NEW DIRECTIONS IN THE DEVELOPMENT OF CYCLOOXYGENASE INHIBITORS

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Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used for nearly a century for alleviation of symptoms of acute and chronic inflammation and represent one of the most used groups of drugs in the general population. NSAIDs group is very numerous and it includes different chemical structures. The main mechanism of action of these drugs is the inhibition of enzyme cyclooxygenase (COX) which catalyzes prostaglandin production (of which some are inflammatory mediators) from arachidonic acid and depending on whether they inhibit both isoforms (COX-1 and COX-2) and just COX-2 they can be classified as nonselective and selective. The need for finding the new NSAIDs with fewer side effects is still persistent because nonselective NSAIDs often cause gastrointestinal side effects which vary from mild to very serious like bleeding, while some selective are withdrawn because of serious cardiovascular side effects with death outcome (1). Several epidemiologic studies have shown a negative correlation between NSAID use and the occurrence of Alzheimer`s disease, as well as some types of cancer, particularly colorectal and breast cancer. The development of compounds that would be used in Alzheimer`s disease therapy is direct on structures that exhibit more effects at the same time, one of which is anti-inflammatory effect mediated via COX-2 inhibition. Although chemoprevention mechanisms are not completely delineated, it is indisputable that both COX isoforms play a role in carcinogenesis, and these findings opened a new field of research for the design and synthesis of new COX inhibitors with chemoprotective, antiangiogenic, and cytotoxic activity.

References

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NOVI PRAVCI U RAZVOJU INHIBITORA CIKLOOKSIGENAZE

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Nesteroidni antiinflamatorni lekovi (NSAIL) se koriste za ublažavanje simptoma akutne i hronične inflamacije već skoro čitav vek i predstavljaju jednu od najčešće primenjivanih grupa lekova u najširoj populaciji. Grupa NSAIL je veoma brojna i obuhvata različite hemijske strukture. Glavni mehanizam delovanja ovih lekova je inhibicija enzima ciklooksigenaze (COX) koji katalizuje produkciju prostaglandina (od kojih su neki medijatori inflamacije) iz arahidonske kiseline, a u zavisnosti od toga da li inhibiraju obe izoforme (COX-1 i COX-2) ili samo COX-2, dele se na neselektivne i selektivne. Potreba za otkrivanjem novih NSAIL sa manje neželjenih efekata je i danas aktuelna, jer neselektivni NSAIL često izazivaju neželjene gastrointestinalne efekte koji variraju od blagih do veoma ozbiljnih kao što je krvarenje, a neki selektivni lekovi su povučeni iz upotrebe zbog ozbiljnih neželjenih kardiovaskularnih efekata sa smrtnim ishodom (1). Nekoliko epidemioloških studija je pokazalo da postoji negativna korelacija između upotrebe NSAIL i pojave Alchajmerove bolesti, kao i nekih tipova kancera, a naročito kolorektalnog i kancera dojke. Razvoj jedinjenja koja bi se koristila u terapiji Alchajmerove bolesti je usmeren na strukture koje istovremeno imaju više efekata, a jedan od njih je antiinflamatorni posredovan inhibicijom COX-2. Iako mehanizmi hemoprevencije nisu potpuno rasvetljeni, nesporno je da postoji uloga obe COX izoforme u karcinogenezi, a ova saznanja su otvorila novo polje istraživanja ka dizajniranju i sintezi novih COX inhibitora sa hemoprotektivnom, antiangiogeneznom i citotoksičnom aktivnošću.

Literatura

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