Gamma-aminobutyric acid as a promoting factor of cancer metastasis; induction of matrix metalloproteinase production is potentially its underlying mechanism.


Source

Departments of Urology, Osaka Medical College, Takatsuki, Osaka, Japan.

Abstract

We investigated expression of gamma-aminobutyric acid (GABA), glutamate decarboxylase, and matrix metalloproteinase (MMP) in the prostates of patients with cancer or benign prostatic hypertrophy by immunohistochemical study. Marked expression of GABA, glutamate decarboxylase 67, and MMPs was observed in the prostates of cancer patients with metastasis (n = 72) and lymph node metastasis, although only sparse expression was noted in those of cancer patients without metastasis (n = 76) or patients with benign prostatic hypertrophy (n = 152). We then investigated the influence of GABA stimulation on in vitro MMP production and the invasive ability of cancer cells using human prostate cancer cell line C4-2. The production of MMPs increased significantly in cancer cells after a 24-h incubation with GABA. Cell invasion assay using a BioCoat Matrigel Invasion Chamber kit revealed that GABA stimulation significantly promoted the invasive ability of cancer cells and that addition of MMP inhibitor GM6001 significantly decreased GABA-induced migration. This may indicate the involvement of MMP activity in GABA-induced cancer cell invasion. We further analyzed the transmission pathway by performing GABA receptor modulation. The GABA(B) receptor agonist baclofen significantly increased MMP production as well as invasive ability. Moreover, blockade of the GABA(B) receptor pathway using GABA(B) receptor antagonist CGP 35348 significantly inhibited GABA-induced MMP production and invasive ability in cancer cells, whereas GABA(A) receptor modulation did not influence MMP production or the invasive ability of cancer cells. Thus, increased expression of GABA may be implicated in cancer metastasis by promoting MMP production in cancer cells, and the GABA(B) receptor pathway may be involved in the process.