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Review

F_2-isoprostane formation, measurement and interpretation: The role of exercise

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ABSTRACT

The level of F_2-isoprostanes (F_2-IsoP) in blood or urine is widely regarded as the reference marker for the assessment of oxidative stress. As a result, nowadays, F_2-IsoP is the most frequently measured oxidative stress marker. Nevertheless, determining F_2-IsoP is a challenging task and the measurement is neither free of mishaps nor straightforward. This review presents for the first time the effect of acute and chronic exercise on F_2-IsoP levels in plasma, urine and skeletal muscle, placing emphasis on the origin, the methodological caveats and the interpretation of F_2-IsoP alterations. From data analysis, the following effects of exercise have emerged: (i) acute exercise clearly increases F_2-IsoP levels in plasma and this effect is generally short-lived, (ii) acute exercise and increased contractile activity markedly increase F_2-IsoP levels in skeletal muscle, (iii) chronic exercise exhibits trend for decreased F_2-IsoP levels in urine but further research is needed. Theoretically, it seems that significant amounts of F_2-IsoP can be produced not only from phospholipids but from neutral lipids as well. The origin of F_2-IsoP detected in plasma and urine (as done by almost all studies in humans) remains controversial, as a multitude of tissues (including skeletal muscle and plasma) can independently produce F_2-IsoP.

Contents

Abbreviations: EDL, extensor digitorum longus; EIA, enzyme immunoassay; F_2-IsoP, F_2-isoprostanes; GC, gas chromatography; $HO_2^{\cdot}$, hydroperoxyl radical; H_2O_2, hydrogen peroxide; LC, liquid chromatography; MS, mass spectrometry; MS/MS, tandem mass spectrometry; $^{\cdot}NO$, nitric oxide; $O_2^{\cdot-}$, superoxide radical; $^{\cdot}OH$, hydroxyl radical; PLA_2, phospholipase A_2; $RO^{\cdot}$, alkoxyl radical; $ROO^{\cdot}$, peroxyl radical; TBARS, thiobarbituric acid reactive substances; VO_{2max}, maximal oxygen consumption.

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1. Introduction

One of the greatest challenges in the field of redox biology is the identification of a reliable non-invasive marker to assess oxidative stress in vivo [1,2]. Most methods available to assess oxidative stress are adequate for in vitro experiments, yet they suffer from a lack of reliability and/or validity in terms of specificity to the substrate oxidized when applied to complex biological fluids and tissues [3]. However, a considerable body of evidence indicates that measurement of isoprostanes (IsoP; prostaglandin-like compounds produced primarily from arachidonic acid catalysed by reactive oxygen and nitrogen species, hereinafter called reactive species) in body fluids such as plasma and urine provides a reliable approach to assess oxidative stress in vivo [4,5]. In fact, the level of one abundant IsoP stereoisomer, 15-F_{2t}-IsoP, in blood or urine is widely regarded as the "gold standard" marker for the assessment of oxidative stress [6–8]. As a result, the number of studies measuring IsoP levels in the biomedicine field has been increasing exponentially every year since the 1990, when the IsoP were discovered [9]. The trend for increased IsoP measure as a marker of oxidative damage is also noticeable in the redox biology of exercise field, in which IsoP has been currently assessed in more than 60 exercise studies (updated on August 25th, 2010 in PubMed).

Nevertheless, determining IsoP is a challenging task and the measurement is neither free of mishaps nor straightforward. In addition, several crucial decisions have to be made before embarking on IsoP measurements. For example, it has to be decided whether to measure free, esterified or total IsoP and whether the assessment will be performed in skeletal muscle, plasma or urine. It is common practice that the type of IsoP and the matrix used to assess them are frequently decided on "common sense" of what is considered "the right thing to do" rather on solid principles. The same also holds true for the interpretation of the IsoP changes, particularly considering the dual role of IsoP, that is, as a marker of oxidative stress and as mediators of vital biological effects [10,11]. In addition, none of the reviews devoted to this topic have examined the role of skeletal muscle or exercise on IsoP production. Exercise is a physiological stimulus that may exert distinctive effects on IsoP metabolism and IsoP levels; in that case a special interpretational framework for the description and comprehension of these effects may be required. As an illustration to this, the typical increase of total antioxidant capacity frequently reported after exercise (e.g. [12,13]) is not related, at least directly, to an orchestrated change in the antioxidant components of plasma, rather it is largely a result of increased uric acid production [13], which is in turn the product of increased ATP degradation during exercise [14]. Therefore, this review aims at presenting for the first time the effect of acute and chronic exercise on IsoP levels in plasma, urine and skeletal muscle, placing emphasis on the origin, the methodological caveats and the interpretation of IsoP alterations. We hope the information presented herein will be appealing to both exercise scientists and biological scientists interested in IsoP biochemistry and physiology.

2. Formation and nomenclature of F_2-IsoP

Since all the relevant exercise studies have focused on the so-called F_2-IsoP of the 15 series (nomenclature explained below), only the production of these IsoP will be presented in this review based on the mechanism proposed by Milne et al. [15], which resides in the earlier work of Pryor et al. [16]. Nonetheless, it is worth mentioning that controversy exists regarding the exact mechanism of F_2-IsoP generation [17,18]. Briefly, reactive species can attack arachidonic acid carboxyl chain at three different sites and abstract a bis-allylic hydrogen [15]. Several reactive species can abstract the first hydrogen atom and include the radicals: hydroxyl (·OH), alkoxyl (RO·), peroxyl (ROO·) and possibly hydroperoxyl ($HO_2^{\cdot}$) but

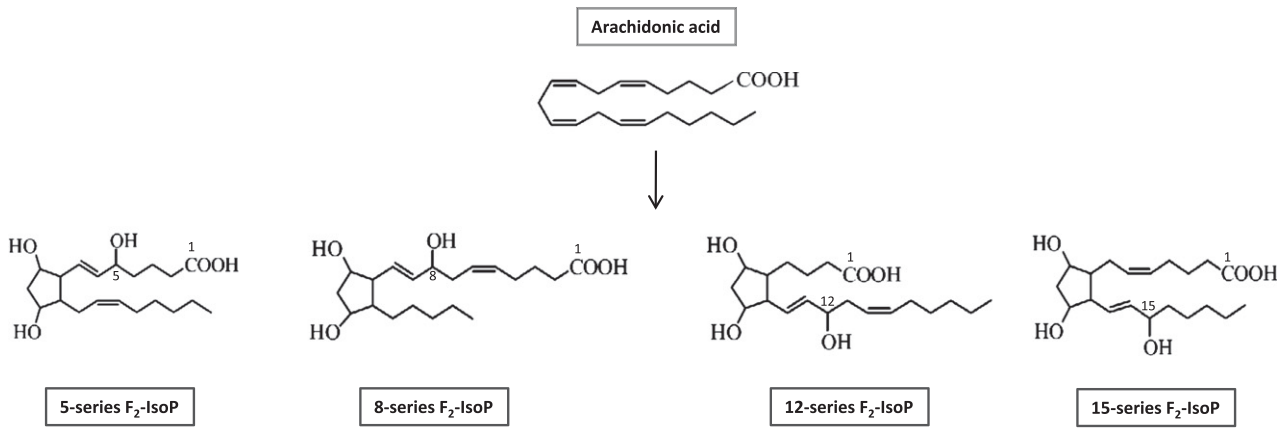

Fig. 1. Chemical structure of arachidonic acid and of the four F_2-IsoP regioisomers. Each of the four regioisomers are comprised of 16 stereoisomers.