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REVIEW

Noscapine, a Non-addictive Opioid and Microtubule-Inhibitor in Potential Treatment of Glioblastoma

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Abstract

Noscapine is a phthalide isoquinoline alkaloid that easily traverses the blood brain barrier and has been used for years as an antitussive agent with high safety. Despite binding opioid receptors, noscapine lacks significant hypnotic and euphoric effects rendering it safe in terms of addictive potential. In 1954, Hans Lettré first described noscapine as a mitotic poison. The drug was later tested for cancer treatment in the early 1960's, yet no effect was observed likely as a result of its short biological half-life and limited water solubility. Since 1998, it has regained interest thanks to studies from Emory University, which showed its anticancer activity in animal models with negligible toxicity. In contrast to other microtubule-inhibitors, noscapine does not affect the total intracellular tubulin polymer mass. Instead, it forces the microtubules to spend an increased amount of time in a paused state leading to arrest in mitosis and subsequently inducing mitotic slippage/mitotic catastrophe/apoptosis. In experimental models, noscapine does not induce peripheral neuropathy, which is common with other microtubule inhibitors. Noscapine also inhibits tumor growth and enhances cancer chemosensitivity via selective blockage of NF-κB, an important transcription factor in glioblastoma pathogenesis. Due to their anticancer activities and high penetration through the blood–brain barrier, noscapine analogues strongly deserve further study in various animal models of glioblastoma as potential candidates for future patient therapy.

Keywords Noscapine · Microtubule · Glial tumor · Glioblastoma

Introduction

High-grade glial tumors continue to demonstrate large rates of mortality even with aggressive management. The most recent treatment standards, which include maximum surgical resection, radiotherapy and adjuvant temozolomide chemotherapy, only provide a median survival of ~ 15 months in patients with glioblastoma multiforme [1]. Despite extensive basic and clinical study, there exist only a very limited number of medicines that are effective in the treatment of neuro-oncological diseases. However, effective remedies could be just within our reach as the potential for relatively inexpensive drugs to exert versatile benefits in a number of different disease conditions may yet to be discovered. In this review, we have focused on such a drug, noscapine, which harbours tremendous potential to be developed as a new agent in neuro-oncological diseases. The second reference of this manuscript is also a review, yet it deals mostly with the history and general clinical applications of the drug. Previously thus far, there has been no review with a selective focus on the potency of noscapine in gliomas. At first, we will outline the general chemistry and history of noscapine.

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Noscapine. General Chemistry and History of the Drug

Noscapine is a phthalide-isoquinoline alkaloid of *Papaversomniferum* (Fig. 1) and its IUPAC name is (3S)-6,7-dimethoxy-3-[(5R)-4-methoxy-6-methyl-7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-5-yl]-3H-2-benzofuran-1-one [2]. Phthalide-isoquinoline compounds exist in the plant families Papaveraceae, Berberidaceae, and Ranunculaceae, but noscapine and the related compound narcotoline are confined to members of the genus Papaver. Noscapine has many other names including capval, coscopin, narcompren, narcosine, narcotine, nectodon, nospen, anarcotine, terbenol, and tusscapine [2, 3]. After morphine, noscapine is the most abundant of the alkaloids of *Papaversomniferum* and was among the first of the alkaloids to be isolated [4]. French chemist Charles Derosne isolated noscapine from opium in 1803 and named the compound ‘ ‘sel narcotique de Derosne’ ’ (Derosne’s narcotic salt). Pierre Jean Robiquet later demonstrated that Derosne’s narcotic salt was not a morphine meconate, but rather a new molecule that he named narcotine (former name for noscapine). Noscapine’s molecular weight is 413.42 g/mol and the molecular formula is $C_{22}H_{23}NO_7$. It is a white powder that is bitter and odorless. Noscapine is insoluble in water, mostly insoluble in vegetable oils, slightly soluble in alcohol and ether, and soluble in benzene and acetone [2]. A historical time line of noscapine’s actions is provided in the second reference of this manuscript. Briefly, the main developments are as follows: in 1954, Hans Lettré defined noscapine as a relatively weak mitotic poison whose anti-mitotic activity acted synergistically with that of *N*-methyl-colchicine. In 1997, noscapine’s efficacy to antagonize dopamine synthesis in PC12 cells was revealed. In 1998, mouse models demonstrated the potent in vivo antineoplastic activity of noscapine against various cancers. In 2003, noscapine’s antistroke efficacy was found. In 2003, brominated noscapine analogs were synthesized and demonstrated a prominent ability to block mitosis in malignant cells. In 2010, studies demonstrated that noscapine might alleviate the disease burden in polycystic ovarian syndrome rodent models. In 2014, third-generation hydrophilic derivatives of noscapine were synthesized. Figure 2 depicts the general structure of noscapine and summarizes its anticancer mechanisms.

Fig. 1 *Papaver somniferum*

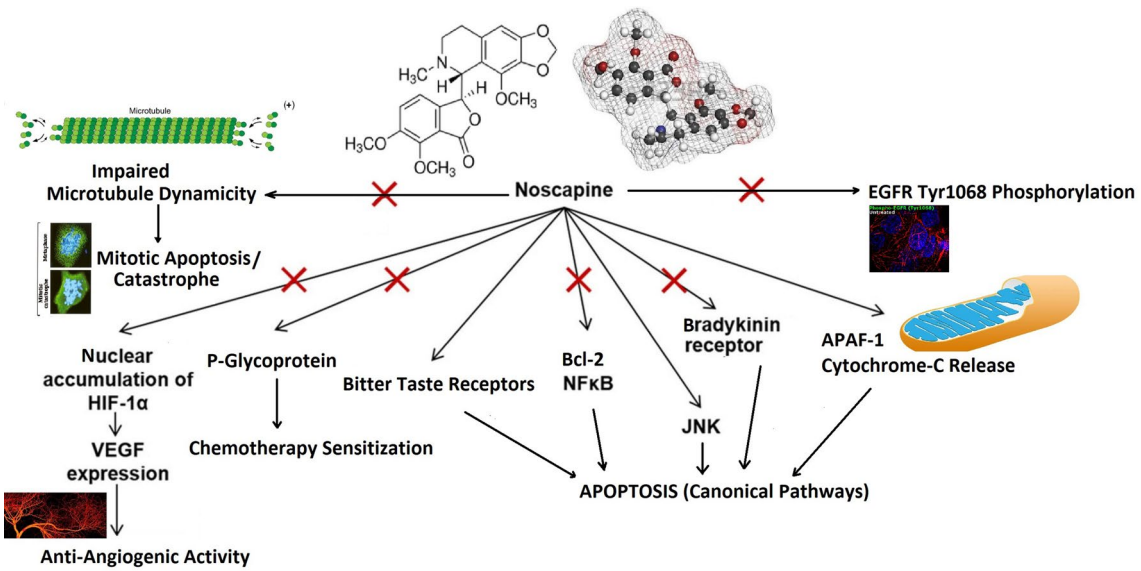


Fig. 2 Putative action mechanisms of noscapine in glioblastoma

In 1930, noscapine was discovered as an antitussive agent that did not cause significant secondary sedative, hypnotic, or euphoric effects. As a result, the drug is nonaddictive and carries mild central nervous system activity similar to that of papaverine [2, 4]. This distinguishes noscapine from codeine, which is frequently abused due to its addictive properties as a result of its metabolite codeine-6-glucuronide [5]. Activity on the μ-opioid receptor causes the clinical effects associated with opioids [6]. However, data indicates that noscapine may bind a different opioid receptor and not the μ-opioid receptor like the stronger addictive opioids [2]. In support of this theory is the finding that noscapine lacks antitussive properties in a dose-dependent manner when the σ-opioid receptor is antagonized [7]. Among neurotrasmitter-related structures, indole amines and carbolines also exert affinity for noscapine sites [4]. Noscapine hinders carbachol-stimulated phosphoinositide turnover in guinea pig and rat brain slices, with structural analogs (hydrastein, bicuculline, papaverine) harbouring similar potencies for binding to noscapine binding sites and blocking phosphoinositide turnover [4]. Noscapine and its derivatives also prominently increase the ability of forskolin to augment cAMP levels in brain slices [4]. Noscapine has chemical moieties similar to those of the microtubule inhibitory drugs colchicine and podophyllotoxin, which led to studies about its possible employment as an anticancer agent [8]. Noscapine undergoes extensive 'first pass' metabolism mainly by C–C cleavage, *O*-demethylation and cleavage of methylenedioxy group in humans. Its main metabolites include cotarnine, hydrocotarnine, and meconine, which are produced via the cleavage of the C–C bond between isoquinoline and phthalide groups [8]. In humans, noscapine has a relatively high biosafety, yet its poor water solubility may attenuate its potential as will be discussed below.

Noscapine. Blood Levels and Biosafety

In humans, oral administration of 50 mg of noscapine results in rapid absorption and a maximum plasma concentration of 182 ng/mL after 1 h [8]. Thereafter, noscapine levels decline with a half-life of 124 min and an absolute oral bioavailability of 30% [8]. Aneja et al. found mean plasma noscapine concentration to be 7.88 μg/mL 5 min after a 10 mg/kg intravenous noscapine bolus in mice [9]. After 4 h, the levels were undetectable, suggesting the mean total body clearance was 4.78 L/h with a mean volume of distribution of 5.05 L [9]. A study on terminally ill cancer patients conducted in 1961 revealed that when using daily doses of up to 3 g, 80% of patients experienced no side effects while the remaining 20% experienced sedation and abdominal discomfort [4, 10]. However, on doses of 4–6 g oral daily, 6 of 7 patients experienced toxicity, including mental confusion and coma [4, 10]. Noscapine has a short biological half-life, poor absorption, and limited water solubility, which make it difficult to harness as an oral anticancer drug [2]. Hence, recent studies have focued on developing novel techniques for targeted delivery and extended serum presence of noscapine. Additional research has been performed to discover novel noscapine analogues with higher water solubility and higher tumoricidal activity at lower dosages [2]. Following explaining the chemistry and biosafety of noscapine, below, we will outline its main mechanism of action–inhibition of microtubules.

Noscapine: Main Mechanism of Action as a Selective Microtubule Inhibitor in Cancer Cells

Dynamic polymerization and depolymerization of microtubules is essential for the formation of the mitotic spindle, a key step in cell proliferation. Thus, this known property has led to a prominent interest in discovering small organic molecules that modulate the dynamics of microtubules in order to block cancer cell mitosis [8]. Mitosis necessitates a fine control of microtubule dynamics for generation of tension across kinetochore pairs and proper chromosome alignment. During mitosis, spindle microtubules are 10–100 fold more dynamic than interphase microtubules, which allows effective capturing, alignment, and segregation of chromosomes [11]. Hence, even minor alterations of microtubule dynamics can signal the spindle checkpoint to hinder anaphase onset and chromosome segregation resulting in exit from the cell cycle and apoptosis [11]. Various drugs have been successfully employed in cancer treatment that function primarliy through alteration of microtubule assembly. Examples include vinca alkaloids drugs (vincristine, vindesine), which block the assembly of microtubules while taxanes do the opposite and block microtubule disassembly. The anti-cancer activity of noscapine was hypothesized and tested as early as 1961 due to its properties as a mitotic poison and synergistic action with colchicine [2, 10]. In one study, 32 terminally-ill cancer patients were treated with noscapine doses ranging from 1 to 6 g daily. Unfortunately, no observable antitumor effects were observed. However, this was likely as a consequence of the tested population having such advanced stage disease that many patients died from their cancer before completing the planned 6-week course of treatment [10]. In 1998, studies from Emory University showed that noscapine blocked solid murine lymphoid tumors. Additionally, human breast and bladder tumors implanted in nude mice treated with noscapine demonstrated almost no toxicity [8]. As a result, noscapine regained significant attention from cancer researchers.

Noscapine binds β-tubulin at a site distinct from that of vincristine and other tubulin-binding agents including

taxanes and colchicine [11]. Rather than exerting a net effect on polymerization versus depolymerization of microtubules, noscapine binds to tubulin and alters its conformation [11]. In contrast to other microtubule-inhibitors such as paclitaxel, nocodazole, and vinblastine, noscapine does not affect the steady-state monomer/polymer equilibrium or the total tubulin polymer mass in cells [12]. Several in vitro studies were performed to reveal the effects of noscapine on tubulins: (i) Tubulin fluorescence was measured in the presence or absence of noscapine; (ii) Experiments were performed with [^{3}H]colchicine competition; (iii) To define the effect of noscapine on the tubulin subunit assembly, turbidity changes were measured in the presence or absence of noscapine in tubulin at 37 °C; (iv) Electron microscopy was used to determine whether the changes in turbidity in microtubule assays in the presence of noscapine are due to aggregate effects or to polymers of abberent morphology [8].

These studies demonstrated that noscapine neither promotes nor inhibits microtubule polymerization in concentrations of upt to 100 µM. Instead, the microtubules spend an increased amount of time in a paused state, which leads to an arrest in mitosis [8, 13]. This unique mechanism may explain the exceptionally low toxicity noscapine demonstrated in both human and animal studies, especially in regard to peripheral neuropathy. The dichotomic actions of microtubule binding agents observed in cancer versus benign cells is likely as a result of tumor cells lacking a normal mitotic spindle assembly checkpoint [13]. Hence, the selective tumoricidal activity of noscapine may be secondary to mitotic slippage and subsequent mitotic catastrophe/death. Indeed, noscapine did not detrimentally affect peripheral axons and did not cause neuropathy. Moreover, it not only relieved vincristine-induced demyelination in oligodendroglia in vitro [11], but also corrected the perturbed axonal transport and alleviated disease severity in experimental models of Amytrophic Lateral Sclerosis and Parkinson's Disease in vivo [14, 15]. So far, no other microtubule-inhibitory agent has demonstrated comparable tumor selective activity. Below, we will provide evidence for the selective potential of noscapine to inhibit glioblastoma growth.

Noscapine's Antitumor Effects on Glioblastoma. Direct Evidence

Noscapine inhibits growth of C6 glioblastoma in vitro and sensitizes the cells to taxane and radiation-induced tumoricidal effects (first declared during the Canadian Neuro-Oncology 10th Biennial Meeting in Montreal Canada) [16]. Noscapine (~11 µM) suppresses both the S-phase and colony growth of C6 glioblastoma cells and on assessment via electron microscopy, induces autophagic changes [17]. Landen et al. established that noscapine suppressed the proliferation of rat C6 glioma cells in vitro (IC_{50} = 100 µM) and also caused C6 glioma cells to re-enter S phase and accumulate abnormal amounts of DNA, which led to mitotic catastrophe [12]. Importantly, noscapine significantly induced cell death in C6 glioma cells at doses that do not induce cell death in primary mouse astrocytes. Mitotic C6 glioma cells, but not normal astrocytes, became polyploid after nuclear endoreplication and demonstrated abnormal spindle formation with excessive misaligned chromosomes leading to multinucleated cells [12]. Primary astrocytes arrested in G2/M without increased DNA accumulation, whereas noscapine-treated GBM cells escaped mitotic arrest and accumulated up to 16 N DNA content by entering successive rounds of DNA synthesis without cell division [12].

Mitotic slippage describes the inability of cells to remain in a mitotic arrested state for prolonged periods and consequently replicating their DNA without cytokinesis. This causes increased aneuploidy and subsequent induction of a specific cell death described as "mitotic catastrophe". As the cell cycle checkpoint mechanisms in tumor cells are frequently dysfunctional, cancer cells may thus be more vulnerable to death than benign cells following noscapine exposure [12]. Noscapine also crosses the blood–brain barrier at rates similar to morphine and [Met]encephalin, which harbour significant central nervous system activity. Daily oral noscapine treatment (300 mg/kg) of mice with rat C6 glioblastoma implanted into their brain striatum demonstrated a significant reduction of tumor volume (~78%) [12]. Moreover, no toxicity was witnessed on the duodenum, spleen, liver, or hematopoietic cells as determined by microscopic examination and flow cytometry. Furthermore, noscapine treatment resulted in little evidence of toxicity in dorsal root ganglia cultures and did not cause peripheral neuropathy, as is frequently observed with other microtubule inhibitors [12].

HIF-1 pathway inhibitor NSC-134754 also belongs to the benzyl-isoquinoline class of alkaloid plant metabolites with anticancer activity. To investigate this property, Newcomb et al. tested whether noscapine (50 µM) exerts blocking activity on HIF-1 pathway [18]. Noscapine exposure of human glioma U87MG and T98G cell lines treated with either hypoxia (1% O_2) or hypoxia mimetic $CoCl_2$ resulted in blocked nuclear accumulation of HIF-1α and targeting for proteosomal degradation [18]. Noscapine also inhibited transcriptional activity of HIF-1α as determined by lowered secretion of VEGF. Furthermore, noscapine was also efficient in inhibiting tube formation of endothelial cells in vitro, which is an indirect indicator of angiogenesis in vivo [18]. The clonogenic potential of human T98G and murine GL261 glioma cell lines treated with noscapine, radiation, or both was determined (10 µM for T98G and 50 µM for GL261 cell lines, respectively) [19]. Noscapine alone reduced clonogenic survival but did not influence

radiation-induced clonogenic death in vitro. Mice inoculated with GL261 glioblastoma in their hind limbs were treated with noscapine, radiation, or both to assess the effect of noscapine on radiation response. In a different experiment with the same groups, tumors were resected 7 days after radiation and immunostained to determine cell proliferation, apoptosis, and angiogenesis [19]. In vivo, noscapine combined with radiation significantly enhanced tumor growth delay [19]. Noscapine with radiation significantly blocked tubule formation by the endothelial 2H11 cells compared with radiation alone in vitro. In vivo, tumors treated with a noscapine and radiation combination exerted lower cell proliferation (BrdU assay), enhanced apoptosis (TUNEL assay) and lower vessel density (CD31 staining) in comparison to tumors treated with radiation alone [19].

Newcomb et al. studied the noscapine sensitivity of four human glioma cell lines and found that noscapine was a strong inhibitor of proliferation and inducer of apoptosis, with IC_{50} values ranging from 85 to 131 μM [13]. Stimulation of apoptosis coincided with the activation of the c-jun N-terminal kinase (JNK) signaling, blockage of the extracellular regulated kinase (ERK) signaling, and phosphorylation of the antiapoptotic protein Bcl-2 [13]. Bcl-2 is an inhibitor of apoptosis and via binding to Bax and other BH3-only proteins like Bim, it affects the overall apoptotic cascade. However, phosphorylation of Bcl-2 by apoptosis signal-regulating kinase-1 reduces its affinity to Bax and Bim thus abolishing its antiapoptotic activity [13]. Noscapine-induced apoptosis occurs with the release of mitochondrial proteins, apoptosis-inducing factor (AIF), and/or Cytochrome-C. However, in some glioma cell lines, AIF release occurred without release of Cytochrome-C or poly ADP-ribose polymerase (PARP)-cleavage. Knock-down of AIF attenuated noscapine induced apoptosis [13].

Temozolomide is the standard chemotherapy agent for the treatment of GBM and acts via alkylating DNA and targeting proliferative cells, yet a significant number of patients are resistant to the drug's effects [20]. Furthermore, temozolomide-resistant glioma cells consistently exert a higher invasive propensity in comparison to sensitive lines [20]. Temozolomide resistance involves several mechanisms including high activity of DNA-repair enzyme MGMT (methyl-guanine methyl-transferase) and high expression of anti-apoptotic proteins and P-glycoprotein. Temozolomide-resistant human GBM cell lines were established by treating the A172, LN229 and U251 cells with increasing doses of temozolomide ranging from 10 to 100 μM over a period of 2 to 3 months [20]. Noscapine alone was capable of blocking proliferation of temozolomide-resistant GBM cell lines. Noscapine was also observed to act synergistically with temozolomide and reduce the invasive capability of drug-resistant GBM cells. IC_{50} values of noscapine to block the growth of the native A172, LN229 and U251 cell lines were 20 μM, 40 μM and 70 μM, respectively. IC_{50} values of noscapine to block the growth of temozolomide-resistant subclones of A172, LN229 and U251 cell lines were 60 μM, 75 μM and 30 μM, respectively [20]. These data suggest that the noscapine concentrations required to block temozolomide-resistant glioblastoma cells are not much higher, and even lower in some resistant glioblastoma clones (eg. resistant subclone of U251). Lastly, and most importantly, noscapine significantly increased survival of animals intracranially inoculated with temozolomide-resistant glioblastoma cells [20].

Qi et al. studied the effects of noscapine combined with temozolomide, bis-chloroethyl-nitrosourea (BCNU), or cisplatin on U87MG human glioblastoma cells [21]. They also treated mice inoculated with U87MG cells with temozolomide (2 mg/kg/day, ip) or cisplatin (2 mg/kg, ip 3 times a week) alone or in combination with noscapine (200 mg/kg/day, ig) for 3 weeks [21]. Noscapine (10 or 20 mol/L) acted synergistically with temozolomide, BCNU, and cisplatin on U87MG cells in vitro with resulting combination indices (CI) of noscapine-cisplatin, noscapine-temozolomide, and noscapine-BCNU (20 μmol/L) as 0.45, 0.51, and 0.57, respectively [21]. Combined treatment with noscapine strongly enhanced the antitumor efficacy of temozolomide and cisplatin in tumor xenografts with an absence of detectable toxicity. The combinations demonstrated significantly increased apoptosis (activated caspase-3 and PARP levels) in U87MG cells in vitro in addition to decreased proliferation (Ki67 index) and increased apoptosis in tumors in vivo [21].

Nuclear factor-κB (NF-κB) is a transcription factor that regulates myriad gene expressions involved in cellular processes such as survival, proliferation, invasion, and angiogenesis [3, 22]. Improper constitutive activation of NF-κB is common in numerous malignancies including glioblastoma, where it propagates cancer stem cells, tumor cell invasion, mesenchymal de-differentiation, and resistance to radiotherapy [22]. Sung et al. revealed that noscapine augments apoptosis stimulated by cytokines and chemotherapeutic agents in human leukemia and myeloma cells [3]. They additionally demonstrated that noscapine blocked the inducible expression of proteins promoting tumor cell survival, proliferation, invasion, and angiogenesis, all of which are controlled by NF-κB [3]. Noscapine inhibited both inducible and constitutive NF-κB activity in malignant cells through inhibition of IκB-Kinase, leading to inhibition of phosphorylation and degradation of IκB-α [3]. Noscapine also blocked phosphorylation and nuclear translocation of p65, leading to inhibition of NF-κB reporter activity induced by various NF-κB-inducing anticancer agents. Noscapine additionally suppressed the activity of the NF-κB-containing cyclooxygenase-2 promoter [3]. Triple negative breast cancer describes a specific kind of cancer that lacks receptors for estrogen, progesterone, and her2 and has the worst prognosis amongst

all breast malignancies [23]. In animal models of triple negative breast cancer, noscapine blocked NF-κB activity and tumor growth in synergy with doxorubicin [24]. Similarly, in drug-resistant ovarian cancer cells, noscapine not only blocked the activity of NF-κB but also sensitized cells to growth inhibition and apoptosis induced by cisplatin [25]. Many different drugs have been shown to inhibit NF-κB activity, yet the high brain permeability of noscapine makes it an especially potent candidate for chemotherapy sensitization in glioblastoma.

Verma et al. synthesized three haloderivatives of noscapine and investigated their in vitro cytotoxicity on U87 human glioblastoma cell lines [26]. Their research revealed 9-chloronoscapine as a more potent tumoricidal agent than noscapine [26]. Based on the the expression of the FRα (folate receptor-α) in diverse types of malignancies and through the use of molecular modelling, Joshi's group in Emory University developed a novel noscapine analogue by conjugating a folate group to the C9 position of noscapine. They called this novel molecule "targetin" [27]. They demonstrated that pediatric glioma cells were more vulnerable to the tumoricidal effects of lower doses of targetin than the precursor compound noscapine. Targetin perturbed tumor microtubules, interrupted DNA synthesis, arrested the cell cycle within the S and G2M cell cycle phases, and blocked anchorage-independent growth and invasion of pediatric glioma cells [27]. Moreover, targetin reduced expression of growth signals of special importance in pediatric gliomas; including Platelet Derived Growth Factor-α (PDGF-α) and members of the Mitogen Activated Protein Kinase (MAPK) cascade including MAP2K6, MAPK8, MAPK12 [27]. Targetin also induced apoptosis along with externalization of phosphatidyl serine and mitochondrial membrane depolarization [27]. Below, we will explain other molecular actions of noscapine, which may be important in management of glioblastomas.

Other Effects of Noscapine Which may Impact Glioblastoma Treatment: Inhibiting Bradykinin Receptors, P-Glycoprotein and EGFR Tyr1068 Phosphorylation

Noscapine is an inhibitor of bradykinin receptors (B1R and B2R) and mitigates cerebral vascular dysfunction in mouse models of brain amyloidosis [28]. Human astrocytic tumor cells express kinin receptors [29]. A strong synergism was found after a combined treatment of a kinin receptor antagonist (BKM-570) and temozolomide robustly increased cytotoxic action in rat and human glioblastoma cells [30]. Moreover, the selective B1R and B2R antagonists (SSR240612 and HOE-140, respectively) triggered cell death of both U138 and U251 human GBM cells via necroptosis [31]. Furthermore, B1R was shown to enhance invasion of human GBM cells in spheroid cultures [32]. Following this evidence, the bradykinin-receptor antagonist efficacy of noscapine may similarly contribute to suppression of both growth and invasion in GBM cells. Cancer cells can gain resistance to chemotherapy agents via P-glycoprotein (P-gp), which is an ATP-dependent transmembrane drug efflux pump [33]. GBM cells can autonomously induce temozolomide resistance via enhanced transcription of the MDR1 gene encoding P-gp [33]. In a model of Adriamycin-resistant DC3F cells (DC3F/Adx), it was shown that an enhanced expression of P-gp caused temozolomide resistance [33]. However, by enhancing active caspase 3, three different P-gp inhibitors overcame the resistance to temozolomide in two GBM cell lines [33]. Molecular modeling studies demonstrated that the binding sites of temozolomide are in the intracellular region of P-gp [33]. Carbonic anhydrase XII (CAXII) seems to be necessary for the P-gp efflux of temozolomide in GBM cells [34]. Of particular significance, noscapine was able to efficiently inhibit cellular efflux of a fluorescent P-gp [35]. Further studies on purified P-gp revealed that inhibition of P-gp was due to direct interaction of noscapine analogs with this transporter [35]. Furthermore, simultaneous administration of vinblastine with two noscapine analogs exerted synergistic inhibition of cancer cell proliferation, even in resistant P-gp-expressing sublines [35]. Hence, it can be deduced that noscapine may also be relevant in suppression of P-gp associated drug resistance in GBM.

The cell membrane receptor Epidermal Growth Factor Receptor (EGFR) is a member of the ErbB family with intrinsic protein tyrosine kinase activity, which is involved in the oncogenesis of several human cancers and has been identified as a potential target of personalized therapy [36, 37]. EGFR is a key player in cancer progression because it is important for both cell proliferation and invasion [36]. The increase of EGFR phosphorylation on the Tyr1068 residue enhances Cyclin D1 expression and induces cell proliferation [36]. EGFR is commonly overexpressed in many gliomas and results in the aberrant activity of molecular signaling cascades such as Growth Factor Receptor bound protein 2 (GRB2), Son of Sevenless 1 (SOS1), Ras protein, and AKT [37]. While EGFR phosphorylation on the Tyr1068 has been associated with an increased invasive phenotype in human GBM 8401 cells, this activity is effectively inhibited by EGFR tyrosine kinase inhibitors and tetrandrine (bisbenzylisoquinoline alkaloid isolated from *Stephania tetrandraS.*) [37]. Of note, noscapine is also found to selectively inhibit EGFR phosphorylation on the Tyr1068 residue, which associates with its inhibitory efficacies on growth and invasion of osteosarcoma cells [36]. Therefore, it would be logical to presume that noscapine may efficiently inhibit EGFR-associated protumorigenic signals in GBM cells. Now, we will compare noscapine with other anti-mitotic agents and

then explain noscapinoids with superior anticancer activity in glioblastomas and multi-drug resistant cancers.

Comparison of Noscapine with Other Anti-mitotic Agents

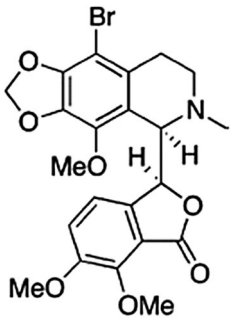
In general, anti-mitotic and anti-S-phase chemotherapy agents target not only cancer cells, but all proliferating cells resulting in severe side effects such as alopecia, gastrointestinal epithelial toxicity, and myelosuppression. Myelosuppression and immunosupression are the most significant and life-threatening side effects of general antimitotic antineoplastics [38]. Noscapine exerts negligible toxicity and does not harm either cell-mediated immunity or humoral immunity [2]. Additionally, noscapine is not toxic to the duodenum, spleen or liver despite these tissues being major uptake sites [2].. It is challenging to discover antineoplastic agents that can traverse the blood–brain barrier without being cytotoxic to the benign brain tissue. Even though serum concentrations of noscapine decrease by 80% within the first hour, it is still able to effectively cross the blood brain barrier [2] Moreover, noscapine does not induce liver toxicity through bioactivation in hepatic tissues as determined by hepatic glutathione content and systemic liver enzymes [39]. Lastly, noscapine also exerts powerful anti-inflammatory effects, a quality not shared by other antineoplastics [2, 40]. Due to the role of chronic inflammation in promoting cancer development, progression, metastasis, and resistance, this could provide a unique advantage of noscapine over other agents [2, 40].

Noscapinoids with Superior Activity to Noscapine in Glial Tumors and Multi-Drug Resistant Cancer Cells

Strategies for the preparation of noscapine analogs include modifications at C9 on the isoquinoline ring (e.g. 9-halogenated and 9-amino derivatives), C7 on the benzofuranone ring (e.g. 7-*O*-alkylated and 7-*O*-demethylated derivatives), and N-substituted derivatives [41, 42].

Brominated noscapine, EM011 ((S)-3-((R)-9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g] isoquinolin-5-yl)-6,7-dimethoxyiso-benzofuran-1(3H)-one) (Fig. 3) exerts superior bioavailability and higher antineoplasticity than the parent compound while still retaining the original nontoxic features [42]. EM011 inhibits cell-cycle progression by inducing an aberrant multipolar mitosis with an activated mitotic checkpoint [42]. This activation is accompanied by recruitment of spindle-assembly checkpoint proteins BubR1 and Mad2 and seems to be essential for the robust pro-apoptotic effects in prostate cancer cells [42]. Additionally, collapse of mitochondrial transmembrane

Fig. 3 Brominated noscapine analog, EM011



EM011

potential, expression changes of Bcl-2 family members, and activation of the executioner caspases occur following EM011 treatment in prostate cancer cells [43]. EM011 also blocked human prostate cancer xenograft growth implanted into tibial bone [43]. Ajeawung et al. analyzed the EM011 effects on the proliferation of two pilocytic and one diffuse pediatric astrocytoma cell lines [44]. Exposure of low grade gliomas to EM011 decreased vitality and proliferation with an arrest in the S and G2M phases of cell cycle, followed by increased apoptosis in a time and dose-dependent manner [44]. EM011 also reduced clonogenicity, migration, and invasion of low-grade glioma cells. EM011 induced release of AIF and also lowered the expression of key protumorigenic genes including mTORC1, JUN, EGFR, and matrix metalloproteases (MMPs) [44].

γ-tubulin is important in the nucleation and polar organization of microtubules and exists primarily in spindle pole bodies and centrosomes since these are the regions of most prominent microtubule nucleation. In these organelles, γ-tubulin and other proteins exist together in γ-tubulin-ring-complexes, which biochemically mimic the plus end of a microtubule and thus regulate microtubule dynamics from this position [45]. Importantly, γ-tubulin is over-expressed in many malignancies, such as breast cancer and GBMs [45]. Hence, γ-tubulin may be a novel chemotherapy target for cancers including GBM. γ-tubulin interactions of noscapine and two of its derivatives, amino-noscapine and EM011 were analyzed. It was revealed that EM011/bromo-noscapine showed the highest binding affinity followed by noscapine and amino-noscapine, indicating that EM011 may be a plausible candidate for GBM treatment by disrupting γ-tubulin kinetics [45].

Zhou et al. developed a reduced derivative of bromonoscapine, EM012, which acts synergistically with paclitaxel to inhibit the growth of human breast cancer, non-small-cell lung cancer, and prostate cancer cells at nanomolar concentrations via promotion of the microtubule-stabilizing efficacy of paclitaxel [46]. In cancer cells, this increased microtubule stabilization was evidenced by an enhancement in tubulin acetylation [46]. EM012 also efficiently inhibited

the growth of P-gp-overexpressing, multidrug-resistant ovarian cancer cells, indicating a potential for use in P-gp-overexpressing gliomas [46]. In mice models, EM012 also prominently blocked growth of ovarian cancer without damaging benign tissues [47]. 9-nitronoscapine and 9-aminonoscapine analogs (Fig. 4) were also found to be active in multidrug resistant cancer cells by inducing cell cycle arrest with subsequent apoptosis and enhanced caspase-3 activity [48]. By reducing the lactone moiety, Aneja et al. synthesized the cyclic ether 9′-fluorinated noscapine analogue (CEFNA). This derivative significantly inhibited the proliferation of drug-resistant human breast cancer cells independent of their hormone status [49]. Massive cell accumulation in G2/M transition phase and prominent formation of micronuclei accompanied the anticancer effects of CEFNA [49]. Cheriyamundath synthesized a novel analogue of noscapine, N-(3-bromobenzyl) noscapine (N-BBN) [50]. N-BBN acted superiorly to many of the previously synthesized noscapinoids in reducing cancer cell viability and prominently inhibited the clonogenicity of an aggressively metastatic breast cancer cell line, MDA-MB-231 [50]. MDA-MB-231 is derived from a triple-negative breast cancer, which lacks receptors for estrogen, progesterone, and Her2 thus rendering these cells resistant to estrogen inhibitor tamoxifen and Her2-inhibitor trastuzumab [23]. Triple-negative breast cancer cells are also more resistant to classical chemotherapy agents due to other unclear mechanisms. Given the demonstrated efficacy in treatment of such a resistant cancer, N-BBN may also be beneficial in multidrug resistant subtypes of GBM. At last, we will outline the preclinical and clinical areas for future investigations in regard to noscapine antineoplasticity in gliomas.

Preclinical and Clinical Areas for Future Investigations

Novel derivatives of noscapine and novel nano-delivery methods to target noscapine into tumor cells will have significant value in providing innovative new drugs for the treatment of GBM. As noscapine has been demonstrated to act synergistically with other anti-microtubule drugs, investigation into the effects of co-infusion of noscapine analogues with anti-microtubule agents in animal models of GBM may yield worthwhile findings. In preclinical models, biolimuniscence monitoring of GBM tumor growth in the brain would illuminate the antineoplastic kinetics of noscapine and chromatographic/mass spectroscopic analyses would reveal which noscapine metabolites enter the tumor mass at which concentration. Recently, noscapine was found to be an agonist of the human bitter taste receptor Tas2R14 [51]. Furthermore it was shown to induce cancer cell apoptosis as a ligand of Tas2R14, independently of its anti-microtubule effects [51]. Interestingly, bitter taste receptors are also expressed in cells of the choroid plexus, which is an interface of the blood–brain barrier and serves to monitor the content of the cerebrospinal fluid [52]. Importantly, P-gp is prominently expressed in the choroid plexus and is presumed to be a key component of the cerebrospinal fluid-brain barrier [53]. Moreover, another multidrug-resistant protein MRP4/ABCC4 is expressed in the basolateral membranes of the choroid plexus epithelia and influences the cerebrospinal fluid content of antineoplastic agents [54]. Hence, it could be advantageous to investigate whether noscapine could modify cerebrospinal fluid concentrations of anticancer agents by regulating the functions of the choroid plexus via binding to

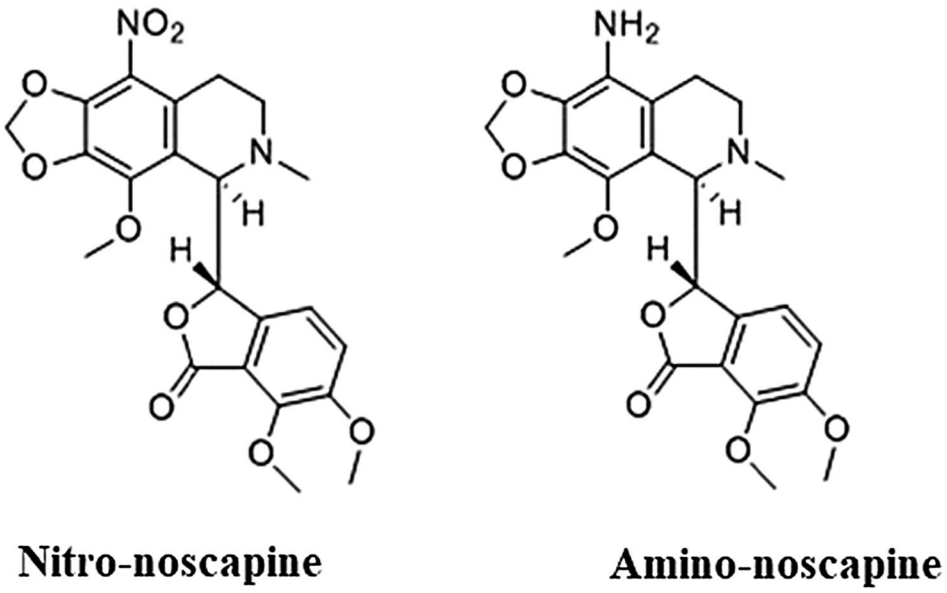


Fig. 4 9′nitronoscapine and 9′aminonoscapine

both bitter taste receptors and P-glycoprotein. In an oxygen-glucose deprivation (OGD)-induced injury model in fetal rodent cortical neurons, noscapine exerted neuroprotective effects by reducing nitric oxide (NO) levels [55]. Low to intermediate levels of NO propagates the growth of many cancers including GBM, hence, it would also be plausible to test whether noscapine acts as an antitumor agent by reducing intratumoral NO levels [56]. In terms of clinical application, testing noscapine as a single agent in very far advanced drug-resistant malignancies would not be appropriate. Rather, its chemo-sensitizing and radiotherapy-sensitizing efficacies shall be tested in combinatory protocols.

Conclusions

As described in the introduction, there exist surprisingly few medicines effective in treating many neuro-oncological diseases. We do not anticipate that noscapine will provide a "cure" for these diseases, yet with versatile mechanisms of action, noscapine analogues could be developed as new adjuvants to augment the efficacy of currently existing treatments. Noscapine is cheap, exerts negligible toxicity, and is non-addictive. Moreover, it is unique among all anti-microtubule drugs in that it selectively eliminates cancer cell microtubules while sparing and even correcting disturbed microtubule machinery in healthy cells. Its relatively short half-life and poor solubility can be changed with pharmaco-chemical approaches to alter its molecular structure and/or by novel delivery systems including nano-liposomes. Taken together, we think that noscapine deserves to be studied in detail as a novel candidate in the armamentarium against neurooncological diseases.

Compliance with Ethical Standards

Conflict of interest All the authors declared that thy have no conflict of interest.

Research Involving Human Participants and/or Animals This study does not involve any human participants and/or animals.

Informed Consent As this study does not involve any human subjects, informed consents were not needed.

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