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Short communication

The importance of AKR1D1 enzyme in drug metabolism

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Introduction

The efficacy as well as the potential side effects of therapy may be affected by drug metabolism. Hence, the most crucial part of drug development and clinical application is understanding metabolic biotransformation. Although cytochrome P450 (CYP)-catalyzed oxidative reactions are the most common in Phase I drug metabolism they are not the only ones involved. Despite its relevance, carbonyl reduction, which is the basic phase I metabolic process of many xenobiotics, has received little research. Insufficient information is one of the key reasons for the limited scientific knowledge of the process of carbonyl reduction in drug metabolism (Malátková et al., 2014).

Aldo-keto reductase superfamily

Aldo-keto reductase (AKR) enzymes, which are encoded by the same name genes, catalyze a series of oxido-reductive reactions involved in the metabolic processes of biosynthesis and detoxification. These enzymes work as separate metabolic units or as interconnected components of metabolic biotransformation in association with other carbonyl-metabolizing enzymes (aldehyde and alcohol dehydrogenases, cytochrome P450s, and cytochrome P450 glutathione S-transferases) (GSTs).It has been reported that a common function of AKR enzymes is the biotransformation and detoxification of aldehydes and ketones produced by endogenous or exogenous metabolism (food, drug, or toxin) (Barski et al., 2008).In addition, the number of potential substratesin recent years has been significantly increased, highlighting their broad substrate specificity. As new information about their potential significance is emerging, AKR enzymes have become more frequently recognized as key mediators in Phase I metabolism of carbonyl drugs. Thirteen different AKR enzymes have been detected in humans, out of the total number of recognized AKR enzymes, which are classified into 15 families. Human AKR enzymes, classified according to homology in the amino acid sequence, belong to three families - AKR1, 6 and 7, and are subsequently divided into subfamilies: AKR1A1 (aldehyde reductase), AKR1B1, B10 and B15 (aldose reductases), AKR1C1, C2, C3 and C4 (hydroxysteroid dehydrogenases), AKR1D1 (Δ4-3-ketosteroid-5-β-reductase), AKR6A3, A5 and A9 (Kvβ proteins) and AKR7A2 and 7A3 (aflatoxin reductases) (Barski et al., 2008).

AKR1D1(Δ4-3-ketosteroid-5-β-reductase)

AKR1D1 enzyme encoded by the *AKR1D1* gene present in three splice variants (AKR1D1-001, AKR1D1-002, AKR1D1-006), is predominantly expressed in liver and testis, although several studies have suggested the presence of 5β-reduced metabolites in the fetal brain, uterus, and plasma (Byrns, 2012), indicating AKR1D1 activity in these tissues as well. The AKR1D1-002

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variant, which is the predominant form of the enzyme, is the most extensively investigated, while the specific activity and expression of AKR1D1-001 and AKR1D1-006 are still poorly understood (Barski et al., 2013). AKR1D1 enzyme is involved in the metabolic biotransformation of glucocorticoids and androgens, modulates the availability of steroid hormones, and catalyzes an important step in the biosynthesis of bile acids.

The emerging role in drug metabolism

According to Chandry et al. (2013), the AKR1D1 gene is a potential trans - regulator of the CYP450 gene co-expression network, particularly the CYP2, CYP3 enzyme families. These authors have reported that the regulation was modifiedas a result of the mononucleotide allelic variation (AKR1D1 * 36; rs1872930) in the gene's 3'UTR. The study revealed that this mechanism is associated with increased hepatic expression and activity of CYP3A4, CYP2C9, CYP2C8, and CYP2C8. These data indicates the possible impact of AKR1D1 in metabolic biotransformation of most often used drugs in clinical practise. Furthermore, in previous pharmacogenetic studies aimed to determine the effect of AKR1D1 * 36 on the pharmacokinetics and outcome of drug therapy - CYP450 substrates (risperidone, ibuprofen, and clopidogrel), we have found a significant association between the allelic variation and the metabolic biotransformation of risperidone (unpublished results), ibuprofen and clopidogrel (Kapedanovska Nestorovska et al., 2019a, b; Nestorovska et al., 2018).

Further research

A rising evidence has demonstrated that AKR1D1 plays a function in the metabolic phenotype of drugs, in addition to the widely acknowledged role of AKR1D1 in controlling the availability of androgens in urogenital tissues. However, despite the large amount of published evidence, the substrate specificity of AKR1D1 is still the subject of scientific debate. The results of previous research using purified recombinant protein AKR1D1 to characterize enzyme substrates are contradictory and inconsistent, owing to discrepancies in protein purification procedures (Rižner and Penning, 2014). Furthermore, no specific AKR1D1 inhibitors have been found yet that could aid in the detailed characterization of its function.

Our recent findings (Kapedanovska Nestorovska et al., 2019a, b; Nestorovska et al., 2018) have suggested that the AKR1D1 enzyme and the * 36 variant allele may play a crucial role in metabolic biotransformation and pharmacokinetic parameters of the drugs under investigation (risperidone, ibuprofen, clopidogrel).However, it is unclear whether the observed effect is due to AKR1D1 genetic trans regulation of CYP450 expression or a direct result of AKR1D1 mediated metabolic transformation of drugs and their detoxification. Further research should be conducted to elucidate the concrete role as well as the contribution in the metabolism of drugs.

Conclusion

A new era has been opened in the research of the AKR1D1 enzyme, in addition to its established role in the metabolism of few endogenous compounds. Next studies should focus on its involvement in the metabolic transformation of drugs since the new data may have practical usein the development and application of individualized drug therapy.

References

Barski, O.A., Tipparaju, S.M., Bhatnagar, A., 2008. The aldo-keto reductase superfamily and its role in drug metabolism and detoxification. Drug Metab Rev. 40(4), 553-624. https://doi.org/10.1080/03602530802431439

Byrns, M.C., 2012. Role of aldo-keto reductase enzymes in mediating the timing of parturition. Front Pharmacol. 2, 92. https://doi.org/10.3389/fphar.2011.00092

Chaudhry, A.S., Thirumaran, R.K., Yasuda, K., et al., 2013. Genetic variation in aldo-keto reductase 1D1 (AKR1D1) affects the expression and activity of multiple cytochrome P450s. Drug Metab. Dispos. 41(8), 1538-1547. https://doi.org/10.1124/dmd.113.051672

Kapedanovska Nestorovska, A., Jakjovski, K., Naumovska, Z., et al., 2019a. AKR1D1*36 C>T (rs1872930) allelic variant is associated with variability of the CYP2C9 genotype predicted pharmacokinetics of ibuprofen enantiomers - a pilot study in healthy volunteers. Acta Pharm. 69(3), 399-412. https://doi.org/10.2478/acph-2019-0032

Kapedanovska-Nestorovska, A., Dimovski, A.J., Sterjev, Z., et al., Mitrev, Z., Rosalia, R., 2019b. The AKR1D1*36 (rs1872930) Allelic Variant Is Independently Associated With Clopidogrel Treatment Outcome. Pharmgenomics Pers. Med. 21(12), 287-295. https://doi.org/10.2147/pgpm.s222212

Malátková, P., Wsól, V., 2014. Carbonyl reduction pathways in drug metabolism. Drug Metab Rev. 46(1), 96-123. https://doi.org/10.3109/03602532.2013.853078

Nestorovska, A., Naumovska, Z., Jakovski, K., et al., 2018. Allele frequency and genotype distribution of aldo keto reductase 1D1 (AKR1D1) rs1872930 genetic variant in a Macedonian population. Mac. Pharm. Bull. 64 (1). https://doi.org/10.33320/maced.pharm.bull.2018.64.01.005

Rižner, T.L., Penning, T.M., 2014. Role of aldo-keto reductase family 1 (AKR1) enzymes in human steroid metabolism. Steroids 79, 49–63. https://doi.org/10.1016/j.steroids.2013.10.012