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Review Article

Interleukin-1 blockers: a new class of nonarachidonate, nonsteroidal antiinflammatory drugs

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Introduction

Corticosteroids are well known as potent antiinflammatory agents although they cause numerous serious side effects (1). As a result, an enormous amount of research has focused on the development of nonsteroidal antiinflammatory drugs (NSAIDs) (1-5). Typical NSAIDs are related to arachidonate metabolites and include cyclooxygenase inhibitors (*i.e.*, aspirin, ibuprofen, indomethacin, mefenamic acid), lipoxygenase inhibitors (*i.e.*, phenidone, *N*-dihydroguaiaretic acid), prostaglandin receptor antagonists and leukotriene (LT) receptor antagonists (3, 4). However, none of these are as potent as corticosteroids and, in addition, they possess marked side effects which limit their widespread use (3, 4).

Platelet activating factor (PAF) antagonists are another class of NSAIDs which have improved potency but also numerous side effects due to the widespread biological activities of PAF (5). Consequently, the search continues for NSAIDs that are equipotent or more potent than corticosteroids and have fewer side effects. The discovery of a natural polypeptide interleukin (IL)-1 receptor antagonist (IL-1ra) that is a potent antiinflammatory agent has prompted the search for safe, stable and long-lasting IL-1 blockers as a new class of NSAIDs (6-8).

The extensive advances in cytokine research have led to the discovery of cytokines such as IL-1, IL-6, tumor necrosis factor (TNF), *etc.*, which are related to the induction of inflammation (9). Most interestingly, endogenous cytokines such as IL-1ra are released from the same tissue or even the same cell to produce the opposite effects, *i.e.*, antiinflammatory actions (10-13). These phenomena are considered natural responses to regulate the degree of inflammatory processes. On the one hand they produce inflammation for the body's protective processes such as wound healing, while on the other hand they induce antiinflammatory actions for the prevention of excess uncomfortable reactions such as fever, pain, swelling, itching, *etc.*, due to inflammatory overreactions (13).

Among the cytokines, IL-1 is probably the most potent, direct acting inflammatory substance that causes widespread inflammatory reactions (9-11). IL-6 and TNF are also inflammatory in nature but are considered to be supplementary to IL-1 (9-11). Many inflammatory reactions that are inducible by IL-1 can be prevented or antagonized directly by IL-1ra, a naturally occurring antiinflammatory substance (15-50), as well as by antibodies to IL-1 receptors.

Inflammation can also be induced indirectly by IL-1 releasing substances such as lipopolysaccharide (LPS) and endotoxin. Therefore, inflammation can also be prevented or blocked by IL-1 releasing blockers, IL-1 synthesis reducers and IL-1 converting enzyme (ICE) inhibitors (10, 11).

Pharmacological classification of antiinflammatory drugs

Inflammation is a natural defense response of the body to repair injuries and lesions caused by exogenous and endogenous insults. These insults can cause a narrow, intermediate or broad spectrum of inflammatory symptoms depending on the source of the insult (10, 11). For example, histamine, kinins, vasoamines, *etc.*, cause a narrow spectrum of inflammatory symptoms such as

itching, hot flashes, swelling, pain, *etc.* Prostaglandins, LTs, PAF and similar substances produce an intermediate spectrum of inflammatory responses including fever, increase in neutrophil lysosomal proteases, muscle proteolysis, wasting effects, *etc.*, in addition to the narrow spectrum symptoms. A broad spectrum of inflammatory responses is caused by certain cytokines, including IL-1, IL-6, IL-8, TNF, *etc.* These symptoms cover all of those mentioned in the narrow and intermediate spectrums plus rheumatoid arthritis, destruction of connective tissue and increases in blood concentrations of zinc, iron, amino acids and hepatocytes (10, 11).

Narrow spectrum inflammation can be blocked by antihistamines, cromolyn sodium and vasocortin, whereas intermediate spectrum inflammation can be antagonized by cyclooxygenase inhibitors, lipoxygenase inhibitors and PAF antagonists. However, broad spectrum inflammation must be treated with more powerful agents such as corticosteroids which are known to produce serious side effects. In order to avoid the side effects while maintaining potent broad spectrum antiinflammatory activity, new classes of drugs have been developed. These include IL-1 synthesis inhibitors, IL-1 converting enzyme (ICE) inhibitors, IL-1 release blockers, IL-1 receptor antibodies and, most importantly, IL-1 receptor blocking agents (10, 11).

Indirect acting drugs

IL-1 synthesis reducers, ICE inhibitors and IL-1 release blockers (10, 11) are indirect acting drugs which act indirectly on the receptor site.

IL-1 synthesis reducers

Many compounds which reduce IL-1 synthesis have been synthesized in order to treat a wide variety of disorders including rheumatoid arthritis, bone resorption diseases, osteoporosis, Paget's disease, endotoxin-induced shock, secondary cachexia, inflammatory bowel disease (IBD), septic shock, autoimmune disorders, tissue rejection, asthma, Bechet's disease and encephalitis. Each compound is effective in treating some but not all of these disorders, depending on the compound's physicochemical properties (10, 11).

Amino substituted piperazine derivatives, azaspirane derivatives, pyridyl substituted imidazoles, glucuronic acid polymers or polymers of β-1,4-linked D-mannuronic acid, peptidic phosphinyloxymethyl ketones and diaryl substituted heterocyclic compounds have been evaluated for their efficacy and safety as antiinflammatory compounds (10, 11).

Although IL-1 synthesis reducers are effective in reducing IL-1 production, they also affect the production and/or release of other cytokines such as IL-6, TNF, *etc.* Thus, in contrast to direct acting IL-1 blockers, these compounds are nonspecific. The IL-1 synthesis reducers have been shown to be effective in the treatment of diabetes, AIDS, viral infections, arteriosclerosis and cancer.

IL-1 converting enzyme inhibitors

IL-1 precursors are cleaved by interleukin converting enzyme (ICE) to the active form of IL-1. Therefore, inhibition of ICE can effectively halt the production of IL-1. Peptidyl aldehyde derivatives have been reported to inhibit IL-1 production and to be useful for the treatment of septic shock, allograft rejection, IBD, rheumatoid arthritis, inflammatory lung disease and tumors, as well as disorders of the CNS, kidney, endocardium, eyes, pericardium, ears, skin, urogenital system, bone and cartilage resorption (10, 11).

IL-1 release blockers

In addition to endogenous and exogenous insults, inflammation can also be induced by a massive release of IL-1 by endotoxin or LPS. Therefore, blockade of IL-1 release can be an effective way to eliminate inflammation. However, IL-1 release blockers are not effective in blocking preexisting tissular IL-1 as they do not act directly on the IL-1 receptor to eliminate its inflammatory actions.

Sometimes inappropriate experimental models are used to evaluate the antiinflammatory actions of certain drugs. For example, IL-1ra is not effective in blocking the release of IL-1 by LPS. Therefore, measurement of IL-1 released by LPS does not reveal the useful pharmacological actions of direct acting IL-1 receptor blockers. The most appropriate experimental model in this case would be IL-1-induced inflammation. The use of appropriate experimental models not only permits evaluation of the efficacy of antiinflammatory drugs but also elucidates their direct *versus* indirect actions.

Various compounds have been developed to block the release of IL-1 by LPS. Tripeptides and tetrapeptides, analogs of lipid A, placenta protein 14, trisubstituted imidazole derivatives, arylcycloalkyl derivatives, oxophthalazines, disaccharide derivatives and natural compounds such as osthole, 2-hydroxychalcone hydrazone, flavanone hydrazone, matrine and tetrandrine (10, 11, 51-57) have been reported to inhibit endotoxin- and LPS-induced release of IL-1. These compounds have been used for the treatment and/or prevention of uveitis, endotoxic shock, gastrointestinal cancer, cachexia, fever, carrageenan-induced edema, viral infections (HIV, herpes, or influenza), allergies, rheumatoid arthritis, IBD,atherosclerosis, multiple sclerosis and anaphylactic shock.

Direct acting drugs

Direct acting drugs are more specific and more widely used than indirect acting drugs because they can

prevent and/or treat diseases induced by IL-1 both directly at the IL-1 receptor and indirectly through the release of IL-1. This class of drugs includes antibodies to IL-1, natural polypeptide IL-1ra, natural organic compounds and synthetic organic compounds. Among these, the synthetic organic compounds are the most exciting and promising as potential new drugs and will be discussed in detail in a following section.

Antibodies to IL-1 receptors

At least 16 peptides, such as Lys-Ile-Cys-Ile-Gln-Ile-Ser, have been reported to bind to IL-1 receptor to block IL-1 actions. Possible use of these peptides includes the treatment of tissue rejection, allergic diseases and autoimmune diseases (*e.g.*, multiple sclerosis, diabetes mellitus, lupus erythematosus). The major problem of using peptide antibodies is their instability as a drug in the blood stream. This is also a problem for IL-1ra (11).

Natural polypeptide IL-1ra

Cytokines are complex natural products which include both inflammatory and antiinflammatory compounds. It is interesting to note that both IL-1 (inflammatory) and IL-1ra (antiinflammatory) can be released from the same cell to induce opposite actions on the inflammatory response (13). The balance between IL-1 and IL-1ra is a precise mechanism which controls the level of inflammation induced in the body. Since inflammatory responses are considered natural defense mechanisms against unwelcome external insults and/or false internal insults (autoimmune responses), the release of IL-1 to induce inflammatory responses is a beneficial defense response. However, when excessive inflammatory responses occur they can lead to uncomfortable and sometimes life-threatening reactions (*i.e.*, anaphylactic shock, extremely high fever, *etc.*). In order to control the degree of inflammatory responses, IL-1ra is also released to ensure that the IL-1 induced inflammatory actions will not overwhelm the body. If the released endogenous IL-1ra is not sufficient, then extraneous IL-1ra can be injected to antagonize the IL-1 reaction.

In animal experiments and clinical trials, IL-1ra has been shown to antagonize IL-1-induced disorders and diseases such as endotoxemia in rats (14-16), preterm labor in mice (17, 18), rheumatoid arthritis through collagenase activation in human rheumatoid synovial tissue macrophages (19), lethal doses of LPS in rabbit blood vessels (20), LPS-induced behavior disorders in rats (21, 22), pulmonary anaphylaxis in guinea pigs (23), immune colitis in rabbits (24-26), uveitis in rabbit models (27), fever in guinea pigs (28-31), carrageenan-induced pleurisy in rats (32), pulmonary hypertension (33), pulmonary allergy in antigen-challenged guinea pigs (34), calcium accumulation in chronic granuloma induced by potassium permanganate (35-37), antigen-induced arthritis in rabbits (38), angiogenesis in rats (39), experimental crescentic glomerulonephritis (40, 41), chorioamnionitis and parturition (42), sepsis (43), sarcoidosis (44), LTB_4-induced disorders in human monocyte cultures (45-47), monocyte chemotaxis by human mesangial cells (48) and inflammation in general (22, 49, 50).

IL-1ra is also able to block IL-1-induced release of prostaglandin E_2, LTB_4, IL-6, TNF and other inflammation mediators (19, 46). However, the clinical use of IL-1ra is limited due to its short half-life (21 min) which requires prolonged intravenous infusion (58). Thus, stable, long-acting compounds are urgently needed.

In addition to IL-1ra, numerous natural polypeptides have been reported to inhibit IL-1 actions and include glioblastoma factor, contra IL-1, Ellner factor, CMV-induced IL-1 inhibitor, Rosenstreich's IL-1 inhibitor, alpha-melanocyte stimulating hormone, uromodulin, CKS 17, submandibular gland IL-1 inhibitor, neutrophil IL-1 inhibitor, virus-induced IL-1 inhibitor, low molecular weight IL-1 inhibitor, IL-1 binding proteins, $alpha_2$-macroglobulin, Duff's inhibitor, Cozzolino's inhibitor, keratinocyte inhibitor, macrophage-derived IL-1 inhibitor, $P388D_1$ factor and Arend's inhibitor. These are natural polypeptides that inhibit the actions of IL-1. Some of them may be the same molecule with different names (6), and further studies should help to clarify this confusion.

Natural organic compounds

Many natural products from medicinal plants have been reported to prevent ocular inflammation induced by lens protein and endotoxin (51-55). However, only a few are capable of blocking inflammation induced by IL-1 injections. These findings indicate that while many compounds can prevent the release of IL-1 by endotoxin, only a few can block the action of IL-1 directly at the receptor site (54, 55).

Flavonone hydrazone is a seminatural product that inhibits uveitis induced by lens protein, endotoxin and IL-1. While it is as stable and potent as osthole, it also is quite toxic at effective doses (54). Therefore, a derivative will have to be synthesized before it can be used safely.

Osthole, a natural product isolated from the medicinal plant *Cinidium monnieri*, blocks both endotoxin- and IL-1-induced uveitis (55). Osthole is much more stable than IL-1ra and can be administered orally. Furthermore, it is equipotent or slightly more potent than prednisolone as an antiinflammatory agent (55). However, osthole is quite toxic at effective doses and, therefore, unless the chemical structure is altered to reduce its toxicity it is not a desirable NSAID.

Tetrandrine, a natural alkaloid isolated from the root of *Stephania tetrandra*, has been reported to inhibit prostaglandin and LT generation (55), including suppression of the release of two major metabolites of arachidonic acid, namely LTB_4 and thromboxane B_2. This is catalyzed by calmodulin-dependent phospholipase A_2 from the membrane phospholipids (59). These findings

indicate that the inflammatory effects of tetrandrine may be partly due to blockade of arachidonate metabolism.

Tetrandrine has also been shown to suppress microvascular leakage, inflammation processes induced by PAF and other allergic mediators (60), in addition to inhibiting TNF-α production by human mononuclear leukocytes and monocytes (61, 62). Interestingly, tetrandrine is 6-18 times more potent than another natural product, berbamine, in terms of its inhibitory effects on the production of TNF-α from monocytes and macrophages and TNF-β from lymphocytes (63). These results suggest that tetrandrine can also inhibit inflammatory responses through blockade of PAF and cytokines.

Nitric oxide (NO) is one of the critical mediators in inflammation. Tetrandrine suppresses the NO production stimulated by LPS from peritoneal macrophages. This is one of the many aspects of the antiinflammatory mechanisms of tetrandrine (64). Tetrandrine also inhibits active oxygen generation by stabilizing plasma membrane and inhibiting protein kinase and NADPH oxidase activation. These potent antioxidant properties of tetrandrine may account for some of its antiinflammatory effects (65-67). The inhibitory effects of tetrandrine on neutrophil function and vascular permeability may be related to the increase in superoxide dismutase activity and cAMP (68). Furthermore, tetrandrine has demonstrated significant inhibitory effects on receptor ligand-mediated histamine release from rat mast cells (69, 70).

Tetrandrine has also been shown to significantly suppress uveitis induced by lens protein and bovine serum albumin (71, 72). The antiinflammatory mechanism in these cases is related to the reduction of prostaglandin production, leukocyte chemotaxis, T-lymphocyte transformation and serum circulating immune complexes formation. Thus, tetrandrine appears to be a nonsteroidal, broad spectrum antiinflammatory drug with IL-1 blocking, immunosuppressive, antiallergic and antioxidative actions.

Tetrandrine has been shown to inhibit IL-1 production and activity (73-75). In studies in rats, tetrandrine significantly suppressed uveitis induced by IL-1α and endotoxin. The dose-response curve of IL-1α was markedly shifted to the right and maximum inflammation was significantly suppressed. Further increase of IL-1α did not reverse the suppression caused by tetrandrine, indicating that the inhibition of IL-1α by tetrandrine is noncompetitive (57).

Short-term toxicology studies have shown that tetrandrine has no toxic effects at therapeutic doses (76). In addition, long-term clinical studies in patients with silicosis have shown no toxic symptoms in patients treated for up to 3 years (77). Thus, tetrandrine is the most promising nontraditional NSAID among all the natural compounds tested to date.

Synthetic organic compounds

Barbiturate derivatives were originally synthesized for use as local anesthetics. Among 100 Chiou Kumainoto (CK) compounds, CK-17 (5-bromo-tetrahydro-5-methyl-3-phenyl-2-phenylimino-4*H*-1,3-thiazinone) was unexpectedly found to have potent antiinflammatory activity in lens protein-, endotoxin- and IL-1-induced uveitis. CK-17 was later found to inhibit carrageenan-induced edema in rat paw (7, 8, 78). These results encouraged us to synthesize improved derivatives and/or hybrid compounds combining parts of other antiinflammatory molecules with CK-17. For example, CK-102 (3,4-dimethyl-9-(10*H*)-acridone) is a combination of CK-17 and mefenamic acid which was as effective as CK-17 in lens protein-, endotoxin- and IL-1-induced inflammation. CK-102 was also as potent as CK-17 in inhibiting carrageenan-induced edema in rat paw (78). Interestingly, CK-101A (2-anilino-3-phenyl-1,3-thiazine) and CK-103A (4,6-dihydroxypyridazino[4,5-*d*]pyridazine-5-(1*H*)-ones) are structurally similar to CK-17 and CK-102, respectively, and both produced equally potent antiinflammatory actions as their parent compounds (7, 8) (Fig. 1).

These exciting findings led to the synthesis of the dihydropyridazino pyridazine derivatives CK-111-122, which have chemical structures similar to CK-103A. Although CK-112-116, CK-119, CK-120 and CK-122 (Fig. 2) showed potent antiinflammatory activity, CK-111, CK-117, CK-118 and CK-121 (Fig. 3) did not (79).

A series of benzylidene hydrazino derivatives was formed by opening of the structural ring. All of the com-

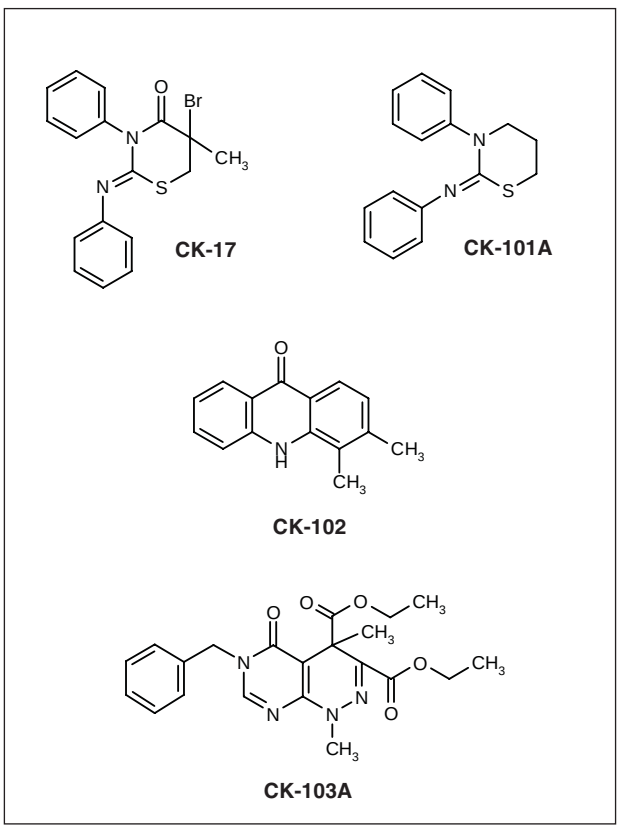

Fig. 1. Chemical structures of CK-17, CK-101A, CK-102 and CK-103A.

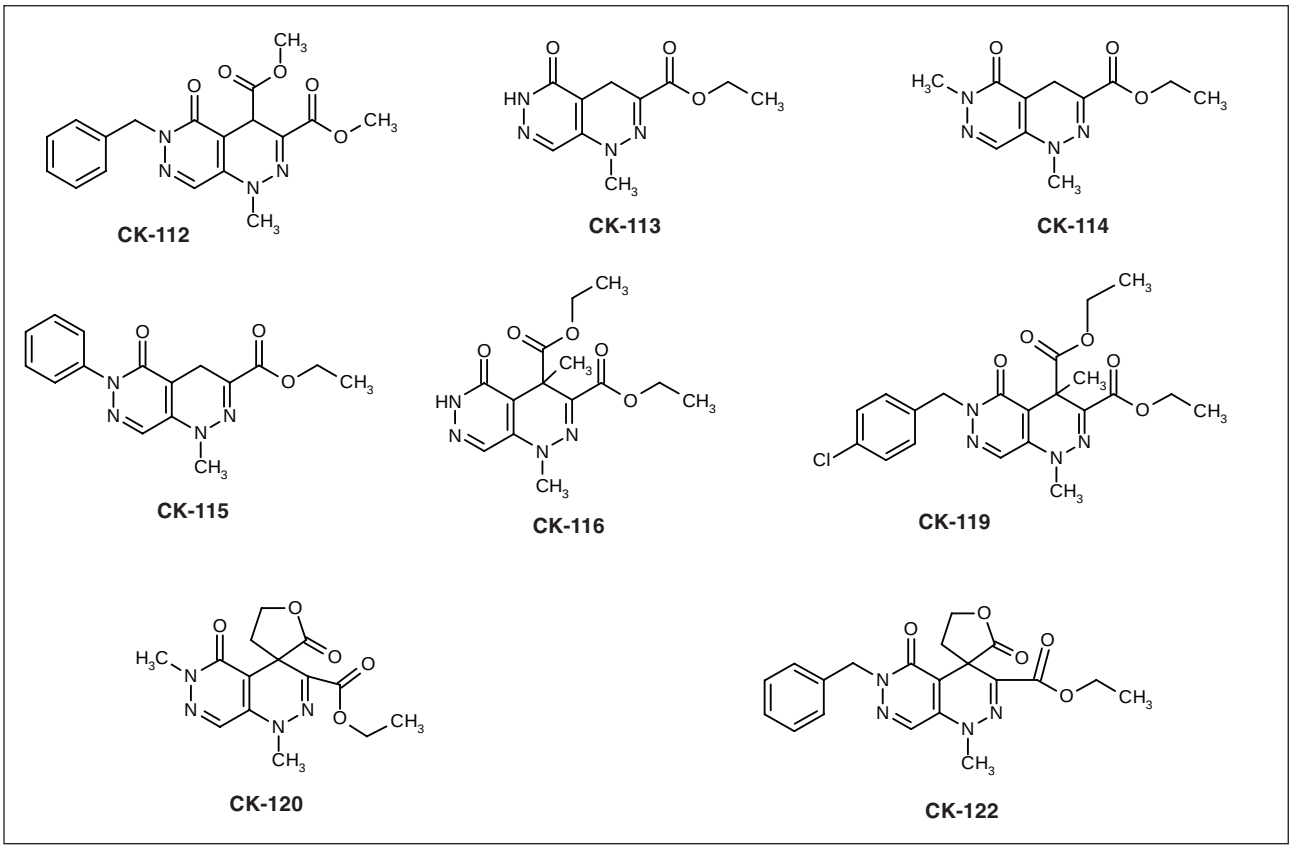

Fig. 2. Chemical structures of CK-112-116, CK-119, CK-120 and CK-122.

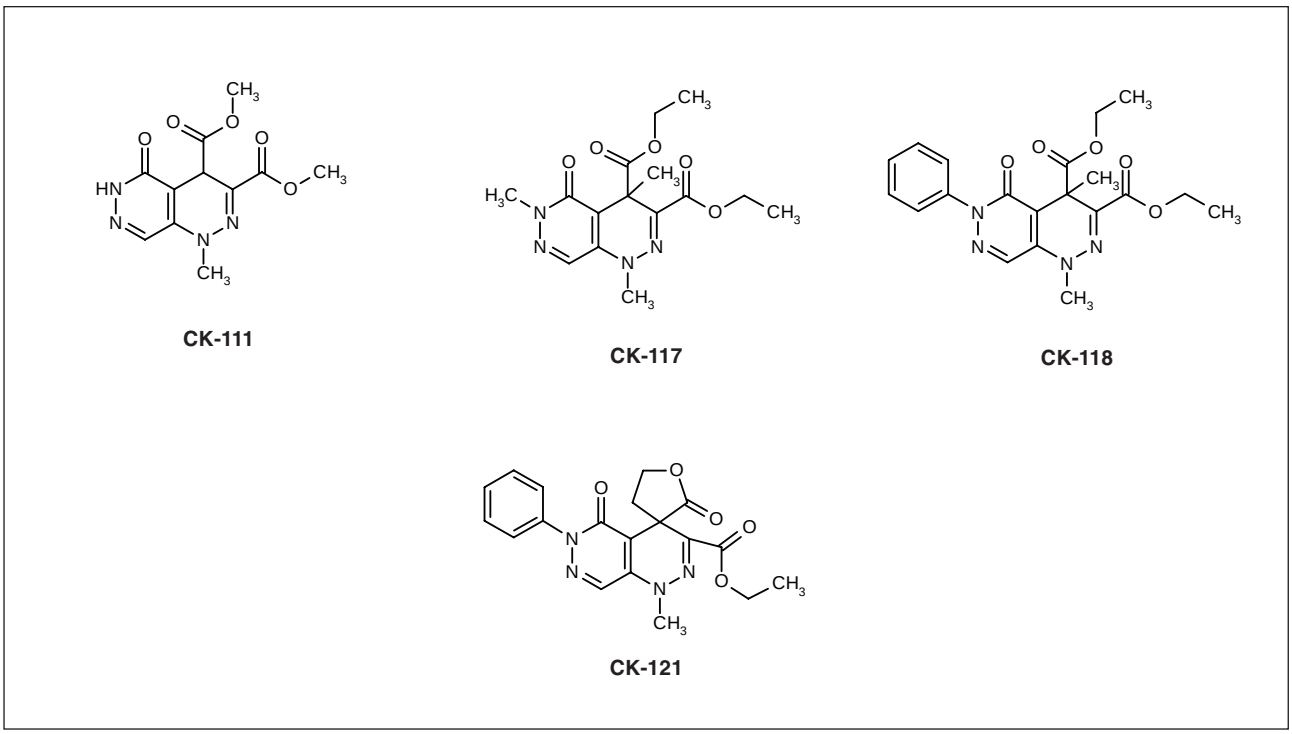

Fig. 3. Chemical structures of CK-111, CK-117, CK-118 and CK-121.

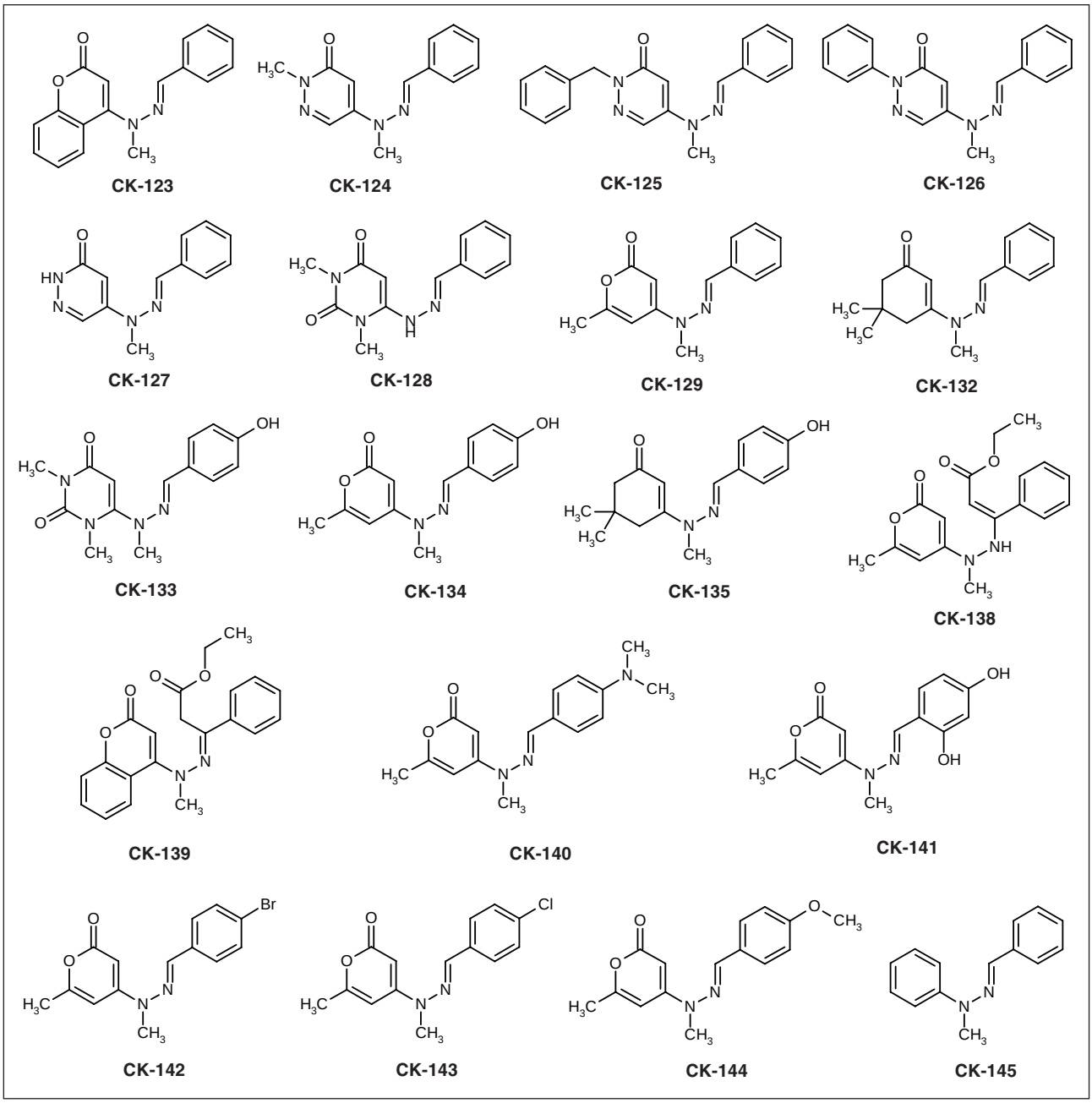

Fig. 4. Chemical structures of CK-123-129, CK-132-135 and CK-138-145.

pounds in this class (Fig. 4) showed potent antiinflammatory activity except for CK-136 and CK-137 (Fig. 5) (80-82). Further modification of the benzylidene hydrazino skeleton resulted in CK-146-149, CK-152 and CK-163 (Fig. 6). These compounds, however, were less active than the benzylidene hydrazino derivatives. Conversion of the molecular structures into more rigid or smaller molecules such as CK-150, CK-151, CK-153 and CK-160 (Fig. 7) resulted in compounds with reasonably good biological activity but did not increase the potency. CK-154 and CK-156 (Fig. 8), although structurally similar, were

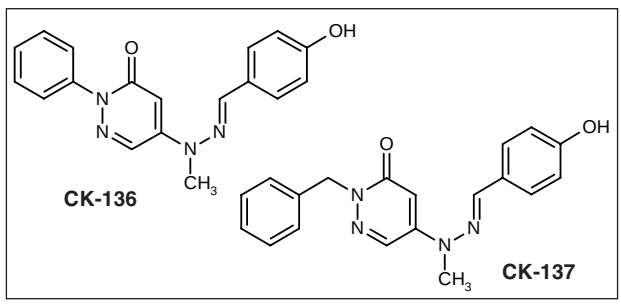

Fig. 5. Chemical structures of CK-136 and CK-137.

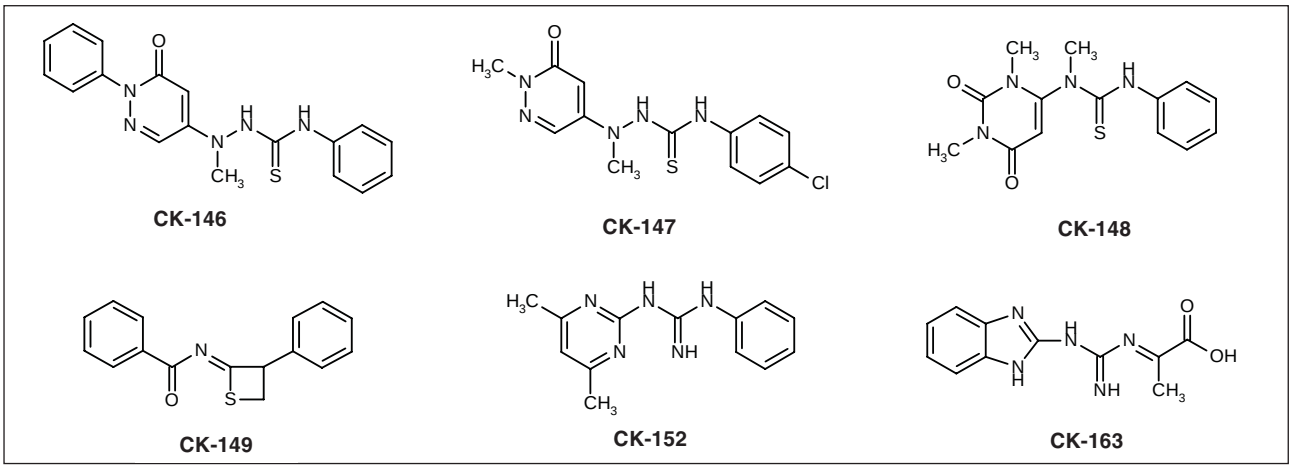

Fig. 6. Chemical structures of CK-146-149, CK-152 and CK-163.

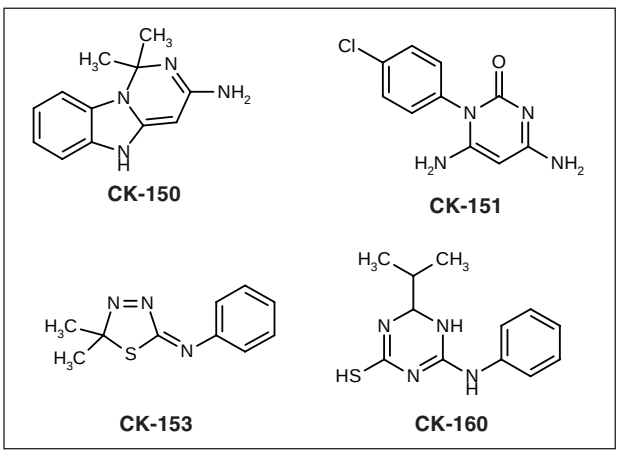

Fig. 7. Chemical structures of CK-150, CK-151, CK-153 and CK-160.

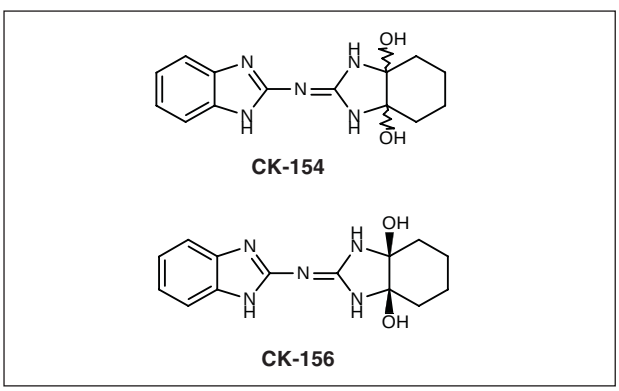

Fig. 8. Chemical structures of CK-154 and CK-156.

not effective. Surprisingly, molecules with double pentagonal rings such as 1,2,3a,4,6a-hexahydro-5-(2-hydroxyphenyl)-3a-methyl-2-oxopyrrolo[2,3-*b*]pyrrole (CK-130) and 1,2,3a,4,5,6,7,8,8a-decahydro-1,8-dibenzyl-3a,6,6d-trimethyl2,4-dioxopyrrolo[2,3-*b*]indole (CK-131) (Fig. 9), exhibited antiinflammatory effects (83).

Other miscellaneous compounds reported to act as IL-1 blockers include substituted pyrrolo(3,2-*c*)quinolines, methanediphosphonic acid derivatives, condensed pyrazole derivatives, cyclic nitrones, 2-phenyl-3-aroyl-benzothiophenes, 2,5-diaryl-4-isothiazolin-3-ones and heterocyclic benzene sulphonylimines. These compounds have been claimed to be useful for the treatment of rheumatoid arthritis, cartilage degradation and related inflammatory diseases (10, 11).

Pharmacology of CK compounds

Mechanisms of action

There are more indirect acting drugs which block endotoxin/LPS-induced inflammation than direct acting drugs which inhibit IL-1-induced inflammation. Whereas indirect acting compounds block IL-1 release but not the direct actions of IL-1 at the receptor site, the direct acting drugs both indirectly and directly inhibit inflammation responses because they act at the IL-1 receptor sites which are the end point of IL-1-induced responses. CK compounds are typical IL-1 blockers which block

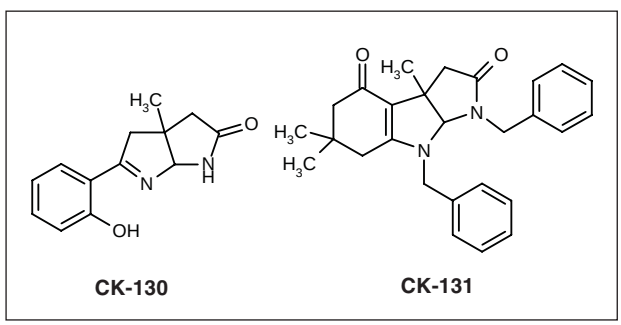

Fig. 9. Chemical structures of CK-130 and CK-131.

inflammation induced by lens protein, endotoxin, LPS and IL-1. The blockade of IL-1 receptors seems to be non-competitive as CK-17 and CK-102 shift the dose-response curve of IL-1-induced uveitis by reducing the maximum efficacy without changing the ED_{50}s (84). CK compounds do not affect lipoxygenase activity and only slightly inhibit cyclooxygenase activity. Therefore, their actions are not related to arachidonate metabolism and are different from traditional NSAIDs such as aspirin, indomethacin, ibuprofen, flurbiprofen, *etc.*

Treatment of uveitis

Uveitis can be induced indirectly by lens protein and endotoxin/LPS or directly by IL-1. In all cases, it can be inhibited by most of the CK compounds mentioned above. Lens protein is released and induces serious autoimmune inflammation during and after cataract surgery. Therefore, intracameral injection of lens protein is a good animal model to study the antiinflammatory effects of a drug in cataract surgery. Endotoxin is released by numerous microorganisms to cause uveitis, so intravitreal injection of endotoxin is a good animal model to study drug efficacy in infectious inflammation. Intravitreal injection of IL-1 induces posterior uveitis which is an excellent animal model for studying the direct effects of a drug on the receptor site. Uveitis can also be studied by lymphocyte chemotaxis into the aqueous humor which is caused by the breakdown of the blood-aqueous barrier due to inflammation.

All of these phenomena can be effectively blocked by most of the CK compounds (7, 8, 79-83). When the eye is injected with lens protein, endotoxin and/or IL-1, the blood-aqueous barrier is broken down to allow the non-permeable large molecule of fluorescein to enter the aqueous humor from systemic circulation. This phenomenon, which can be measured objectively in animals with a fluorophotometer, is inhibited by treatment with most CK compounds which are as effective or more effective than prednisolone, the representative corticosteroid used for uveitis treatment (7, 8, 79-83). This is quite exciting as all classic NSAIDs are much less potent than corticosteroids. The effective doses of CK compounds reported are 3-10 mg/kg i.p. or 1 drop of 1% solution instilled locally into the eye.

Trabeculectomy for glaucoma

Trabeculectomy (filtration surgery) is commonly used for the treatment of narrow- or closed-angle glaucoma and low-tension glaucoma to improve the outflow of aqueous humor from the anterior chamber through an operative artificial canal (85, 86). The success of trabeculectomy is measured by the artificial canal remaining open, by reduced intraocular pressure and by the lack of inflammation after eye surgery. Surgery can fail as a result of the overcompensation of the wound healing responses due to fibroblast proliferation (9, 85-89). Because the scar is formed from IL-1-stimulated fibroblast proliferation, it seems reasonable to predict that IL-1 blockers could inhibit fibroblast proliferation and prevent subconjunctival and bleb fibrosis (85-89).

Corticosteroids, 5-FU and mitomycin C have been widely used to prevent inflammation and to prolong functioning of the artificial canal (90-93). Because they cause serious side effects, alternative compounds are needed in order to improve the success rate of trabeculectomy. Subtenons injection of methylprednisolone acetate (10 mg/injection) prolonged the functional time of the artificial canal by 21%, whereas CK-103A (10 mg/injection) did so by 79%. CK-17, CK-101A and CK-102 (10 mg/injection) also markedly improved the functional time of the canal by 55, 55 and 30%, respectively (85, 86). There are several advantages to using CK compounds in trabeculectomy: (a) they are more efficacious than corticosteroids in prolonging the functional time of the canal; (b) the intraocular pressure remains low for a longer period of time than after corticosteroids; (c) ocular inflammation due to surgery is prevented; and (d) no serious side effects have been noted. Therefore, CK compounds could be used in combination with trabeculectomy in the future (85, 86).

Systemic antiinflammation

The animal model most commonly used to test the systemic antiinflammatory actions of drugs is carrageenan-induced rat paw edema. Drugs that are effective in preventing rat paw edema are considered to be useful for the treatment of systemic inflammatory diseases such as rheumatoid arthritis, IBD, glomerulonephritis, chorioamnionitis, sepsis, sarcoidosis, monocyte chemotaxis, *etc.* Interestingly, CK-17 and CK-102 are 10-to 30-fold more potent than the standard NSAID, aspirin, in inhibiting rat paw edema (79). These results indicate that CK compounds can be used not only for local inflammation responses but also for systemic inflammatory diseases.

Safety

The major disadvantage in using corticosteroids as antiinflammatory drugs is their potential for inducing serious side effects. In many cases, treatment must be discontinued because patients are unable to tolerate the side effects. Although NSAIDs are less toxic, they also cause side effects including gastrointestinal bleeding, eye irritation, *etc.* Since CK compounds do not interact with steroid receptors, they do not cause the side effects associated with corticosteroids. As demonstrated on the Draize test, CK compounds do not irritate the eys and are nonlethal up to oral doses of 20 g/kg. This is very unusual because the therapeutic index (LD_{50}/D_{50}) can be as high as 2000. These results further suggest that CK

compounds may be useful for treating inflammatory diseases with little or no significant side effects (78).

Conclusions

IL-1ra is a naturally occurring polypeptide which has been found to antagonize various inflammatory responses induced by IL-1, endotoxin, infection, TNF, LPS, *etc.* Although IL-1ra is effective at blocking inflammation, it is unstable in the blood stream due to its polypeptide molecule. Obviously, organic compounds would be more desirable than polypeptides because they are stable in the blood stream and can be administered orally or intravenously. Tetrandrine is a natural alkaloid which blocks the IL-1 receptor noncompetitively. It is the most promising antiinflammatory drug among all natural compounds tested to date because of its efficacy and lack of significant side effects.

A new class of synthetic IL-1 blockers (CK compounds) has been studied with encouraging results. These compounds block inflammation *in vivo* induced by lens protein, endotoxin, IL-1 and carrageenan. Because they inhibit fibroblast proliferation, they can also prolong the functioning time of the artificial canal created by trabeculectomy. Most importantly, they do not produce serious side effects which makes them superior to corticosteroids, PAF antagonists and arachidonate metabolite blockers. Other classes of drugs, such as the IL-1 synthesis inhibitors and IL-1 release inhibitors, also achieve the same antiinflammatory effects indirectly. However, since they have more diffued actions they are associated with more side effects than the IL-1 blockers, which act directly only at the IL-1 receptor site.

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