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Buthionine Sulfoximine (BSO)

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Paper IV

Abbreviations

BSO: buthionine sulfoximine or S-n-butyl homocysteine sulfoximine
GSH: glutathione GSSG: glutathione disulfide
MSO: methionine sulfoximine

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Abstract

Buthionine sulfoximine (S-n-butyl homocysteine sulfoximine, BSO), an irreversible inhibitor of γ-glutamylcysteine synthetase, has been widely used to inhibit glutathione (GSH) synthesis. BSO was developed from methionine sulfoximine (MSO), which is an inhibitor of γ-glutamylcysteine synthetase and glutamine synthetase, by substitude S-methyl group of MSO with S-Alkyl moieties. After this structure changing, BSO only selective inhibit γ-glutamylcysteine synthetase, not inhibit glutamine synthetase.

Introduction

Methionine sulfoximine (MSO) is an inhibitor of γ-glutamylcysteine synthetase and glutamine synthetase; thus it leads to decreased tissue levels of glutathione and glutamine [1]. During glutathione or glutamine synthesis, enzymes bound γ-glutamyl phosphate with cysteine or ammonia to form γ-glutamylcysteine or glutamine. MSO is an analog of γ-glutamyl phosphate (Figure 1, 2), so it can inhibit both γ-glutamylcysteine synthetase and glutamine synthetase [2].

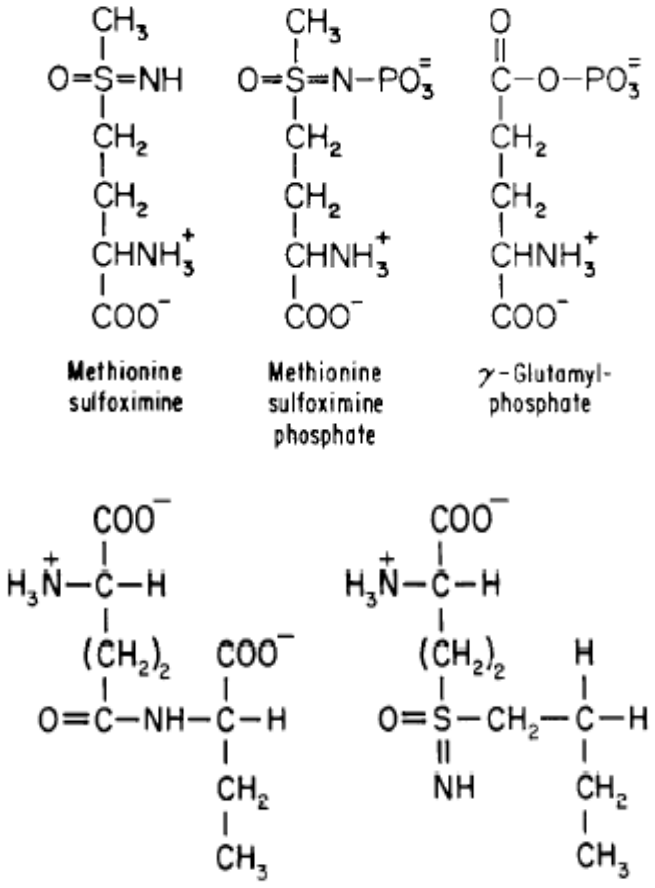

Figure 1: Structure of compounds. Methionine sulfoximine (MSO) and its phosphate are analogs of γ-glutamyl phosphate. BSO is a derivative of MSO. BSO is analogs of γ-glutamyl-α-aminobutyrate and γ-glutamylcysteine.

Meister's group wanted to achieve a derivative of MSO that only inhibit γ-glutamylcysteine synthetase without perturbing glutamine synthetase. They found that the S-methyl group of MSO attaches to the glutamine synthetase enzyme site that normally binds ammonia [3] (Figure 2). So, they proposed that substitution of bulkier moiety in place of methyl group of MSO interferes with the attachment of the inhibitor to glutamine synthetase, the analogous region of the active site of γ-glutamylcysteine synthetase would be expected to bind a larger group since the acceptor amino acid (cysteine, α-aminobutyrate) is much larger than ammonia or methyl group (Figure

1,2). Proprothionine sulfoximine, buthionine sulfoximine, derivatives of MSO, are very effective inhibitors of γ-glutamylcysteine synthetase and no significantly affect the synthesis of glutamine [4,5].

Inhibit mechanism

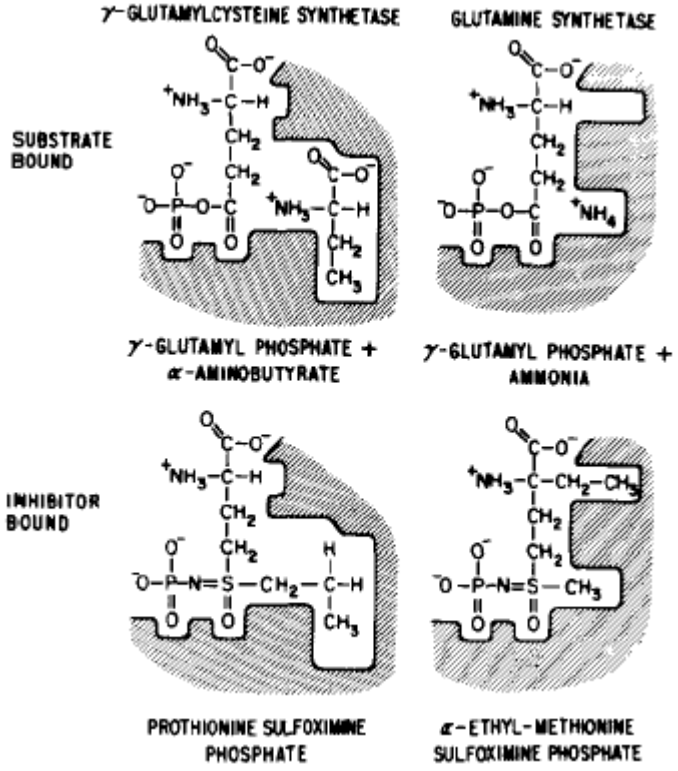

Figure 2: Diagramatic representation of the binding of substrates and inhibitors to the active sites of the synthetase. Adapted from [4]

BSO is analogs of γ-glutamyl-α-aminobutyrate and γ-glutamylcysteine (Figure 1). It can bind to γ-glutamylcysteine synthetase like the prothionine sulfoximine bind to γ-glutamylcysteine synthetase in figure 2, but it can't bind to glutamine synthetase because the side chain is bigger

than ammina. BSO is more efficient in γ-glutamylcysteine synthetase inbitition than prothionine sulfoximine (table 1) [4].

TABLE I

Inhibition of γ-glutamylcysteine synthetase by analogs of methionine sulfoximine

Sulfoximine	Inhibition of γ-glutamylcysteine synthetase[a]		Isosteric acceptor amino acid[b]	K_m of amino acid[c]
	10 μM[d]	100 μM[d]		
	% inhibition			*mM*
L-Methionine-(*SR*)-sulfoximine	8	52		
L-Ethionine-(*SR*)-sulfoximine	3	35	Glycine	>250
DL-Prothionine-(*SR*)-sulfoximine	25	96	L-Alanine	75
DL-Buthionine-(*SR*)-sulfoximine	100 52[e]	100	L-α-Aminobutyrate	3.3
α-Methyl-DL-buthionine-(*SR*)-sulfoximine	72 9[e]	100	L-α-Aminobutyrate	3.3

Table 1: The ability of γ-glutamylcysteine synthetase inhibition of different derivatives of MSO. Adapted from [4].

Physiological functions

Summary

BSO is a derivative of MSO. BSO is analogs of γ-glutamyl-α-aminobutyrate and γ-glutamylcysteine, so it can inhibits GSH synthesis by selectively inhibiting γ-glutamylcysteine synthetase. Because BSO can deplete the GSH, it change the redox environment in side the cell.

References

1. Griffith, O. W., Meister, A. (1978) Differential inhibition of glutamine and gamma-glutamylcysteine synthetases by alpha-alkyl analogs of methionine sulfoximine that induce convulsions**.** *J Biol Chem* **253**: 2333-2338.
2. Meister, A., Tate, S. S. (1968) Glutathione and related gamma-glutamy compounds: biosynthesis and utilization (review) *annu rev biochem* **45**:559-604
3. Meister, A. (1974) The enzymes 3rd ED, **10**:699-754
4. Griffith, O. W., Meister, A. (1979) Potent and specific inhibition of glutathione aynthesis by buthionine sulfoximine (S-n-butyl homocysteine sulfoximine) *J Biol Chem* **254**: 7558-7560.
5. Griffith, O. W., Anderson, M. S., Meister, A. (1979) Inhibition of glutathione aynthesis by prothionine sulfoximine (S-n-propyl homocysteine sulfoximine), a selective inhibitor of γ-glutamylcysteine synthetase. *J Biol Chem* **254**: 1205-1210.
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