0026-895X/03/6304-799–807$7.00
MOLECULAR PHARMACOLOGY
Vol. 63, No. 4
2211/1052153
Mol Pharmacol 63:799–807, 2003
Printed in U.S.A.

Brominated Derivatives of Noscapine Are Potent Microtubule-interfering Agents That Perturb Mitosis and Inhibit Cell Proliferation

JUN ZHOU, KAMLESH GUPTA, SHEFALI AGGARWAL, RITU ANEJA, RAMESH CHANDRA, DULAL PANDA, and HARISH C. JOSHI

Graduate Program in Biochemistry, Cell and Developmental Biology (J.Z.) and Department of Cell Biology (J.Z., H.C.J.), Emory University, Atlanta, Georgia; Bhupat and Jyoti Mehta School of Biosciences and Bioengineering, Indian Institute of Technology, Bombay, Mumbai, India (K.G., D.P.); Dr. B. R. Ambedkar Center for Biomedical Research (S.A., R.C.) and Department of Chemistry (R.A.), University of Delhi, Delhi, India

Received October 11, 2002; accepted December 16, 2002

This article is available online at http://molpharm.aspetjournals.org

ABSTRACT

Noscapine, a microtubule-interfering agent, has been shown to arrest mitosis, to induce apoptosis, and to have potent antitumor activity. We report herein that two brominated derivatives of noscapine, 5-bromonoscapine (5-Br-nosc) and reduced 5-bromonoscapine (Rd 5-Br-nosc), have higher tubulin binding activity than noscapine and affect tubulin polymerization differently from noscapine. In addition, they are able to arrest cell cycle progression at mitosis at concentrations much lower than noscapine. Interestingly, whereas noscapine-arrested cells have nearly normal bipolar spindles, cells arrested by 5-Br-nosc and Rd 5-Br-nosc form multipolar spindles. Nevertheless, noscapine and the two derivatives all affect the attachment of chromosomes to spindle microtubules and they impair the tension across paired kinetochores to similar degrees. 5-Br-nosc and Rd 5-Br-nosc are also more active than noscapine in inhibiting the proliferation of various human cancer cells, including those that are resistant to paclitaxel and epothilone. Our results thus indicate a great potential for the use of 5-Br-nosc and Rd 5-Br-nosc both as biological tools for studying microtubule-mediated processes and as chemotherapeutic agents for the treatment of human cancers.

Microtubules are helical polymers assembled from the heterodimer of α- and β-tubulin. They play important roles in shaping cells and directing intracellular motility. During cell division, microtubules form a bipolar apparatus called the mitotic spindle, which mediates chromosome distribution into two daughter cells (McIntosh, 1994). Microtubules are intrinsically dynamic and they alternate abruptly and stochastically between periods of growth and shortening. The dynamic nature is crucial for the organization and function of microtubules, especially for spindle morphogenesis and chromosome movement during mitosis (Desai and Mitchison, 1997). Eukaryotic cells have evolved a surveillance mechanism called the spindle assembly checkpoint, which blocks cell cycle progression at mitosis when the spindle has a defect or when chromosomes are not properly aligned at the equatorial plane (Zhou et al., 2002d). Not surprisingly, chemical compounds that target microtubules can arrest cells at mitosis, a property attributed to the use of microtubule-interfering agents in cancer chemotherapy (van Tellingen et al., 1992; Rowinsky, 1997; Crown and O'Leary, 2000).

There are two classes of microtubule-interfering agents: those that inhibit microtubule polymerization (such as colchicine, nocodazole, and the vinca alkaloids) and those that promote microtubule polymerization, such as the taxoids and epothilone (Jordan and Wilson, 1999). It is now clear that although all of these agents can efficiently block cell cycle progression, only a select few have been used clinically for the treatment of human cancers. In addition, there are differences regarding the toxicity and the efficacy of these antimicrotubule agents for distinct classes of tumors. Even for drugs that are currently in clinical use (e.g., paclitaxel and vinblastine), although patients have impressive initial response, many of them relapse after treatment because of the development of drug resistance. Thus, the development of more potent and selective antimicrotubule drugs are greatly needed, especially for the treatment of human cancers resistant to currently used drugs.

We have recently identified noscapine (Fig. 1A), a phthalideisoquinoline alkaloid from opium, as a microtubule-inter-

This work was supported by funding from the National Institutes of Health (to H.C.J.) and from the Department of Science and Technology, Government of India (to D.P.).

ABBREVIATIONS: 5-Br-nosc, 5-bromonoscapine; Rd 5-Br-nosc, reduced 5-bromonoscapine; FBS, fetal bovine serum; PIPES, piperazine-*N*,*N*′-bis(2-ethanesulfonic acid); PBS, phosphate-buffered saline; PI, propidium iodide; DMSO, dimethyl sulfoxide; FITC, fluorescein isothiocyanate.