Biochemical Pharmacology, Vol. 31, No. 19, pp. 3017–3021, 1982.
Printed in Great Britain.

0006-2952/82/193017-05 $03.00/0

COMMENTARY

DOES SULFATE CONJUGATION CONTRIBUTE TO THE METABOLIC INACTIVATION OF CATECHOLAMINES IN HUMANS?

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The existence of an enzymatic pathway in humans which is capable of sulfating the catecholamine neurotransmitters has been known for over four decades. The importance of this degradative pathway relative to the other amine catabolic pathways and its overall contribution to the enzymatic breakdown of these neurotransmitters have generally been disregarded, and few studies have adequately addressed the problem. Evaluation of the current literature leads one to the conclusion that only deamination by monoamine oxidase (MAO) and *O*-methylation by catechol-*O*-methyltransferase (COMT) play a predominant role in the enzymatic inactivation of the catecholamines in humans [1]. However, it has recently become apparent that the enzyme, phenol sulfotransferase (PST), has a relatively high affinity for the catecholamine neurotransmitters, dopamine and norepinephrine. The importance of this enzyme and the reaction it catalyzes has only recently become evident, and further study of this enzymatic process as it relates to sulfate conjugation of the catecholamines in human CNS and periphery is warranted. Since a number of comprehensive reviews [2, 3] have recently appeared in the literature, it is not the purpose of this commentary to present another overview of this subject. This article is intended to present a critical evaluation of the relevant literature concerning sulfate conjugation, and its role in regulating catecholamine degradation in humans, in the hopes of generating interest in a potentially important degradative pathway for the neurotransmitters, dopamine and norepinephrine.

Before describing any of the specific studies regarding sulfate conjugation of catecholamines in humans, it is necessary to present a very brief discussion of the nature and diversity of sulfation reactions that occur in mammalian systems. A wide variety of substances, both endogenous and exogenous, are capable of undergoing sulfate conjugation. These include a variety of lipids, steroids, phenolic drugs, alcohols, ascorbate and calciferol as well as the catecholamines and their metabolites [4]. The sulfate donor for all these reactions is 3′-phosphoadenosine-5′-phosphosulfate. Although extensive studies have been performed attempting to characterize the enzymes which catalyze sulfate conjugation, the exact number and identity of these sulfotransferases have not been determined satisfactorily. A major problem in this area has been the difficulty in comparing results from different laboratories, since a variety of substrates have been used to assay and characterize these enzymes [4]. Multiple forms of PST have been identified [5, 6] and, as is now apparent, these enzymes have very broad and overlapping substrate specificities. Except for some recent reports [5–7], most studies have attempted to characterize a single form of the transferase using only a single substrate.

Classification of the different forms of sulfotransferase has been primarily based on their substrate specificity. Thus, those enzyme species which sulfate estrone, corticosteroids, androstenolone or other structurally related compounds have been classified as steroid sulfotransferases, whereas those transferases which esterify hydroxylated aromatic substances have been labeled as phenol sulfotransferases. However, as pointed out above, all sulfotransferases have very broad substrate specificity and ascribing a specific class to a given enzyme species based on assays with one substrate may be misleading and an oversimplification of the actual function of the enzyme. Recent reports [5, 6, 8] have demonstrated that a family of enzymes probably exists for each class of sulfotransferase.

Sulfation of catecholamines in vivo

The first paper to demonstrate that catecholamines undergo extensive sulfate conjugation in humans appeared in 1940 [9]. In this paper, Richter reported that up to 70% of an orally administered dose of epinephrine was present in the urine as the sulfate ester. Richter indicated that, unlike phenylethylamine and most other amines, conjugation of epinephrine predominates over oxidation by MAO and suggested that it is probably the main physiological pathway by which this catecholamine is degraded in the body. In the following year, Richter and MacIntosh [10] demonstrated that epinephrine sulfate was pharmacologically inactive when tested on blood pressure, nictitating membrane and intestine of the cat. These initial observations of Richter were confirmed in 1943 by Deichmann [11] and in 1945 by Beyer and Shapiro [12]. Similarly, Kahane *et al.* [13] have demonstrated that approximately 70% of the endogenous catecholamines, norepinephrine and epinephrine, are present in human urine as the sulfate ester.

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The first report [14] that metabolites of the catecholamines also undergo extensive sulfation in humans appeared in the literature in 1960. In this paper, LaBrosse and Mann reported that the *O*-methylated metabolites of norepinephrine and epinephrine are excreted in urine mainly as their sulfate conjugate. Goodall and Rosen [15] found that, 60–70 min after i.v. injection of tracer doses of radiolabeled norepinephrine, 14% of this amine was excreted as the sulfate ester. They reported finding that the deaminated metabolites, 3,4-dihydroxyphenylglycol, 3,4-dihydroxymandelic acid and 3-methoxy-4-hydroxymandelic acid were also present as sulfate esters in urine. Similar experiments performed with epinephrine revealed that greater than 30% of the total metabolites formed was normetanephrine sulfate [16, 17]. Although the results of Goodall and coworkers demonstrate extensive sulfate conjugation of the *O*-methylated and deaminated metabolites of epinephrine and norepinephrine, little, if any, sulfation of the parent compound was observed. The sulfate ester of the major CNS metabolite of norepinephrine, 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG), has also recently been identified in human cerebral spinal fluid (CSF) and brain [18]. Approximately 20% of the total MHPG in the CSF was conjugated, whereas the levels of this sulfate ester varied from 10 to 40% in several areas of human brain. The content of the sulfate conjugates of the other metabolites of norepinephrine and the other catecholamines has not been estimated in human CNS.

The data presented above have primarily dealt with conjugation reactions involving epinephrine and norepinephrine. Numerous reports have similarly shown that dopamine and its metabolites are extensively conjugated *in vivo* in man. Goodall and Alton [19] were the first to examine the metabolic fate of dopamine injected into human subjects. They found that only 1.5% of the injected dose was recovered in the urine as dopamine sulfate. The conjugates of the deaminated and *O*-methylated products varied between 2 and 6% of the total dose. This is in contrast to excretion patterns observed for endogenous dopamine which indicated that greater amounts of the sulfate esters are formed *in vivo*. Weil-Malherbe and VanBuren [20] reported that Parkinsonian patients excreted significantly less free dopamine than normal control subjects, but that the levels of dopamine sulfate in urine were comparable between the two groups. The sulfate ester of dopamine represented up to 80% of the total dopamine excreted.

Other than the reports above, the majority of the studies in man have concentrated on examining the metabolic fate of the precusor of dopamine, L-DOPA. The first of these studies by Goodall and Alton [21] found that after i.v. administration of L-DOPA approximately 64% of the L-DOPA was converted to either dopamine or dopamine catabolites. The catabolites consisted of the conjugates of dopamine and the free and conjugated forms of 3-methoxytyramine, homovanillic acid (HVA), dihydroxyphenylacetic acid (DOPAC), and several unknown metabolites. Dopamine sulfate in urine represented 6.2% of the total L-DOPA dose administered or about 80% of the total dopamine present in urine. The extensive conversion of dopamine to its sulfate ester has been confirmed in several laboratories [22–25]. Bronaugh *et al.* [24] have also shown that the amount of conjugate formed *in vivo* is dependent on the route of administration. When L-DOPA is given orally, greater than 90% of the dopamine formed is converted to the sulfate ester, whereas only 40% is conjugated after i.v. injection of L-DOPA. The major metabolites of dopamine, DOPAC and HVA, are also extensively conjugated when L-DOPA is given orally. It is similarly shown that the levels of dopamine sulfate and DOPAC sulfate are increased when tracer doses of L-DOPA are administered compared to when larger, more therapeutic, doses are employed.

It can be argued that the metabolic patterns obtained from L-DOPA treatment described above may reflect the fate of endogenous dopamine in tissues rather than the catabolic fate of the catecholamine in the circulation. This is most likely to be true when tracer doses of L-DOPA are given as opposed to the larger more pharmacological treatment with this dopamine precusor. In support of this is the fact that, when dopamine was injected directly into the circulation, a lower percentage of dopamine sulfate was formed, 1.9% of the total dose [19] as compared to 6.2% of the total dose [21] after treatment with L-DOPA. These results imply that catecholamines formed from L-DOPA within tissues have a greater propensity to undergo sulfate conjugation. In contrast, when these amines are present in the circulation, degradation occurs primarily by either deamination or *O*-methylation. Consistent with these findings are the results described above by Goodall and coworkers [15–17] for norepinephrine. These investigators reported finding only a minor fraction of the sulfate ester of norepinephrine in urine after tracer doses of this catecholamine were administered to human subjects. This is surprising since Johnson *et al.* [26] have shown that greater than 99% of circulating dopamine and approximately 70% of circulating norepinephrine and epinephrine are present in plasma as the sulfate esters. The fact that endogenous catecholamines are present in the vasculature as the conjugates whereas exogenously administered amines undergo extensive deamination and/or *O*-methylation inplies that formation of the sulfate esters of the neurotransmitters occurs prior to their release into the circulation.

Clearly, the data presented above demonstrate that catecholamines undergo extensive conjugation in the periphery of humans. The question has to be asked, does sulfation play an important role in the enzymatic inactivation of catecholamines in the CNS? In this regard, a form of PST which is capable of sulfating the catecholamines has been shown recently to be present in human brain, and the sulfate conjugates of the catecholamines have been identified in human CSF (see below). As indicated above, the sulfate ester of at least one metabolite of norepinephrine has been identified in human brain. Detection of the sulfate esters of the catecholamines in human brain has not been reported, although Buu *et al.* [27] have recently reported finding the sulfate esters of the catecholamines in several areas of rat brain.

Characterization of human phenolsulfotransferase

The enzyme or enzymes responsible for sulfate conjugation have been identified in various organs of the human body. In a series of papers, Bostrom and coworkers [28–30] measured phenol and steroid sulfotransferase activity in a number of human tissues including liver, adrenal, jejunum, kidney, spleen and ovary. Depending on the substrate employed, the activity in each of the tissues varied considerably. Phenol sulfotransferase activity was assayed with phenol as substrate and, as will be pointed out later, the actual sulfotransferase activity responsible for catecholamine metabolism may not have been measured. As is the case in much of the literature dealing with this topic, the substrates used to assay sulfotransferase activity were often chosen for simplicity and, unfortunately, the reactions that may have been measured do not necessarily reflect the ability to sulfate dopamine and norepinephrine.

In the late 1960's and early 1970's, several reports appeared in the literature describing methods to purify PST from a number of animal species including rat [31–33] and guinea pig [34]. Again, the substrate employed varied, making it difficult, in retrospect, to accurately assess the enzyme form or forms which were being examined by each investigator. It is not the purpose of this commentary to examine in depth each of these reports since, as will be discussed, the substrate specificity of animal phenol sulfotransferases may be quite different from that found in humans. These studies, nevertheless, reveal the existence of multiple forms of PST which are capable of conjugating a variety of phenols and structurally similar substances including the catecholamines and their metabolites. Recent reports by Jakoby and coworkers [5, 6, 35] have demonstrated the presence of four distinct forms of the PST in rat liver. Three of these enzymes have been purified to homogeneity and only one, PST IV, catalyzes the sulfation of dopamine under the chosen assay conditions. All three of the enzymes which were characterized by Jakoby and coworkers, however, effectively esterified phenol.

The first report [36] that human brain was capable of sulfating phenol appeared in the literature in 1974; however, it was not until 1980 that this tissue was also shown to be capable of conjugating catecholamines and their *O*-methylated and deaminated metabolites [37]. The substrates found to have the lowest K_m values were the catecholamines and their 3-*O*-methylated derivatives. In addition, Rein *et al.* [7] reported that at least two forms of phenol sulfotransferase exist in human brain. They labeled the transferase which selectively sulfated dopamine as the M form and that which conjugated phenol as the P form. The relative amounts of these two sulfotransferases varied in several human tissues including the jejunum, platelets, adrenals, placenta and brain. The jejunum and platelets had the highest percentage of the M form under the conditions employed. Several compounds, such as 3-methoxy-4-hydroxyphenylethyleneglycol, were found to be substrates for both forms of the transferase. Other studies [38, 39] have confirmed the existence of at least two distinct species of PST in humans by selective inactivation of the M form by heat treatment. Of the substrates tested, the M form catalyzes sulfation of phenolic and catechol amines as well as their neutral metabolites, whereas the P form sulfates both the neutral and acid catabolites of the biogenic amines. Phenol and *p*-nitrophenol appear to be substrates for both forms of human PST although both compounds have lower K_m values for the P form of the transferase.

The form of PST in human brain which conjugates catecholamines appears to be distinct relative to this enzyme in common laboratory animals [39]. Recent studies in our laboratory have demonstrated that the affinity of human sulfotransferase for dopamine is almost 100 times greater than that of the sulfotransferase in rat, mouse, guinea pig, bovine and dog brain. Specifically, the K_m value for sulfation of dopamine in humans is approximately 1 μM whereas the K_m value in these animals is greater than 100 μM. The only animal examined in our laboratory for which PST has a K_m value for dopamine similar to that of the human transferase is the African green monkey. Whether the large difference between the K_m values for dopamine binding in commonly used laboratory animals and that in primates actually reflects functional differences in these enzymes, of course, is not known at this time. Clearly, a difference in K_m values of this magnitude suggests distinctive roles for PST in the different animal species. It is important to emphasize that simple metabolic studies assessing the levels of sulfation of catecholamines in animals, accordingly, may not reflect the extent to which these reactions occur in humans.

Contribution of PST to catecholamine metabolism

It is difficult, at this point, to assess the overall importance or contribution of sulfate conjugation to the catabolic inactivation of the catecholamine neurotransmitters in humans. Studies in our laboratory [39, 40] have attempted to address this problem by quantitating the extent to which each degradative pathway contributes to the metabolism of dopamine and norepinephrine in frontal cortex of human brain. These studies are based on determining the true kinetic constants and the rate equation for each of the enzymes involved in the three major enzymatic pathways for catecholamine inactivation. These five enzymes include the A and B forms of MAO, membrane-bound and soluble COMT, and PST. By substituting the kinetic constants into the appropriate rate equation, the percent contribution of each enzyme at any given concentration of dopamine or norepinephrine can be calculated. For control lobe preparations of human brain, it was determined that the maximum contribution of the sulfation pathway, at dopamine and norepinephrine concentrations of 10 μM or less, was approximately 15 and 7% of the total degradative process, respectively. The values obtained for percent conversion of dopamine and norepinephrine by the different metabolic routes most likely represent an oversimplification of the actual process in the intact tissue, since it does not take into account selective localization of the enzymes within specific cell types or access of the amines to the different enzyme sites. However, the data indicate the total capacity of each enzyme to metabolize these catecholamines in frontal cortex of

human brain. It is important to point out that the range in the relative activities of the five enzymes varied considerably in each of the brain preparations examined in our study. Interestingly, the data generated suggest that each individual has a unique composition of the five enzymes involved in metabolism of the catecholamines.

Little is known about the cellular location of the catecholamine-specific form of PST in human brain. Jansen *et al.* [41] have suggested that in rat brain PST is localized in oligodendroglial cells or, more probably, a specific type of neuron. Unfortunately, in this latter publication the substrate used was 4-methylumbelliferone, and it is not known which form of PST metabolizes this substrate. Unpublished studies in our laboratory with kainic acid lesioned rat striata strongly suggest that the dopamine-sulfating form of PST is selectively localized in neurons within the striatum. In these studies it was found that PST activity in the kainic acid treated striata was decreased significantly compared to that in the control contralateral unlesioned striata. This decrease in PST activity was similar to that seen for the neuronal marker enzyme glutamate decarboxylase. If these results also hold true for the localization of PST in human brain, then the activity measured in these frontal lobe preparations may likely reflect neuronal PST activity.

Platelet phenol sulfotransferase

Based on the data presented above, PST has the potential to play a significant role in regulating the concentrations of the catecholamine neurotransmitters in the body and, accordingly, altered levels of this enzyme may subsequently influence the levels of these neurotransmitters in both the CNS and the periphery. It is now possible to assess the activity of PST *in vivo* because it has been demonstrated recently that human platelets are capable of sulfating catecholamines and their metabolites [42–44]. Assuming that PST activity is under genetic control, then the activity measured in platelets may reflect sulfotransferase activity throughout the body. In support of this view, Anderson *et al.* [45] found a significant correlation between platelet PST activity as measured by the sulfation of 3-methoxy-4-hydroxyphenylethleneglycol in various individuals and PST activity in the kidney and gut. It should be pointed out that the substrate used in the previous study is metabolized by at least two different forms of PST. Detection of PST activity in platelets now provides us with a noninvasive procedure to evaluate the levels of PST activity in persons inflicted with a variety of diseases possibly relating to abnormal levels of the catecholamines.

Two forms of PST have been detected in human platelets and the properties of these enzymes appear to resemble those previously described for human brain [37–42]. Of the substrates that have been tested, the catecholamines have the lowest K_m values for the platelet transferases. A recent study [46] has demonstrated that the relative activities of the two enzymes in platelets vary in different individuals. Also, there was no correlation between the two PST activities and either age or sex, nor was there any correlation with platelet MAO activity.

There have been two recent clinical studies [46, 47] that have attempted to determine whether platelet PST is altered in disease states hypothesized to be associated with altered catecholamine levels. Abenhaim *et al.* [47] have reported finding that platelet PST activity is lower in two subjects having essential hypertension. Bonham Carter *et al.* [46] found that platelet PST in normal subjects was not significantly different from that in depressed patients of a diagnostic type characterized by low excretion of tyramine-*O*-sulfate after oral loading of tyramine.

The purpose of this article was to evaluate the literature regarding sulfation of the catecholamine neurotransmitters in humans in order to reassess its importance and potential role in the enzymatic inactivation of these transmitters. To this end the data clearly demonstrate the following: (1) sulfate conjugation of the catecholamines occurs both in the CNS and in the periphery of humans, (2) at least one form of sulfotransferase has a relatively high affinity for the catecholamines, (3) the form of PST which sulfates catecholamines appears to be selectively localized in neuronal cells in brain, (4) a noninvasive procedure is available to assay the activity of PST in man, and (5) prior studies that have examined the magnitude of this reaction in commonly used laboratory animals may be misleading. The cumulative effect of these observations suggests a potentially important role for sulfation in regulating the levels of the catecholamines *in vivo*. Whether altered levels of this enzyme are associated with neurological, behavioral or vascular diseases is not known, although, as pointed out above, methods are now available to address this question. Also, the effect of drugs which inhibit PST on behavior or neurological disorders has not been evaluated. It is also likely that the pathway for sulfate conjugation of the catecholamines may become more predominant in patients receiving various drugs which alter the activity of either MAO or COMT. One such example would be in depressed patients who are receiving MAO inhibitor drugs. There are many questions that need to be answered before we can adequately assess the significance of this reaction in regulating catecholamine concentrations in the human body.

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