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Editorial

Aspirin esterase(s) – Much known, more to learn

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1. Introduction

Esterases, so called because they catalyze hydrolytic splitting of ester bonds, remain quite intriguing – they partake in the biotransformation of drugs/xenobiotics, but their physiological/biological functions remain unknown. An exception is acetyl cholinesterase that catalyses hydrolysis of the neurotransmitter acetylcholine.

Hydrolysis of a xenobiotic/drug can, at times, be catalyzed by different esterases in different tissues or organs. For example, aspirin hydrolysis to salicylate and acetate is catalyzed by carboxylesterases (EC 3.1.1.1) in human gastric mucosa and liver [1], resulting in bioavailability of 65% [2]. Once in the systemic circulation, further hydrolysis is catalyzed by other esterases in the plasma (pseudo cholinesterase, EC 3.1.1.8; and albumin) and red blood cells. Albumin-associated esterase activity is minor, and the main plasma aspirin esterase activity is associated with the plasma cholinesterase [3]. About 80% of aspirin esterase activity in the blood is due to the enzyme in erythrocytes. It is different from that in plasma – there is no significant correlation in levels of the two, and the red cell enzyme is resistant to 1.66 mmol/L physostigmine (in final assay system) that completely inhibits the form in plasma [4]. The suggestion that it is probably 'non specific' has been contested by the isolation from human erythrocyte of an esterase with specificity for aspirin by Costello and Green [5].

2. Factors affecting aspirin esterase activity

2.1. Drugs

Available evidence indicates that aspirin hydrolysis is susceptible to modulation by various factors. Rylance and Wallace [6] reported that, at approximately usual concentrations attained during normal use, alclofenac, caffeine, indomethacin, mebeverine hydrochloride, naproxen, neostigmine bromide, paracetamol, and physostigmine sulphate inhibited aspirin esterase activity by 18.3–54.1%. This study was, however, done in whole blood, and the relative susceptibility of the red cell and plasma aspirin esterases to each of these inhibitors cannot be established. Serum aspirin esterase is, however, inducible by anticonvulsants, namely carbamazepine, phenobarbital, phenytoin, and valproic acid [7].

2.2. Diseases

While the finding of 28.7% lower activity of plasma aspirin esterase activity in aspirin sensitive asthmatics and of 29.5% in those with aspirin sensitive urticaria, compared with controls, awaits explanation [8], low activities in chronic hepatitis, cirrhosis and heart failure are probably a reflection of reduced synthesis resulting from hypoxia [9–11]. Reduced levels have also been reported in Reye's syndrome [12]. In acute viral

hepatitis, an initial rise in the activity of the enzyme, in parallel with SGPT and SGOT (probably reflecting release from damaged hepatocytes) was followed by a decrease [11].

Response to anaesthesia and surgery has also been reported to result in reduced activity of plasma aspirin esterase activity [13,14]. The amount of injury would appear to, at least in part, determine effect on enzymatic activity, given the observation that, in contradistinction to hip replacement after fractured neck of femur, inguinal herniorraphy was not associated with reduction in plasma aspirin esterase activity [15].

3. Physiological

There is no unanimity with regards to the possible effect of gender on plasma aspirin esterase activity. Some reported higher activities in males [9,16], but others found no significant difference between males and females [3,4,7]. Age has no effect on aspirin esterase activity in adults, unless there is frailty, whereupon activity is reduced because of reduced enzyme synthesis without any accompanying qualitative change in the protein [17–19].

Study on aspirin esterase activity in early life was probably first undertaken by Windorfer et al. [20]. Using the percentage of acetylsalicylic acid hydrolyzed over one hour in blood as a measure of aspirin esterase activity, they observed lower activity in premature neonates (49%, $n = 21$) than in full-term ones (63%). Activities in adults averaged 76%, being greater in males (about 82%) than in females (about 70%). Their data suggest that aspirin esterase activity in full-term neonates is about 83% that in adults. In this issue, Gugliucci et al. [21] reported that serum aspirin esterase activity in the newborn ($n = 28$) is about 69% that in adults ($n = 30$). Notwithstanding the use of different measures of aspirin esterase activity in these studies, it could be accepted as factual that neonatal plasma aspirin esterase activity is much lower than that in whole blood. Although aspirin esterase activity in adults has been similarly reported to be much higher in blood (due to greater contribution from erythrocytes) than in plasma [4], it should be noted that protein synthesis is probably in the steady state at that stage of life. This condition is not met in the neonates in whom the synthesis of pseudocholineterase (started before gestational age of 28 weeks), a major determinant of aspirin esterase activity, increases after birth till about a year, whereupon it slows down as it approaches that in adults. Erythrocyte, immature and incomplete before birth, similarly undergoes developmental transformation, which is reflected in an increase in its acetyl cholinesterase content [22]. In all probability, therefore, neither the plasma nor the erythrocyte aspirin esterase has attained optimal or full catalytic activity in the neonates. We do not know the rate of development of one relative to the other; and neither Windorfer et al. [20] nor Gugliucci et al. [21] measured aspirin esterase activities in blood and plasma (serum) in the same sample. In the absence of such data the relative contribution of the cellular and plasma (serum) enzymes to aspirin esterase activity in whole blood of the newborn will remain a matter of conjecture.

Yet, providing a definitive answer may prove worthwhile, given the possibly different roles of the two forms of the enzyme in determining aspirin level in adults. The finding that about 80% of aspirin esterase activity in blood is due to the form of the enzyme on red cells [4], has been supported by the observation of a significant negative correlation between aspirin half-life in blood and haematocrit ($r = -0.96$). This brings in its trail the suggestion that blood level of aspirin is determined mainly by the enzyme on red cells [23]. Interestingly, when the same group used washed erythrocytes, a direct relationship was noted between aspirin half-life and albumin concentration in saline solution [24]. It would, therefore, appear that the plasma enzyme, in some way, regulates interaction between aspirin and the enzyme on red cells.

Gugliucci et al. [21], prompted by a report that enhanced plasma acetylsalicylic acid degradation in type 2 diabetics was modulated by plasma cholesterol, also provide information on paraoxonase in neonate. They confirmed what we currently know about paraoxonase in newborn of non-diabetics; and that is welcome and useful. However, despite the unanimity that aspirin esterase activity is accounted for by or probably identical to pseudo cholinesterase activity in adults, some observations – modest correlation between the two when quantified in the same serum/plasma samples, and different patterns of spread in healthy adults for example – await explanation. It is tempting to wonder whether this is also the case and/or to the same degree in the neonatal period when the enzyme systems haven't attained maturity. There is currently no data on aspirin esterase activity and pseudo cholinesterase activity in the same serum sample from neonates. On this score, one cannot help but wonder whether the absence of data on pseudo cholinesterase in the neonates studied by Gugliucci et al. [21] is not a rather high opportunity cost

for their confirmation of already available information on paraoxonase levels in neonates.

The aspirin we initially regarded as just an antipyretic and analgesic has confounded us all by its spectrum of usefulness. The indications are that there is probably more about this drug that we are yet to know – and as well, it would appear, about the enzyme system that degrade it after intake.

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