SUMMARY

The availability of inorganic sulfate as a factor determining the rate and the extent of sulfate conjugation of xenobiotics in vivo is investigated in the rat.

To estimate the pool size of inorganic sulfate under various experimental conditions the concentration of sulfate in serum or plasma, and the excretion of sulfate in urine has been determined. In mammals rather large species differences were found in the serum concentration of sulfate. In addition, we observed in the rat a daily circadian rhythm in serum sulfate (Supplement I).

The serum concentration of sulfate was significantly increased by oral administration of sodium sulfate (Supplement II) or cysteine (Supplement III). Inorganic sulfate was rapidly absorbed from the gastro-intestinal tract and was almost completely excreted in urine within 24 hr. The extent of sulf-oxidation of cysteine to inorganic sulfate was different for the two stereo-isomers of cysteine, L- and D-cysteine. D-cysteine was degradated to sulfate more rapidly and to a larger extent than L-cysteine, probably because D-cysteine cannot be incorporated into glutathione and various proteins.

To investigate the role of sulfation in the metabolism of its xenobiotic substrates, two methods to decrease the availability of inorganic sulfate in the rat have been developed. The serum concentration of sulfate was decreased (a) by feeding a low-protein diet, or (b) by administration of a large dose of a substrate of sulfation (Supplement IV). Low sulfate availability limited sulfation capacity and, thereby, increased the risk of toxic effects of xenobiotics that are substrate of sulfation (Supplement V).

When the plasma concentration of sulfate in the rat decreased below its physiological concentration (about 0.9 mM) the rate of sulfation of harmol was significantly decreased. An increase of plasma sulfate above the physiological level caused no additional increase in sulfation rate. The apparent K_m for sulfate in the overall sulfation of harmol (sulfate activation and sulfate transfer) was estimated to be about 0.3 - 0.4 mM (Supplement VI).

LIST OF PUBLICATION

Weitering, J.G., Kr
inorganic sulfat
of xenobiotics i
Biochem. Pharmac

Krijgsheld, K.R., F
G.J.: Absorptio
fate after oral
Biochim. Biophy

Krijgsheld, K.R.,
inorganic sulfa
Comp. Biochem.

Krijgsheld, K.R.,
to decrease the
gation in the r

Krijgsheld, K.R.,
oxidation of L-
rat. Biochim.

Krijgsheld, K.R.,
static effect
induced choles
col. Exp. Ther

Mulder, G.J. and
for sulfate co
health researc
Publishers Ltd

Krijgsheld, K.R.
as a rate-lim
in vivo, in:
G.J., Caldwel
Francis Ltd.,