Inhibitors of H_2S-generating enzymes reduce the survival of human multiple myeloma-derived KMS-11 cells with resistance to bortezomib, a proteasome inhibitor

Fumiko Sekiguchi[1], Yukiho Fukushima[1], Shiori Hiramoto[1], Hirokazu Tanaka[2], Ryuji Ashida[2], Itaru Matsumura[2], Atsufumi Kawabata[1]

[1]Lab. Pharmacol. Pathophysiol., Fac. Pharm., Kindai Univ., [2]Dept. Hematol. Rheumatol., Fac. Med., Kindai Univ.

H_2S is endogenously produced by cystathionine-γ-lyase (CSE), cystathionine-β-synthase (CBS) or 3-mercaptopyruvate sulfurtransferase (3-MST). In the present study, we examined the role of endogenous H_2S in the survival of human multiple myeloma (MM)-derived KMS-11 cells and KMS-11/BTZ cells that acquired resistance to bortezomib (BTZ), a proteasome inhibitor. BTZ significantly decreased the viability of KMS-11 and KMS-11/BTZ cells at 10-1000 and 100-1000 nM, respectively. Both Na_2S, an H_2S donor, and GYY4173, a long-lasting H_2S releaser, slightly increased the viability of those cells. Aminooxyacetic acid (AOAA), a CBS inhibitor, strongly suppressed the viability of KMS-11 and KMS-11/BTZ cells, regardless of the presence of BTZ, and DL-propargylglycine (PPG), a CSE inhibitor, exhibited relatively minor cytotoxicity. In contrast, a 3-MST inhibitor had little or no such effect. GYY4173 significantly reversed the cell toxicity of PPG or AOAA in the presence of BTZ. BTZ treatment at 10 nM for 24 h markedly increased protein levels of CBS among three H_2S-generating enzymes in KMS-11, but not KMS-11/BTZ, cells. These data suggest that H_2S generated mainly by CBS promotes the survival of both KMS-11 and KMS-11/BTZ cells, regardless of the presence of BTZ, and that CBS inhibitors are useful to treat BTZ-resistant MM.