ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4 ,2022

The Role of Sulfonation in the Fields of Pharmacology and Toxicology

Dr. Jyotsna Sharma[1]*, Dr. Shaktibala Dutta[2], Dr. Vaishali Lote[3]

[1] Professor, Department of Pharmacology, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, India

[2] Professor, Department of Pharmacology, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, India

[3] Assistant Professor, Department of Pharmacology, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, India

ABSTRACT:

Sulfonation plays a crucial role in regulating the biological actions of numerous endogenous and exogenous compounds, such as medicines, harmful substances, hormones, and neurotransmitters. Many xenobiotics and endogenous chemicals undergo sulfonation reactions that can either activate or inactivate them. At least 10 functional genes in humans are involved in the cytosolic sulfotransferase (SULT) superfamily that catalyses the process. There is a possibility that arylsulafatase in the endoplasmic reticulum can counteract this process in healthy cells. The availability of the co-substrate/donor molecule 3'-phosphadensoine-5-phosphosulfate (PAPS) and the transport mechanisms that allow sulfated conjugates to enter and leave cells play a role in regulating sulfonation under physiological settings. There is evidence that genetic variations in each of the aforementioned pathways contribute to the observed variation in the response of individuals to various medications and harmful substances. Sulfonation plays a pivotal role in endocrine regulation, affecting not only the receptor activity of oestrogens and androgens but also steroid production and the metabolism of catecholamines and iodothyronines. Since SULTs are extensively expressed in the human foetus, sulfonation, a critical process in the body's defence against harmful substances, may play a significant role in early development. Sulfonation, as the final stage in the activation of numerous dietary and environmental substances to highly reactive hazardous intermediates implicated in carcinogenesis, is similar to many Phase I and Phase II processes.

Keywords*:* Sulfonation; Sulfation; Sulfotransferase; SULT; Sulfatase; PAPS

INTRODUCTION:

Members of the cytosolic sulfotransferase multigene family (SULT) catalyse the sulfonation of low molecular weight molecules, which plays a significant role in determining the pharmacology and toxicity of a wide variety of endogenous and exogenous substances (Coughtrie, 2002; Strott, 2002). The universal donor 3'-phosphoadenosine 5'-phosphosulfate (PAPS) transfers a sulfonate group (SO3) to a specific substrate along this pathway. However, since a SO4 ester is formed when a SO3 group is transferred to a hydroxyl acceptor, sulfonated conjugates are commonly mislabeled as sulphates [1]. A schematic of

ISSN PRINT 2319 1775 Online 2320 7876

Research paper **© 2012 IJFANS. All Rights Reserved, UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4 ,2022**

the sulfonation pathway and its many parts. Sulfonation occurs mostly in the cytosol, although it also requires the endoplasmic reticulum's arylsulfates-c (ARSc) and membrane-bound transport molecules. The linkage of sulfonate conjugate production with transport out of and into cells has been linked to both organic acid transport molecules (OAT; Bust et al., 2003) and multidrug resistant proteins (mdrs; Chu et al., 2004) [2].

Conjugates containing sulfonates may also allosterically govern the transport of other conjugates, including glucuronides, through the mrp (Chu et al., 2004). The bifunctional enzyme ATP sulfurylase/APS kinase (about 56 kDa) is responsible for PAPS synthesis (Lyle et al., 1994). Cytosolic sulfotransferases catalyse the formation of sulfonated conjugates from a wide variety of substrates (SULTs). Net sulfonation can be affected by arylsulfatases, which are present in healthy cells and can reverse the sulfonation process (Coughtrie et al., 1998; Kauffman et al., 1991; Tan and Pang, 2001) [3, 4]. The net availability of sulfonated conjugates under physiological conditions is affected by the presence or absence of substrate and PAPS, as well as the activities of synthetic SULTs and hydrolytic sulfatases.

PHARMACOGENTICS:

Human pharmacologically and toxicologically important SULT isoforms show substantial inter-individual variation in expression [for reviews see (Coughtrie, 2002; Weinshilboum and Aksoy, 1994)] [5, 6]. Numerous molecular epidemiology studies have been published that link SULT polymorphisms to disease susceptibility (Bamber et al., 2001; Seth et al., 2000; Zheng et al., 2001), and a great deal of information is available about the molecular basis behind variation in SULT activities. Platelet phenol sulfotransferase activity and thermal stability were shown to be associated with SULT1A1 genotype, according to groundbreaking research by Weinshilboum and colleagues (Haenen et al., 1991; Weinshilboum and Aksoy, 1994) [7, 8]. The presence of both thermally stable and thermally labile forms of phenol sulfotransferase in platelets, a readily available tissue, allowed for the initiation of studies into the heredity of biochemically separate forms of SULT. Genetic variation in the thermal stability of platelet phenol sulfotransferase correlates with individual variability in the sulfonation of acetaminophen following oral administration, according to early investigations using biochemical measures (Reiter and Weinshilboum, 1982) [9]. Research conducted by Raftogianis et al. (1997) using 4-nitrophenol as a substrate revealed a more than 50-fold difference in phenol sulfotransferase activity across 905 individuals [10]. SULT1A1 is a "wide spectrum" sulfotransferase that plays a role in the bioactivation of various dietary and environmental procarcinogens as well as the metabolism and detoxification of many medicines and other foreign substances (Coughtrie and Johnston, 2001; Glatt et al., 2000) [11, 12].

SULFONATION OF ENDOGENOUS AND FOREIGN CHEMICALS:

Each of the three main subfamilies of sulfotransferases has a role in the metabolism of several kinds of exogenous and endogenous chemicals. These responses have been summarised in various recent reviews. Miller and Surh (1994) provided a concise summary

ISSN PRINT 2319 1775 Online 2320 7876

Research paper **© 2012 IJFANS. All Rights Reserved, UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4 ,2022**

of the fundamental role that sulfonation plays in the activation of a wide variety of chemical carcinogens. In addition, Glatt and coworkers have published multiple reviews (Glatt et al., 2000; Thomae et al., 2001) that provide a concise summary of the literature on the activation of chemical carcinogens by individual members of the SULT family. Recent publications include a comprehensive assessment of the enzymatic properties of SULT1 family members and reviews of the role of SULTs in the biotransformation of endogenous substances (Coughtrie, 2002; Strott, 2002) [13, 15].

The hydroxysteroid metabolic pathways are closely linked to the SULT2A family of enzymes (Thomae et al., 2001; Weinshilboum and Otterness, 1994). We briefly examine some of the instances illustrate the role of sulfonation in the biotransformation of endogenous chemicals and xenobiotics [16].

FUTURE DIRECTIONS:

The primary goal of this review was to highlight the significance of sulfonation in the biotransformation of a wide variety of small compounds that are of interest in pharmacology and toxicology. Biotransformation of various endogenous and exogenous substances may play a unique role during foetal and early postnatal life, and this process regulates the actions of many endogenous molecules, such as steroid hormones and neurotransmitters. Understanding the processes that control the expression of different parts of the sulfonation system, as well as the physiological effects of modifications to this system at a young age, will be crucial [14].

According to data gathered over the past decade, sulfonation plays a vital role in controlling the effects of steroids on the brain and spinal cord. Important concerns remain unanswered about the processes that regulate the expression of different components of the sulfonation system in the brain and other tissues. It is possible that transcriptional induction of cytosolic sulfotransferases is regulated by some of the same components that control expression of cytochrome P450 enzymes. An example is the stimulation of endogenous SULT2A1 expression by the farnesoid X nuclear receptor and the vitamin D receptor, both of which are known to promote cytochrome P450 expression (Echchgadda et al., 2004; Song et al., 2001). Although studies focusing on this isoform's regulation have been published (e.g., Runge-Morris et al., 1999) [13, 12], relatively little is known about the processes that control the production of other SULT isoforms.

CONCLUSION:

At last, a picture is forming of how the many parts of the sulfonation system in the body's organs and tissues interact with one another. Recently, steroid sulfatase and other organic acid transport proteins have been located in human temporal lobe biopsy samples using mRNA expression and immunohistochemistry (Steckelbroeck et al., 2004) [16]. It is tempting to hypothesise that these factors, in conjunction with de novo production of DHEA-sulfonate and other 3-bhydroxy steroids, regulate levels of these steroids at crucial places in the brain.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper **© 2012 IJFANS. All Rights Reserved,** **UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4 ,2022**

REFERENCE:

1. Adjei, A. A., Weinshilboum, R. M. (2002). Catecholestrogen sulfation: possible role in carcinogenesis. Biochem. Biophys. Res. Commun. 292:402–408.
2. Adjei, A. A., Thomae, B. A., Prondzinski, J. L., Eckloff, B. W., Wieben, E. D., Weinshilboum, R. M. (2003). Human estrogen sulfotransferase (SULT1E1) pharmacogenomics: gene resequencing and functional genomics. Br. J. Pharmacol. 139:1373–1382.
3. Aldred, S., Waring, R. H. (1999). Localisation of dehydroepiandrosterone sulphotransferase in adult rat brain. Brain Res. Bull. 48:291–296. [In Process Citation].
4. Axelson, M. (1985). 25-Hydroxyvitamin D3 3-sulphate is a major circulating form of vitamin D in man. FEBS Lett. 191:171–175.
5. Bamber, D. E., Fryer, A. A., Strange, R. C., Elder, J. B., Deakin, M., Rajagopal, R., Fawole, A., Gilissen, R. A., Campbell, F. C., Coughtrie, M. W. (2001). Phenol sulphotransferase SULT1A1*1 genotype is associated with reduced risk of colorectal cancer. Pharmacogenetics 11:679–685.
6. Barker, E. V., Hume, R., Hallas, A., Coughtrie, M. W. H. (1994). Dehydroepiandrosterone sulfotransferase in the developing human fetus: quantitative biochemical and immunological characterization of the hepatic, renal, and adrenal enzymes. Endocrinology 134:982–989. Baulieu, E. E. (1998). Neurosteroids: a novel function of the brain. Psychoneuroendocrinology 23:963–987.
7. Baumann, E. (1876). Ueber sulfosauren im harn. Ber. Dtsch. Chem. 54–58. Besset, S., Vincourt, J. B., Amalric, F., Girard, J. P. (2000). Nuclear localization of PAPS synthetase 1: a sulfate activation pathway in the nucleus of eukaryotic cells. FASEB J. 14:345–354.
8. Boberg, E. W., Miller, E. C., Miller, J. A., Poland, A., Liem, A. (1983). Strong evidence from studies with brachymorphic mice and pentachlorophenol that 1'-sulfooxysafrole is the major ultimate electrophilic and carcinogenic metabolite of 1'-hydroxysafrole in mouse liver. Cancer Res. 43:5163–5173.
9. Bock, K. W., Frohling, W., Remmer, H., Rexer, B. (1973). Effects of phenobarbital and 3-methylcholanthrene on substrate specificity of rat liver microsomal UDPglucuronyltransferase. Biochim. Biophys. Acta 327:46–56.
10. Buist, S. C., Cherrington, N. J., Klaassen, C. D. (2003). Endocrine regulation of rat organic anion transporters. Drug Metab. Dispos. 31:559–564.
11. Buonarati, M. H., Turteltaub, K. W., Shen, N. H., Felton, J. S. (1990). Role of sulfation and acetylation in the activation of 2-hydroxyamino-1-methyl-6-phenylimidazo[4,5-b]pyridine to intermediates which bind DNA. Mutat. Res. 245:185–190.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4 ,2022

12. Buu, N. T., Duhaime, J., Savard, C., Truong, L., Kuchel, O. (1981). Presence of conjugated catecholamines in rat brain: a new method of analysis of catecholamine sulfates. J. Neurochem. 36:769–772.

13. Cascio, C., Guarneri, R., Russo, D., De Leo, G., Guarneri, M., Piccoli, F., Guarneri, P. (2000). Pregnenolone sulfate, a naturally occurring excitotoxin involved in delayed retinal cell death. J. Neurochem. 74:2380–2391.

14. Chang, H. J., Shi, R., Rehse, P., Lin, S. X. (2004). Identifying androsterone (ADT) as a cognate substrate for human dehydroepiandrosterone sulfotransferase (DHEA-ST) important for steroid homeostasis: structure of the enzyme-ADT complex. J. Biol. Chem. 279:2689–2696.

15. Chen, G., Yin, S., Maiti, S., Shao, X. (2002). 4-Hydroxytamoxifen sulfation metabolism. J. Biochem. Mol. Toxicol. 16:279–285.

16. Chu, X. Y., Huskey, S. E. W., Braun, M. P., Sarkadi, B., Evans, D. C., Evers, R. (2004). Transport of ethinylestradiol glucuronide and ethinylestradiol sulfate by the multidrug resistance proteins MRP1, MRP2, and MRP3. J. Pharmacol. Exp. Ther. 309:156–164.