INVITED COMMENTARY
Role of sulfate in thyroid hormone sulfation
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Although the identification of T₃ sulfate (T₃S) in humans was reported in 1958 (1), sulfation has only recently been recognized as a unique pathway of thyroid hormone metabolism (2). Sulfation is a so-called phase II detoxification pathway by which a variety of lipophilic endogenous and exogenous compounds are converted into water-soluble conjugates to facilitate their excretion in bile or urine (3). The sulfotransferases catalyzing these reactions represent a family of homologous enzymes located in the cytoplasm of many tissues, in particular liver (3). Sulfation of the phenolic hydroxyl group of T₃ and other iodothyronines has been observed in rat liver, brain and kidney, and in human liver (4–6). Normally, concentrations of iodothyronine sulfates in plasma, bile and urine are low. However, in conditions associated with a low activity of the type I iodothyronine deiodinase (ID-I), such as administration of propylthiouracil or iopanoic acid, selenium deficiency, non-thyroidal illness (NTI) and fetal development, iodothyronine sulfates accumulate in plasma and bile (7–13). The paper by Santini et al. (14) published in this issue of European Journal of Endocrinology deals with the possible mechanisms for the increase in plasma T₃S in patients with NTI.

Type I iodothyronine deiodinase is located primarily in liver, kidney and thyroid (15). It catalyzes the outer ring deiodination (ORD) and/or inner ring deiodination (IRD) of different iodothyronines, e.g. ORD of T₄ to T₃, IRD of T₄ to rT₃, IRD of T₃ to 3,3'-T₂, and ORD of rT₃ to 3,3'-T₂. Because among all iodothyronines T₃ has by far the highest hormone activity, ORD is generally regarded as an activating and IRD as an inactivating pathway. Sulfation has a dramatic effect on these processes (2). The IRD of T₄ sulfate (T₄S) and T₃S by rat ID-I is about 200 and 40 times faster, respectively, than the IRD of the non-sulfated compounds, whereas the ORD of T₄S is completely blocked. Also, human ID-I catalyzes the IRD of T₃S much more efficiently than the IRD of T₃ (16).

Because it strongly facilitates the IRD of T₄ and T₃ by ID-I, sulfation appears to be a primary step in a pathway mediating the rapid, irreversible degradation of thyroid hormone when ID-I activity is normal. However, the lifetime of these conjugates is markedly prolonged if their deiodination by ID-I is prevented (8, 17), resulting in their accumulation in plasma and a subsequent increase in their biliary excretion (7, 8). The thus excreted conjugates are hydrolyzed in the intestine by bacterial sulfatases, and at least part of the liberated iodothyronines is reabsorbed (18). However, iodothyronine sulfates are also hydrolyzed by tissue sulfatases: this has been observed for instance in liver, kidney and brain (19). Therefore, because T₃S has no affinity for the T₃ receptor (20), T₃S is truly inactivated by sulfation, but it becomes a reversible pathway for T₃ inactivation if ID-I activity is low. It has been suggested that T₃S is a reservoir from which T₃ may be recovered by intestinal and tissue sulfatase activities, depending on the tissue requirements (21). Sulfation of thyroid hormone may serve a special purpose during fetal development, providing protection to tissues that should not be exposed to T₃ while allowing T₃-dependent tissues to desulfate T₃S by expression of sulfatases (22). However, to date, evidence in support of this hypothesis is limited.

The increase in plasma T₃S in patients with NTI is explained by a decrease in its clearance either due to an inhibition of ID-I activity or to an inhibition of T₃S uptake in tissues expressing this enzyme, i.e. liver and kidneys (23). The latter may seem unlikely because the liver and kidneys are prominent sites for T₃ sulfation, but previous studies in rats suggested that the T₃S produced in these tissues is released into the circulation, recaptured and then deiodinated rather than degraded in the same cell in which it is produced (8). However, it is not excluded that production of T₃S is also altered in NTI, and the findings reported by Santini et al. (14) suggest that T₃ sulfation may be increased in patients with chronic renal failure (CRF). In comparison with patients with end-stage neoplastic disease (ESND), the patients with CRF have a mild form of NTI, showing a modest decrease in the serum T₃/T₄ ratio and a modest increase in the serum rT₃/T₄ ratio. This is further supported by the finding that, in contrast to the strong decrease in serum free T₃ (FT₃) in ESND patients, serum FT₃ in CRF patients is normal. Yet, the serum T₃S is even more elevated in the patients with CRF than in those with ESND. This is explained in part by the higher serum FT₃ levels and, hence, higher substrate availability in CRF patients than in ESND patients. However, the increase in serum T₃S/FT₃ ratio in CRF patients compared with the controls appears greater than expected on the basis of the mild degree of NTI in these patients. This suggests an additional mechanism(s) for the increased serum T₃S in CRF patients compared with other patients with NTI.
Santini et al. (14) put forward two possible explanations for the disproportionate increase in serum T₃S levels in patients with CRF. The first of these implies a decreased renal clearance of T₃S in CRF. They suggest that renal clearance of T₃S is by glomerular filtration, followed by tubular reabsorption and intracellular deiodination. However, in normal humans the glomerular filtration rate (GFR) amounts to about 125 ml of serum per minute. Because only the free fraction of T₃S (0.25%) is available for filtration, the calculated renal clearance rate of T₃S amounts to only about 450 ml/day, which is negligible compared with its metabolic clearance rate of 1351/day (17). Although active tubular uptake of T₃S from blood and subsequent intracellular deiodination is not excluded, the second explanation provided by the authors for the “more than expected” increase in serum T₃S in patients with CRF is more appealing.

Santini et al. (14) found that the serum inorganic sulfate concentration was markedly higher in the CRF patients (mean 10.9 mmol/l) than in controls (mean 0.3 mmol/l), which is known to be due to a decreased renal excretion of this ion in CRF. Previous studies in our laboratory have shown that sulfation of iodothyronines is impaired in sulfate-depleted cultures of rat hepatocytes (24, 25). (The synthesis of the co-factor for sulfotransferases, 3'-phosphoadenosine-5'-phosphosulfate, is obviously strictly dependent on the sulfate supply). This defect is rapidly restored after readdition of inorganic sulfate, and maximum iodothyronine sulfation is observed at a medium sulfate concentration of about 1 mmol/l (24, 25). Furthermore, it has been demonstrated in rats that half-maximal rates for the sulfation of drugs in vivo occur at a serum sulfate concentration of about 0.3 mmol/l (26). Although similar data are not available for humans, these findings suggest that, also in humans, deviations in the serum inorganic sulfate concentration from the normal mean of 0.3 mmol/l result in parallel changes in tissue sulfotransferase activity. The increase in serum T₃S in CRF patients may thus indeed be due in part to the strongly increased serum inorganic sulfate concentration. Conversely, T₃ sulfation may be decreased if inorganic sulfate stores become depleted, for instance by a low-protein diet or by administration of drugs that are metabolized importantly by sulfation (26). The physiological relevance of such changes in T₃ sulfation remains to be explored.

References

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