Spirooxindoles, a potential novel class of anti-inflammatory agents

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Received: October 16, 2014
Published online: November 13, 2014

In a previous study, we described a class of spirooxindole-pyranopyrimidine compounds that had a wide range of anti-cancer activity. In a most recent study, we found that one such compound, JP-8g, were also found to exhibit potent in vivo anti-inflammatory activity. In vitro and in vivo experiments suggested that JP-8g exerts this activity through nitric oxide (NO) signaling pathway. Herein, we discuss the potential of the use of these compounds as anti-inflammatory agents. The new data in this study also suggested that JP-8g exerts its anti-inflammatory activity through NF-κB-independent signaling pathway.


Non-steroidal anti-inflammatory drugs (NSAIDs) are a diverse class of compounds with distinct chemical structures. NSAIDs are among the most broadly used medications worldwide for the treatment of pain and inflammation [1]. The anti-inflammatory activity of NSAIDs is dependent on the suppression of cyclooxygenases (COXs), the enzymes that catalyze the synthesis of prostaglandin (PG) H₂ from arachidonic acid. PGH₂ is further converted into thromboxane A₂, prostacyclin and other PGs, which can trigger a variety of inflammation-related events [2].

In the United States, commercialized NSAIDs consist of nearly 40 different compounds and more than 1000 brands [2]. These NSAIDs, however, are often found to be associated with adverse side effects, including gastrointestinal and recently identified renal and cardiovascular complications [1, 3, 4]. Despite the efforts and achievements over the past several decades, there remains strong interest for developing new NSAIDs with high efficacy yet low side effects [5].

Recently, accumulating evidence from epidemiologic, clinical and experimental studies have reported that NSAIDs can inhibit tumor genesis in various tissues or delay progression of malignant diseases [6]. While the dual functions of NSAIDs have attracted much attention, the underlying mechanism is yet to be elucidated [7, 8]. It has been proposed that the chemopreventative activity of NSAIDs is attributed to the inhibition of COX-dependent PG production. However, this hypothesis was challenged by the observation that only low doses of NSAIDs are required for the inhibition of PG synthesis whereas high doses of NSAIDs are generally needed for tumor inhibition [9].

Accumulating evidence has suggested that COX-independent signaling pathway may be involved in the chemopreventative activity of NSAIDs [10-13].

Chiral spirooxindoles are a class of important lead compounds for a variety of biologically active molecules [14-16]. In a previous study, we described a new approach for
the synthesis of a new class of chiral spirooxindole-type alkaloids by asymmetric Michael/cyclization reactions \[17, 18\]. Our reactions allow facile synthesis of spiroheterocycles with both high enantioselectivity and high yield. Notably, one spirooxindole-pyranopyrimidine compound, JP-8g (Figure 1), exhibited broad spectrum anti-tumor activity \[18\]. This unique feature suggested that JP-8g may play an important role in a major signaling pathway that is involved in tumor progression. We hypothesized that JP-8g may mediate other biological processes as well.

Intriguingly, we found in a recent study that JP-8g exhibited potent in vivo anti-inflammatory activity when evaluated on three mouse inflammation models \[19\]. In a xylene-induced ear edema model, oral (p.o.) or intraperitoneal (i.p.) administration of JP-8g prevented an exudative process with efficacy comparable to a reference drug indomethacin. Most surprisingly, subcutaneous (s.c.) injection of JP-8g inhibited carrageenan-induced paw swelling with efficiency approaching to that of a steroidal anti-inflammatory drug dexamethasone (DEX). In addition, JP-8g could significantly reduce the LPS-stimulated neuroinflammation \[19\].

When compared with indomethacin (a traditional NSAID), JP-8g resulted in significantly reduced acute gastric damage (Figure 2). Although this result suggested that JP-8g may lead to less gastrointestinal complications than traditional NSAIDs, it is yet unclear if JP-8g bears the same in vivo target as traditional NSAIDs. In future studies, it will be interesting to examine whether JP-8g inhibits gastric PG synthesis to the same extent as other NSAIDs.

Recent study suggested that inflammation and tumorigenesis may be linked via NF-κB signaling pathway \[20\]. As JP-8g exhibits dual anti-cancer and anti-inflammatory effects, we set to explore the role of NF-κB in JP-8g activity. We found that though JP-8g can suppress LPS-stimulated NO release \[19\], it exhibited no significant effect on nuclear translocation of NF-κB triggered by LPS (Figure 3A). Furthermore, administration of NF-κB pathway inhibitors pyrrolidine dithiocarbamate (PDTC) \[21\] and BAY 11-7082 \[22\] had no effect on the in vivo anti-inflammatory activity of JP-8g (Figure 3B). Taken together, these results and our previous experiments \[19\] indicated that JP-8g exerts the anti-inflammatory activity via an NO-dependent,
In a continuous effort to develop spirooxindoles as anti-inflammatory agents, we intended to optimize the synthesis route of spirooxindole-pyranopyrimidine compounds or perhaps, develop new agents with facile synthesis. JP-8g and most marketed NSAIDs require multi-step syntheses. Most recently, we identified another series of spirooxindoles with simplified structures which require only one-step synthesis. This series of compounds showed varying degree of anti-inflammatory activity when evaluated on mouse inflammation model, with the most active compound achieving similar or even higher effectiveness when compared with JP-8g. We anticipate to report these compounds in our future studies.

Overall, our study of JP-8g shed light on the use of spirooxindoles as anti-inflammatory agents. However, the therapeutic potential of these compounds still requires careful assessment in further studies. The in vivo target, toxicity and pharmacokinetics of these spirooxindole compounds are largely unknown. We hope that characterization of these compounds can provide useful information on inflammation biology, especially cancer-associated inflammation. We also hope that our previous and future work can facilitate the development of new agents with high efficacy and low side effects for the treatment of inflammation.
Conflict of interest

The authors declare no competing financial interests.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (Nos. 81200469, and 21272102), the Key National S&T Program “Major New Drug Development” of the Ministry of Science and Technology of China (2012ZX09504001-003), and the Fundamental Research Funds for the Central Universities Izujbky-2012-166.

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