Depletion of Endogenous Inorganic Sulfate in the Mammalian Central Nervous System by Acetaminophen

Keyphrases □ Acetaminophen—cerebrospinal fluid, sulfate depletion in rats □ Endogenous inorganic sulfate—depletion in cerebrospinal fluid of rats by acetaminophen

To the Editor:

Acetaminophen is metabolized in part by conjugation with sulfate (1, 2), a process that causes transient depletion of endogenous inorganic sulfate in plasma of rats and humans (3, 4). Sulfate activation (5) and conjugation (6) occur in the mammalian brain and may have a significant role in regulating the levels of biogenic amine neurotransmitters (7). Sulfate is also needed for the synthesis of certain brain tissue constituents such as mucopolysaccharides and sulfatides (5). It is of interest, therefore, to determine if the widely used analgesic and antipyretic agent acetaminophen can deplete inorganic sulfate in the central nervous system.

Female Lewis rats, 170–195 g, were cannulated (right jugular vein) under light ether anesthesia 1 d before the experiment. On the next day, the animals were placed in individual plastic metabolism cages, and food and water were withdrawn. Acetaminophen (10 mg/mL in normal saline solution) was infused at a rate of ~12 mg/h/rat for 6 h; control rats received an infusion of drug-free saline solution. At the end of the infusion, the animals were anesthetized with ether, ~0.1 mL cerebrospinal fluid (CSF) was obtained from the cisterna magna, and blood was collected from the abdominal aorta into heparinized tubes. The concentrations of inorganic sulfate in CSF and plasma were determined by single-column ion chromatography, using a mobile phase of 4 mM potassium hydrogen phthalate adjusted to pH 4.5 with potassium hydroxide, a Wescan anion exchange column, and conductivity detection (8). Potassium nitrate was added to the plasma samples as an internal standard; CSF samples were assayed without internal standard because of the presence of interfering peaks. Heparin did not affect the assay.

The results of the study are summarized in Table I. The normal concentration ratio of endogenous sulfate, CSF-plasma, was on average 0.224. This is similar to the reported concentration ratio of 0.24 in cats (9), 0.17 in rabbits (9), and 0.30 in humans (10). The 6-h infusion of acetaminophen caused a pronounced reduction of inorganic sulfate concentrations in plasma, as already reported (3), and also reduced the concentration of inorganic sulfate in CSF. However, the CSF-plasma concentration ratio increased to 0.530 on the average. There was a significant negative correlation between the CSF-plasma concentration ratio and the plasma concentration of inorganic sulfate ($r = -0.926$, $p < 0.01$).

Table I—Effect of Acetaminophen Administration on Endogenous Inorganic Sulfate Concentrations in the Cerebrospinal Fluid and Plasma of Rats [a]

	Controls ($n = 5$)	Acetaminophen Treated ($n = 8$)
Cerebrospinal fluid	0.164 ± 0.023	0.067 ± 0.022[b]
Plasma	0.731 ± 0.020	0.132 ± 0.055[b]
CSF-plasma concentration ratio	0.224 ± 0.028	0.530 ± 0.141[b]

[a] Results are expressed as mean ± *SD*. Concentrations are millimolar. [b] Significantly different from corresponding control value, $p < 0.01$ by two-sample rank test.

These observations demonstrate that treatment with acetaminophen can cause depletion of endogenous inorganic sulfate not only in plasma but also in the central nervous system. Since plasma protein binding of inorganic sulfate is negligible (10, 11), the substantially lower concentration of the anion in CSF than in plasma suggests that sulfate is transported by a specialized process from CSF to plasma, as already suggested by others (12). Moreover, the increased CSF-plasma concentration ratio in the sulfate-depleted acetaminophen-treated rats (Table I), and the decreased ratio when plasma sulfate concentrations are increased by intravenous injection of sodium sulfate (9), indicate that the transport process is saturable. In this respect, sulfate homeostasis in CSF is facilitated as is plasma sulfate homeostasis, the latter by a specialized renal transport process (4, 13). While the specialized transport processes dampen fluctuations of endogenous sulfate concentrations, they do not prevent substantial concentration changes due to depletion of endogenous sulfate resulting from its utilization for sulfate conjugation of phenolic drugs such as acetaminophen. It is desirable, therefore, to determine the effect of acetaminophen on endogenous sulfate concentrations in the CSF of human subjects and such studies are now in progress.

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