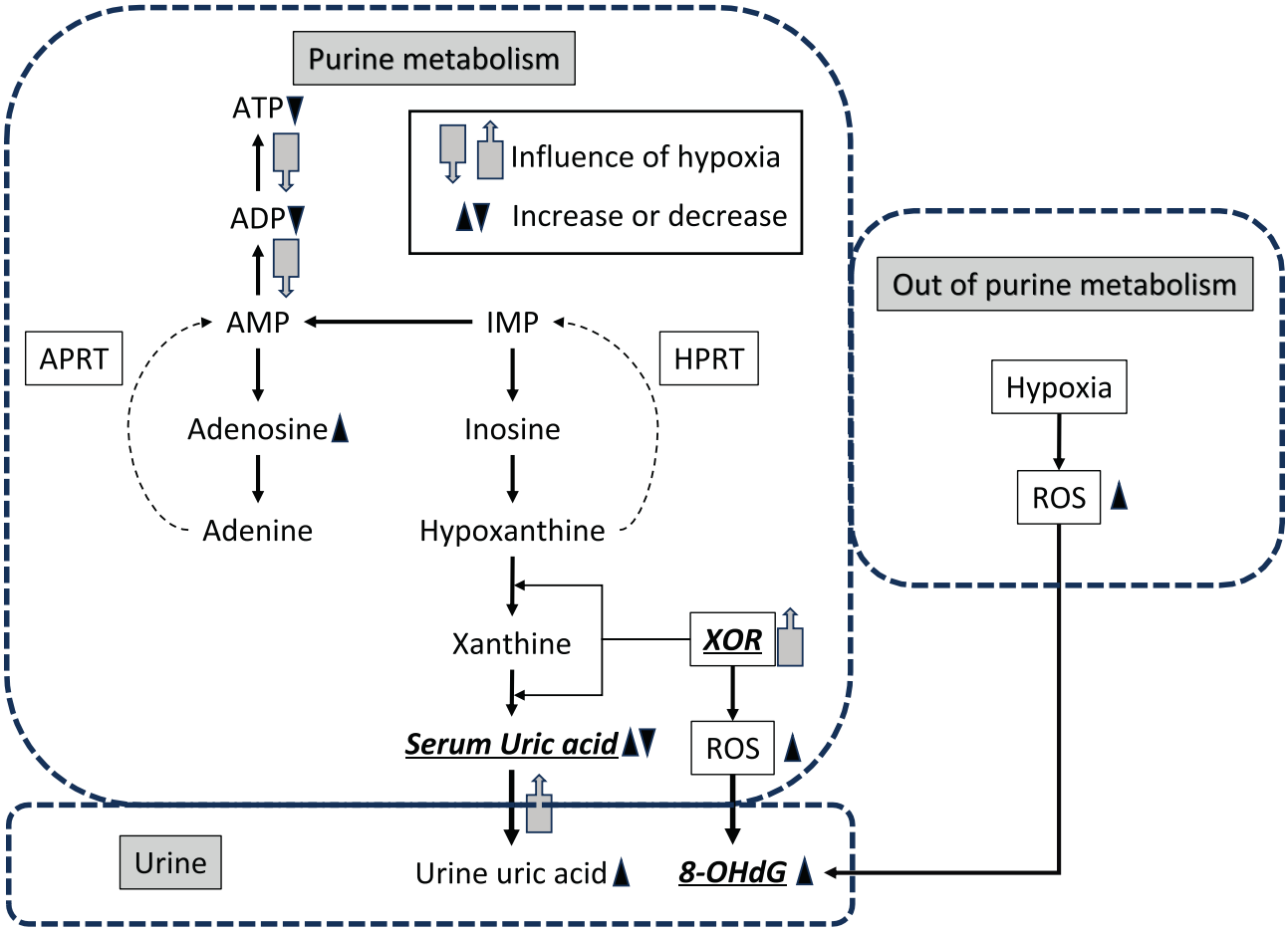

Fig. 1 Hypoxia and purine metabolism. 8-OHdG 8-hydroxyl-2'-deoxyguanosine, ADP Adenosine diphosphate, APRT Adenine phosphoribosyltransferase, AMP Adenosine monophosphate, ATP Adenosine triphosphate, IMP Inosine monophosphate, HPRT Hypoxanthine phosphoribosyltransferase, ROS Reactive oxygen species, XOR Xanthine oxidoreductase, ------: Salvage pathway

reported that serum uric acid (UA) levels, XOR activity and urinary 8-OHdG levels significantly increased overnight in 32 coronary artery disease patients with SDB [13]. They also reported that the degree of desaturation (3% ODI) was correlated with the overnight changes in XOR activity and urinary 8-OHdG levels, which implies that impact of hypoxic burden can be somewhat quantitively estimated from these parameters. Importantly, they also explored mediating effect of XOR linking 3% ODI to 8-OHdG and found that the association between 3% ODI and 8-OHdG was no longer significant after adjusting XOR, which suggests XOR should be considered as a primary parameter which reflects the hypoxic burden. From this result and other previous studies, the activity change in XOR or serum adenosine level might have the potential to be the reliable markers indicating the net negative impact of the hypoxia on the body of SDB patients.

As for the question which has greater impact on the oxidative stress caused by SDB, the degree of desaturation or the frequency of desaturation, the result of the study by Shimizu et al. showed that the time below 90% of oxygen saturation did not show statistically positive influence on XOR or 8-OHdG in the multivariable analysis, although 3% ODI showed the influence. This fact means that the repetitive desaturation has more negative impact than the continuous desaturation on human body through the oxidative stress, which was shown in the previous studies [14].

It might not be easy task to find a simple and reliable parameter which can be simply used to evaluate hypoxic burden in the daily clinical setting because numerous other physical stresses are always affecting human body. However, it is mandatory to continue the effort to find such ones to obtain the critical information in an individual patient to tailor the treatment and to improve the result of SDB treatment.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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