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Prospects of Treating Ocular Hypertension and Glaucoma with Peptidic and Non-Peptide Kinin Mimetic Drugs

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Abstract

The endogenously generated small nonapeptide bradykinin (BK) is often associated with inflammation, edema and pain amongst many other functions and pathologies. However, the latter aspects pertain to locally produced BK from circulating plasma precursor polypeptide kinninogen (KNGN). Recent work in ocular tissues and cells have a revealed a novel local synthesis of BK and other kinins from tissue-derived KNGN via action of kallikrien enzymes, quite independent from the blood-derived polypeptide. Furthermore, the whole ocular kininergic system machinery including local KNGN, kallikrein enzymes to generate kinins from KNGN, two sub-types of kinin receptors (B_1 ocular- and B_2-receptors), and the complete signal transduction pathways coupled to these receptors have been mapped out. Additional work has highlighted a number of downstream signaling and other biological responses that ensue following activation of B_1- and B_2 receptors in human ocular cells and tissues. One key aspect to be discussed in detail in this review is the novel finding that BK, peptidergic BK analogs, and especially non-peptide mimetics of kinins (e.g. FR-199097; BK2A78), profoundly lower and control intraocular pressure in a number of species, including ocular hypertensive (OHT) monkeys. These novel observations strongly suggest that kinin agonists represent a novel class of ocular hypotensive agents that could be of immense value in treating OHT associated with primary open-angle glaucoma (POAG) and perhaps other forms of glaucoma.

Ocular Hypertension Associated with Glaucoma

At a simplistic level, our knowledge has advanced to a point where it is now clear that elevated intraocular pressure (IOP) results from a fundamental imbalance between the generation of aqueous humor by the ciliary body and its efflux from the anterior chamber of the eye via one of two pathways [1-3]. The most physiologically relevant mechanism of AQH drainage involves the IOP-dependent outflow via the trabecular mesh work (TM) and Schlemm's canal (SC) route [1-3]. The lesser utilized pathways under normal conditions are the uveoscleral [1-3] and ocular lymphatic [4] pathways, but the latter can be engaged by certain drugs such as FP-class prostaglandin analogs (FPGAs) like latanoprost and tafluprost [1-6]. The chronically increased IOP, a condition generally termed as ocular hypertension (OHT), caused by blockage of the AQH drainage TM/SC pathways [7] during the aging process or due to ocular inflammation and deposition of various debris, along with apoptotic death of retinal ganglion cells, can lead to a clinically defined disease called glaucoma [8-10]. This high IOP initiates the death of RGCs and/or breakage of RGC axons at the back of the eye. These elements then cause a retrograde demise of the RGCs leading to severing of nerve fibers connecting the retina to the brain [11-13]. Many deleterious neurotoxic elements (e.g. high levels of extruded glutamate, endothelin, inflammatory cyto-and chemo-kines, noxious gases (e.g. nitric oxide; hydrogen sulfide)) and proteolytic enzymes (e.g. caspases and matrix metalloproteinases) released by activated macrophages [12-19], injured RGCs and interneurons are the culprits responsible for such neurotoxicity/chemically-induced axotomy of the RGCs. Hypoxia and ischemia [20,21] are also involved in the initiation phase of vascular dysfunction-induced death of RGCs since the thinning of the optic nerve at the level of the optic nerve head (ONH) forces the retinal blood vessels attached to the optic nerve to bend thereby restricting blood supply to the retina. While this progressive loss of RGCs occurs over several decades, if OHT is not treated to reduce the IOP the resulting glaucomatous optic neuropathy causes severe

visual impairment, reduction of visual acuity and visual field and eventually results in irreversible blindness. Although many forms of glaucoma exist (e.g. open-angle glaucoma; closed-angle glaucoma; exfoliation glaucoma; myopic glaucoma) [8,9,22-26], the most prevalent is primary open-angle glaucoma (POAG) [26-28]. Behind cataracts, POAG is the second leading cause of blindness afflicting several millions of patients. It is estimated that by 2020, the global glaucoma-related blindness will reach ~80 million [26-28]. Elevated IOP and advancing age are the two major risk factors associated with POAG even though genetic factors [26] and race (especially African and Asian heritage) [29], myopia, diabetes and oxidative stress [30-36] and various vascular irregularities and dysfunctions [20,22], and intracranial cerebrospinal pressure [37,38] have been also linked to the development of POAG. The seriousness of POAG is often underestimated since it causes no overt discomfort or pain to the patient and insidiously progresses unnoticed over time. Considerable damage to the retina [33-36] and optic nerve and optic nerve head (ONH) [14,29,39-41] continues unyieldingly leading to scotomatous damage that manifests as loss of peripheral vision followed by a "tunnel vision" syndrome, thereby finally signaling the demise of ~40% of the original million RGCsof the patient and equivalent loss of connections to the brain and visual cortex [8,9,42-45]. Those lost or dying RGCs cannot be resuscitated and their axonal connections revived [46-48], and if left untreated the glaucomatous optic neuropathy due to OHT and oxidative /neurotoxic elements would claim the remaining RGCs causing total blindness [49-53].

Table 1: [Ca^{2+}]I mobilization assays, data for human CM, TM, and NPE type cells.

A	Compound Agonist Potency (EC_{50}; nM) and In Vitro Efficacy (E_{max}, % max relative to BK)		
Agonist Compound	h-CM Cells	h-TM Cells	h-tNPE Cells
BK (Peptide B2> B1 receptor agonist) (n = 20-34 in different cell-types)	2.0±0.2 (E_{max}=102±1%)	8±1 (E_{max}=102±1%)	6.0±1.0 (E_{max}=101±1%)
FR-190997 (Selective Non-peptide B2-receptor agonist)(n = 9-29 in different cell-types)	155±14 (E_{max}=64±3%)	150±16 (E_{max}= 80±3%)	276±42 (E_{max}= 38±3%)
Des-Arg9-BK (selective B1-receptor agonist)(n = 2-4 in different cell-types)	4,260±572 (E_{max}=94±1%)	2,570±756 (E_{max}=113±5%)	16000 (E_{max}= 70%)

B	Compound Antagonist Potency (K_i; nM) Using FR-190997 as Agonist (n>3 for each compound & cell-type)		
Antagonist Compound	h-CM Cells	h-TM Cells	h-tNPE Cells
HOE-140 (peptide agent)	0.8±0.1	7.0±0.4	4.6±0.8
WIN-64338 (non-peptide agent)	157±13	425±47	197±50

Data are mean±SEM from [Ca^{2+}]I mobilization assay in cells derived from several different human donors' eyes. h-tNPE cells are SV40-virus-immortalized human non-pigmented ciliary epithelial cells derived from human ciliary epithelium that respond just like normal primary NPE cells. [145,146,157]

A number of treatment options have been developed to deal with POAG-associated OHT including ocular hypotensive medications [1-3,54-56], laser therapy and surgical interventions [57-64]. Unfortunately, as is the case with most drugs and surgical procedures, these treatment modalities have numerous side-effects (e.g. Burning and stinging, foreign-body sensation, brow-ache, ocular surface dryness, pulmonary hypertension and bradycardia, etc.), and adverse complications associated with them [1-3,54,55]. Additionally, poor compliance [65] and adherence to prescribed topical ocularly administrated medications by the OHT POAG patients (due to forget fulness, poor dexterity,lack of symptomatic pain or other cues due to OHT, poor understanding of the treatment regimen, and perhaps distrust, etc.) contributes to the progression of the disease process. Similarly, laser therapies, although effective at the beginning, lose their efficacy over time [57-62]. Reports have surfaced that indicate that POAG/ OHT is only controlled in ~50% of patients who received laser treatment, and indeed due to scarring,the procedure often needs repeating within one-five years [57-64]. Indeed, such lasering and filtration procedures also have certain risks of complications and adverse events associated with them. Thus, there remains a continued unmet medical need to discover new and improved eye drop-medications and other novel surgical techniques to help the OHT/POAG patients mitigate and treat their underlying glaucomatous optic neuropathy caused by elevated IOP. To this end, a better understanding of the many complex pathways involved in AQH dynamics [4,7-10] has culminated in the discovery and development of many novel targets and ligands [1-3,54,55] that can modulate IOP via these targets to accomplish a level of homeostasis of AQH production and drainage. In order to address poor patient compliance, a number of innovations leading to sustained drug-release devices (e.g. implants, punctal plugs or contact lenses) [60-64,66-70] have been developed such that the patient need not remember to self-administer the medication. Likewise, a revolutionary set of novel surgical

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interventions [57-64] with much reduced surgical time and effort required and minimal adverse events and complications are becoming available [57-64]. These include the following: non-penetrating glaucoma surgery (NPGS), non-invasive glaucoma procedure, minimally invasive micro sclerostomy, blebless ab externo glaucoma surgery, ab externo bleb surgery, and the elegant minimally-invasive glaucoma surgery (MIGS) [60-64] that involve insertions of tiny drainage devices into the anterior chamber of the eye that appear to be highly effective in decreasing IOP [62-64]. Time will tell if indeed these innovations become mainstay treatment options for POAG/OHT patients in the near future. Regardless, however, the ordinary patient who is unable to afford the latter surgical procedures and devices, and those patients who are refractory to or cannot tolerate existing medications, will still require new topically administered drugs to lower and control the IOP in order to preserve their vision.

Table 2: Prostaglandins production in h-CM and h-TM cells by BK and FR-190997 ,Bradykinin B2 receptor agonist [145,146].

	h-CM Cells		h-TM Cells	
Test agonist	**Agonist Potency (EC_{50}, nM) & In Vitro Efficacy (E_{max}, % of BK)**		**Agonist Potency (EC_{50}, nM) & In Vitro Efficacy (E_{max}, % of BK)**	
	PGE_2 Production	$PGF_{2\alpha}$ Production	PGE_2 Production	$PGF_{2\alpha}$ Production
BK	7±3 nM (E_{max}=100%)	9±1nM (E_{max} =100%)	12±6nM (E_{max}=100%)	14±2nM (E_{max}=100%)
FR-190997	19±9nM (E_{max}=33%)	21nM (E_{max}=30%)	17±16nM (E_{max}=27%)	15±12nM (E_{max}=29%)

Table 3: Conscious ocular hypertensive and normotensive cynomolgus monkey eyes IOP-lowering responses to bradykinin and FR-190997 [155,159].

			% Change In Monkey IOP (Relative To Baseline) (Topical Ocular Dosing W ith 30µg of Bradykinin or FR-190997 as a Single Topical Ocular Dose)			
Lasered Eyes (ocular hypertensive; n = 10 monkeys)	Baseline IOP (mmHg)	1 h post-dose	3 h post-dose	6 h post-dose	24 h post-dose	48 h post-dose
Bradykinin	41.4	-1.5±3.2	-2.3±3.5	-14.5±3.4	-5.6±4.0	Not determined
FR-190997	41.4	0.3±2.8	-5.4±3.2	-21.0±5.7	-37.7±5.4 ($p < 0.005$)	-19.7±3.9 ($p < 0.001$)
Normal eyes (normotensive; n = 10 monkeys)	Baseline IOP (mmHg)	1h post-dose	3h post-dose	6h post-dose	24h post-dose	48h post-dose
FR-190997	27.8	10.5±3.6	12.1±2.3	13.4±4.0	9.5±3.8	Not determined

Present Day Pharmacotherapy for OHT

One of the earliest pharmacological agents to be used to lower elevated eye pressure is a muscarinic receptor agonist, pilocarpine [1-3]. It just happened that it promoted egress of AQH through the TM, hence pilocarpine became the first known conventional outflow promoter. Since it strongly constricted the pupil, made accommodation difficult and painful due to brow-ache, and needed to be administered up to 4-times a day, newer drugs with higher efficacy and lesser side-effects were sought and discovered over the next few decades. These included carbonic anhydrase inhibitors such as dorzolamide and brinzolamide, beta-adrenergic antagonists (e.g. timolol; betaxolol) and alpha-adrenoceptor agonists such as brimonidine and para-amino-clonidine [1-3,54,55]. Whilst these drugs lowered IOP well, they required at least twice daily dosing and they primarily inhibited the production of AQH by the ciliary processes of the ciliary body. Eventhough compliance increased and a greater efficacy was achieved, these agents had their own short-comings in terms of side-effects including ocular surface irritation (hyperemia), burning and stinging,allergy and drowsiness (α-agonists), and some pulmonary and cardiac insufficiency (with β-blockers) [1-3,55]. Furthermore, we have learnt that AQH constituents serve important nutritional needs of the tissues inside the anterior chamber of the eye [10], and thus reducing its availability negatively impact the ciliary body, lens, corneal endothelial cells, and may in fact damage the TM and SC endothelial cells. Thus, a major breakthrough in OHT / POAG treatment occurred in the mid-90s when FP-receptor-selective prostaglandin (PG) agonists (PGAs) (e.g. latanoprost; travoprost; bimatoprost; tafluprost; unoprostone isopropyl ester) [3,5,6,71-73] were discovered and introduced into ocular clinical medicine. These

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PG drugs revolutionized the POAG/OHT treatment paradigm since they required once-daily ocular administration (before bed-time) and were much more potent and efficacious than the existing medications since they created new drainage pathways across the ciliary muscle and sclera (uveoscleral pathway) to help drain the AQH [1-5]. Nevertheless, these novel PGAs had some significant side-effects that included hyperemia, darkening of the iris color and increased pigmentation of the periorbital skin, growth of eye-lashes, deepening of the eye orbit, and in some cases cystoid macular edema [1-5,71-74]. Additionally, some OHT/POAG patients were quite refractory to the PGA drugs such that they required multiple drugs to control their IOPs. Not surprisingly, a multitude of fixed-dose combination products [73,74] containing different dual combinations of various ocular hypotensive drugs (and even a triple combination product) have now become available. However, due to the inherent genetic and biological variation in responses of patients to the different classes of IOP-lowering medications and their relative susceptibility to the side-effects of the drugs, there still remains a great need to hunt for and discover new drugs that are more effective, longer acting, efficacious in majority of OHT patients, and that induce fewer and milder off-target side-effects, thus having a greater therapeutic index than the existing drugs [67,76,77] .

Future OHT/POAG Pharmacotherapy

The potential additivity of new pharmacological agents to PGAs in the treatment of OHT and POAG has spurred the recent surge in research for novel agents exhibiting IOP-lowering properties. The realization that POAG is not only caused by elevated IOP since patients with normal IOPs still lose vision [78-80], but perhaps is a reflection of enhanced RGC susceptibility to oxidative stress [7-9,12,32-36,42] and apoptotic process [15,47,81-90], has stimulated a renewed interest in finding drugs that have dual or multiplicity of mechanisms of action, including direct potential neuroprotective activity. The latter aspect stems from the finding that agents like betaxolol [91-95] and brimonidine [89,91,95], whilst lowering IOP, also upregulate the release of endogenous neurotrophins [89] in retinal tissues that could heal/rescue some of the RGCs that are compromised from the elevated IOP and oxidative stress. Likewise certain PGAs stimulate blood flow at the ONH in addition to reducing IOP [1-6,100-102]. Additionally, as the tools to monitor IOP [98,99] have become more accessible at a lower cost and with a greater sensitivity, including round-the-clock monitoring of IOP [99,100], and as new models of OHT/POAG are introduced using various species [48,23-25,101-104], the potential for such innovations to enhance drug discovery have dramatically increased in recent years. The ability to perform AQH dynamic measurements in small laboratory animals like mice [104], and to exploit enucleated and ex-vivo perfused bovine [102,105], porcine [102,105] and human eye anterior segments, and even whole eye [106], has further accelerated the mechanistic approach to ocular drug discovery and characterization. Accordingly, pharmacological agents that have exhibited ocular hypotensive efficacy in some of these animal/ ex-vivo models include K^+-channel openers [107], Na^+-K^+ -ATPase inhibitor digoxin analogs [108], angiotensin-II receptor antagonists [110,111], renin inhibitors [110-112], angiotensin converting enzyme (ACE) inhibitors [113-116], ACE-2 activators [116,117], cannabinoids [119], rho-kinase inhibitors [119-121], nitric oxide (NO) donors and their conjugates [122-126], serotonin (5-hydroxy-tryptamine (5-HT)) receptor agonists [102,127,128], hydrogen sulfide donors [129], dopamine receptor agonists [3], melatonin receptor agonists [1-3], adenosine receptor agonists and antagonists [131], guanylate cyclase activators [131], novel EP2 receptor agonists [133,134], dual pharmacophoric PGs encompassing FP and EP3-receptor agonistic properties [134,135], etc. The most recent unexpected discoveries of potential drug candidates for OHT/POAG treatment pertain to the kallikrein-kinin (KNK) system which will be addressed in detail below [136-164]; Figure 1.

Table 4: Aqueous humor dynamics in the ocular hypertensive eyes of mildly-sedated cynomolgus monkeys using topical ocular FR-190997 (3µg) , a non peptide bradykinin B2 receptor agonist.

Baseline Day						Treatment Day			
	Normotensive Eye OD	n	Hypertensive Eye OS	n	p-values‡		Hypertensive Eye OS	n	p-values§
F_a	1.63±0.54	12	1.54±0.80	12	0.5	F_a	1.48±0.53	12	0.79
C_{fl}	0.42 ± 0.21	9	0.16 ± 0.17	12	0	C_{fl}	0.18±0.16	9	0.47
C_{ton}	0.22±0.14	12	0.15±0.09	10	0.21	C_{ton}	0.17±0.11	9	0.59
Fu_{fl}	0.16±0.51	7	0.47±0.57	11	0.14	sFu_{fl}	1.23 ± 0.91	9	0
Fu_{ton}	0.48±0.99	12	0.37±1.04	9	0.46	Fu_{ton}	1.45 ± 0.45	10	0.03
ACvol	76.0±11.3	12	79.9±9.12	12	0.16	ACvol	79.8±9.2	12	0.74
CCT	0.48±0.03	12	0.48±0.03	12	0.36	CCT	0.48±0.03	12	0.74

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* Values are means±standard deviation. ‡, comparing hypertensive with contralateral normotensive eyes; §p-values: comparing baseline day with treatment day by Student's two-tailed paired t-test. ACvol, anterior chamber volume, µl; CCT, central cornea thickness, mm; C_{fl}, fluorophotometric out flow facility, µl/min/mmHg; C_{ton}, tonographic outflow facility, µ1/min/mmHg; F_a, aqueous flow, µl/min; FuFl, uveoscleral outflow calculated with C_{fl}, µl/min; Fu_{ton}, uveoscleral outflow calculated with C_{ton}, µl/min; Times are 30 minutes. FR-190997 (0.01%) was applied as a 30µl drop (total dose of 3µg) to each eye of each monkey Modified from Ref 155.

Kallikrein-Kinin (KNK) System in the Eye

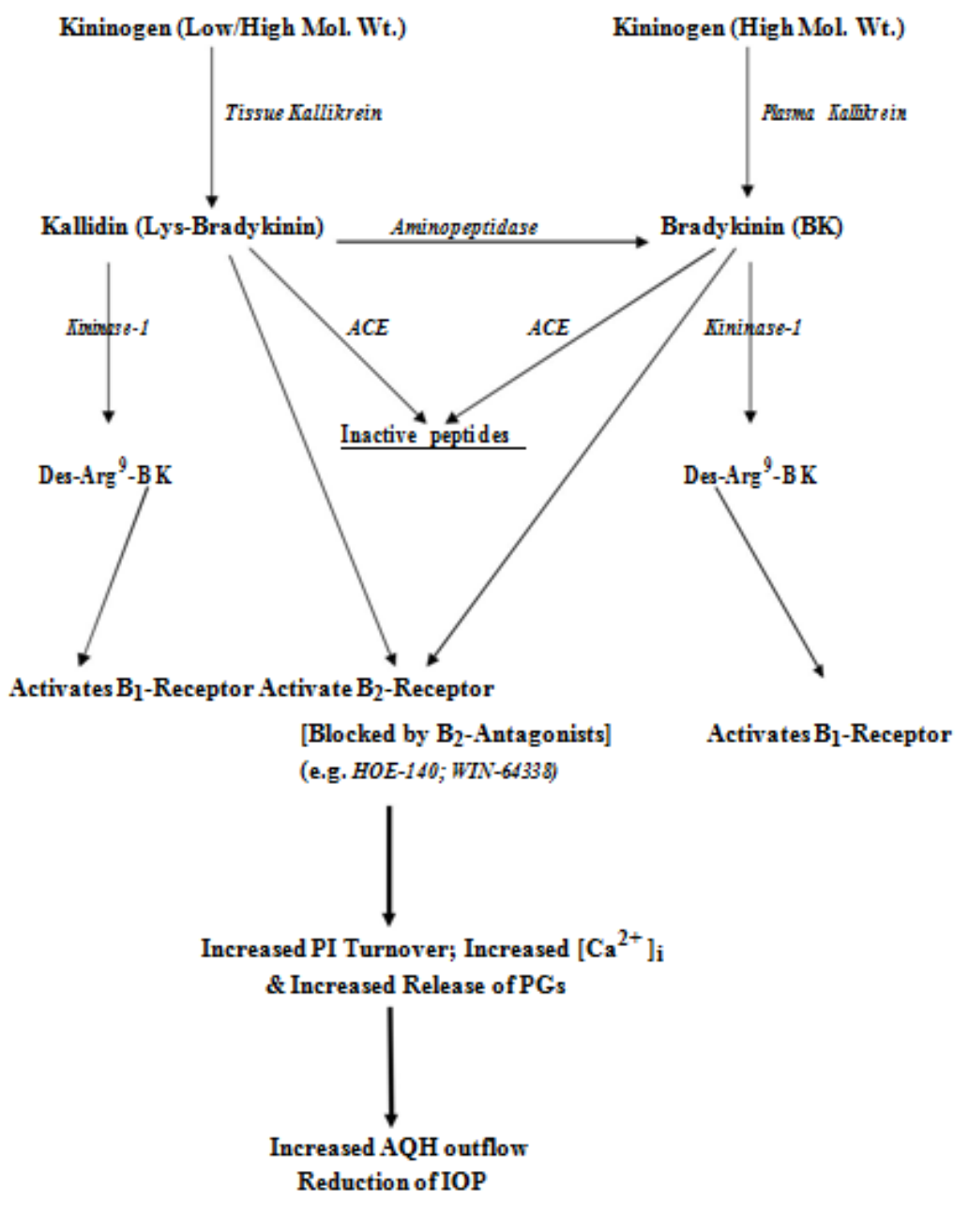

Figure 1: Pathways of kinin generation and their cognate receptor sub-types that mediate the biological actions of kinins in ocular cells.

The peptide bradykinin (BK) was discovered many decades ago and the pathway to its generation has since been fully delineated. Today, we know that a precursor polypeptide, kinninogen (KNGN), is cleaved by specific enzymes (kallikreins) to produce a 10-amino acid -and a nine-amino acid containing peptide, Lys-BK and BK respectively [137,138]. Lys-BK is then converted to BK by an aminopeptidase, but both Lys-BK and BK act on the B_2-receptor subtype of BK receptors, which is the predominant homeostatic receptor found Under normal physiological situations [136-138]. Kininase-1can convert both

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Lys-BK and BK to an octapeptide (Des-Arg9-BK) that interacts specifically with B_1-receptor subtype of BK receptors which get upregulated during injury, trauma and other deleterious situations [137,138]. ACE inactivates both Lys-BK and BK to small inert peptides (Figures 1, 2). The notoriety surrounding BK and Lys-BK (kallidin) originates from their ability to cause deleterious vasodilation, inflammation, pain and cell proliferation [137,138]. These undesirable effects of kinins have been noted in all parts of the body and either trigger or are manifestations of various underlying diseases ranging from angioedema, diabetes, pulmonary and systemic hypertension, and aneurysms and diabetic retinopathy in the central nervous system and retina [137-139]. It was quite a revelation when various components of the KNK system were found in various compartments of the eye under normal circumstances and associated with cells and tissues of the eye [139-146]. Soon it became clear that BK and perhaps Lys-BK could be formed locally by the actions of tissue-based kallikriens on tissue-derived KNGN thereby creating a paracrine kininergic system within ocular tissues [140,141]. To support this notion further, both B1 and B2-receptor subtypes were found in various ocular cells that were functionally active mediating the actions of BK and related analogs of BK, generating intracellular second messengers [141-148] (Tables 1 and 2) (Figure 3) producing further downstream effects such as promoting liberation of PGs [143-146] and causing ocular tissue contraction/ relaxation [148-150], etc. While circulating KNGN and kallikriens in ocular blood vessels do produce BK and Lys-BK to cause the vasodilator and pro-inflammatory effects as in the rest of the body, that system is distinctly different from the tissue-based KNK system in the ocular systems.

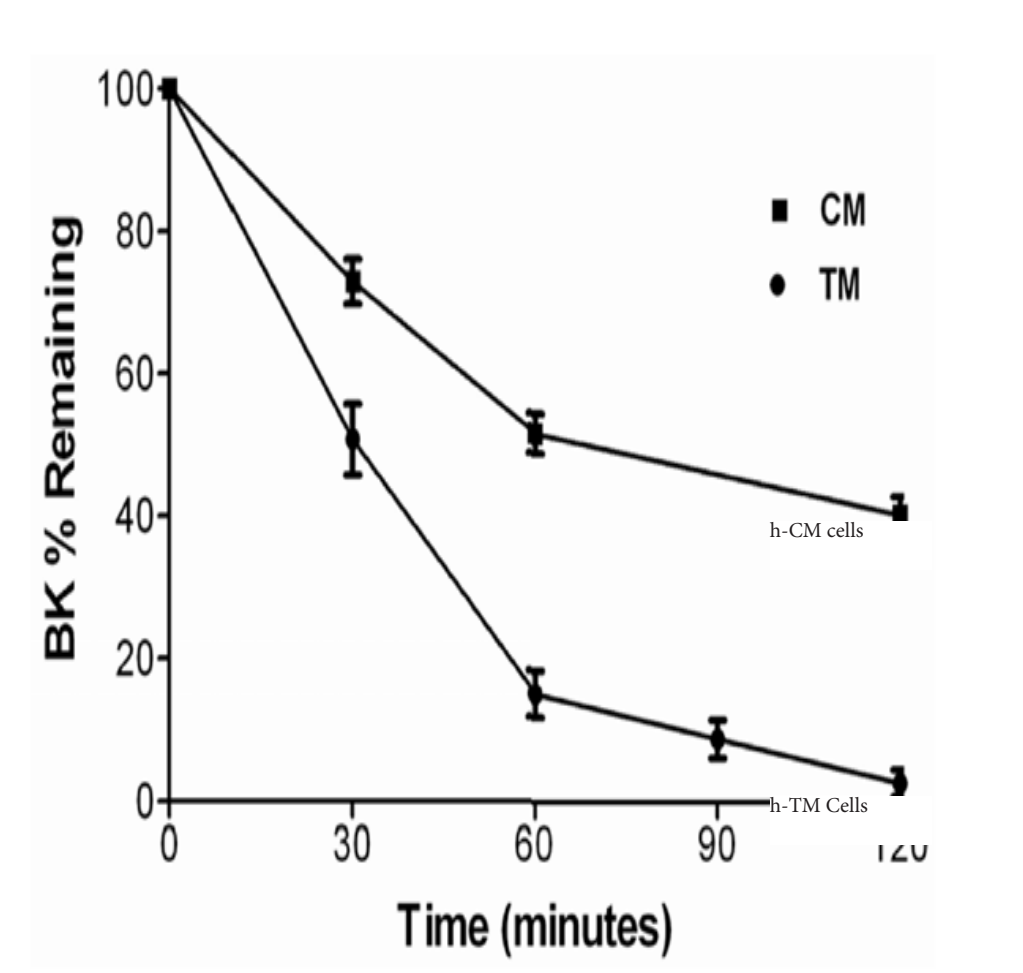

Figure 2: Bradykinin degradation by intact h-CM and h-TM cells.Modified from Ref.[144,156].

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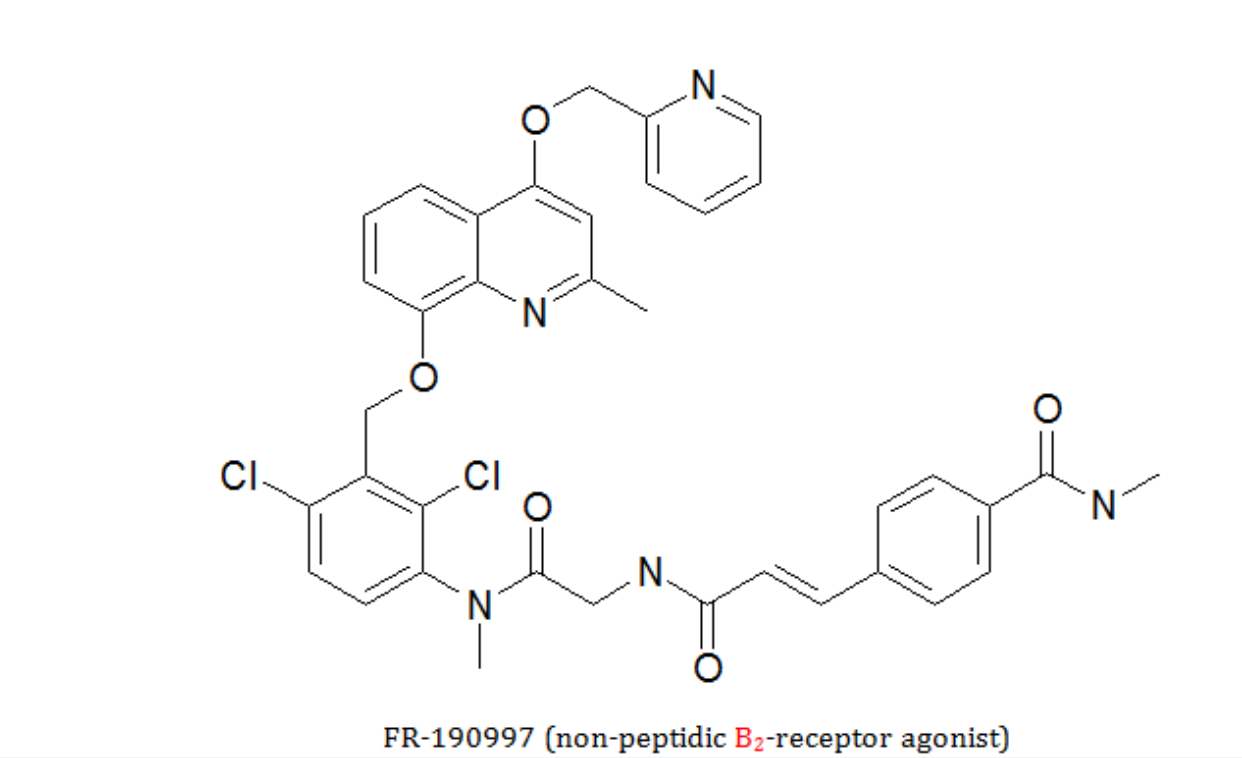

Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg (BK)

Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg (Lys-BK)

Met-Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg (Met-Lys-BK)

H-Arg-Pro-Hyp-Gly-Thi-Ser-Pro-4-Me-Tyrψ(CH_2NH)-Arg-OH (Labradimil; RMP-7); (CH_2NH denotes a reduced peptide bond between the 4-Me-tyrosine and arginine amino acids)

Figure 3: Examples of some key peptide and non-peptide kinin analogs and mimetics.

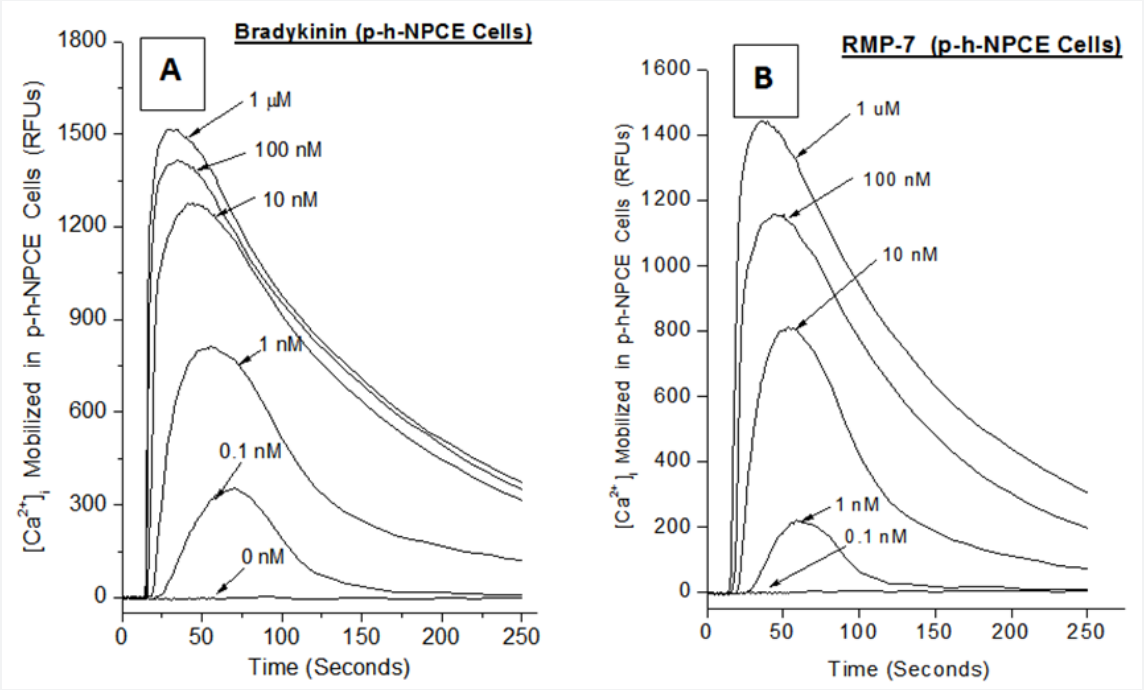

Figure 3: Rapid mobilization of $[Ca^{2+}]i$ in primary human NPE cells in response to BK and RMP-7, a metabolically stabilized BK analog. Modified from Ref. [157].

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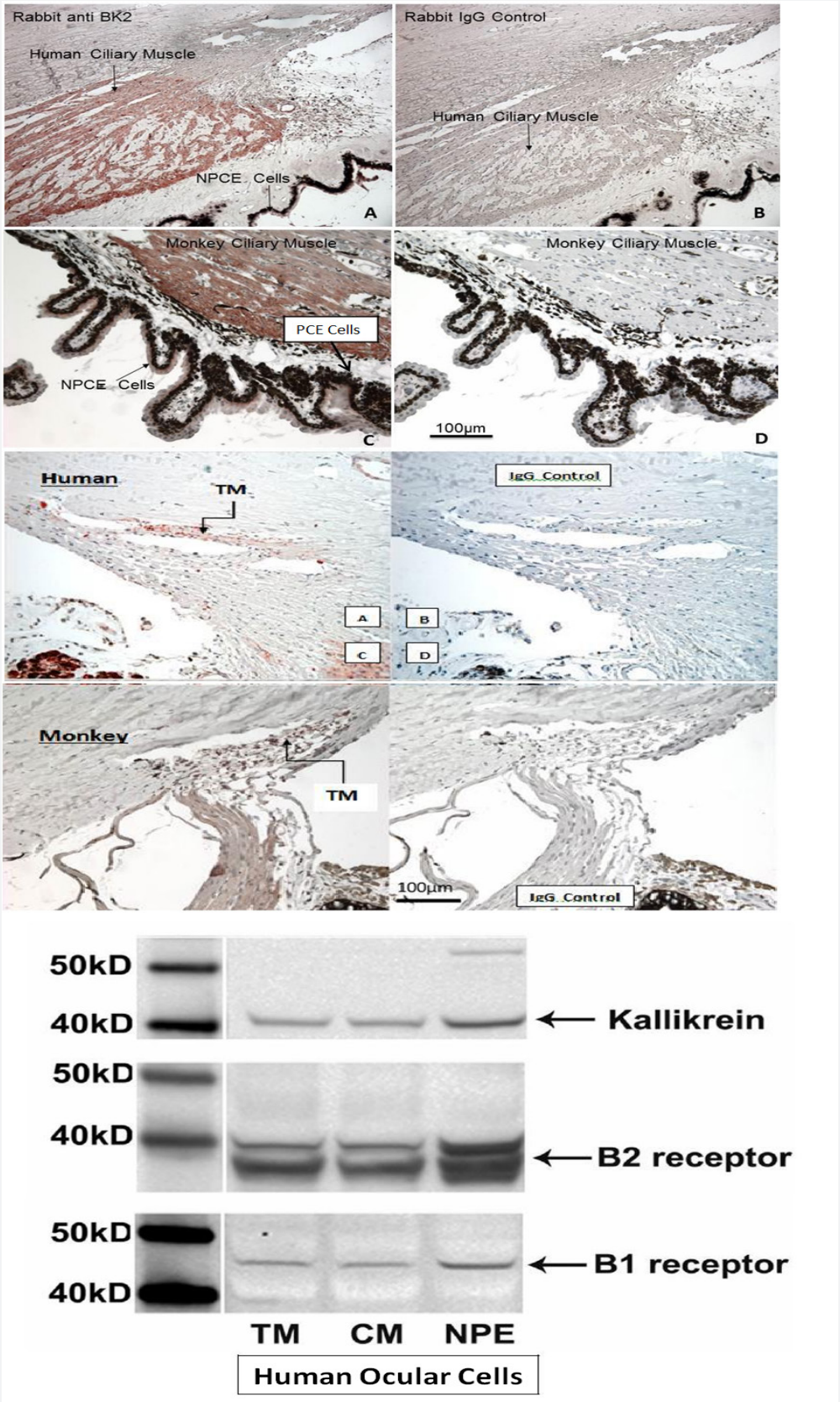

Figure 4: Immunohistochemical visualization of B2-receptors in human and monkey ocular tissues related to AQH production and drainage first two panels. (Modified from Refs. [145,146,157]. Last panel depicts the Western blot visualization of presence of Bk-receptor sub-types in human ocular cells Modified from Ref. [144].

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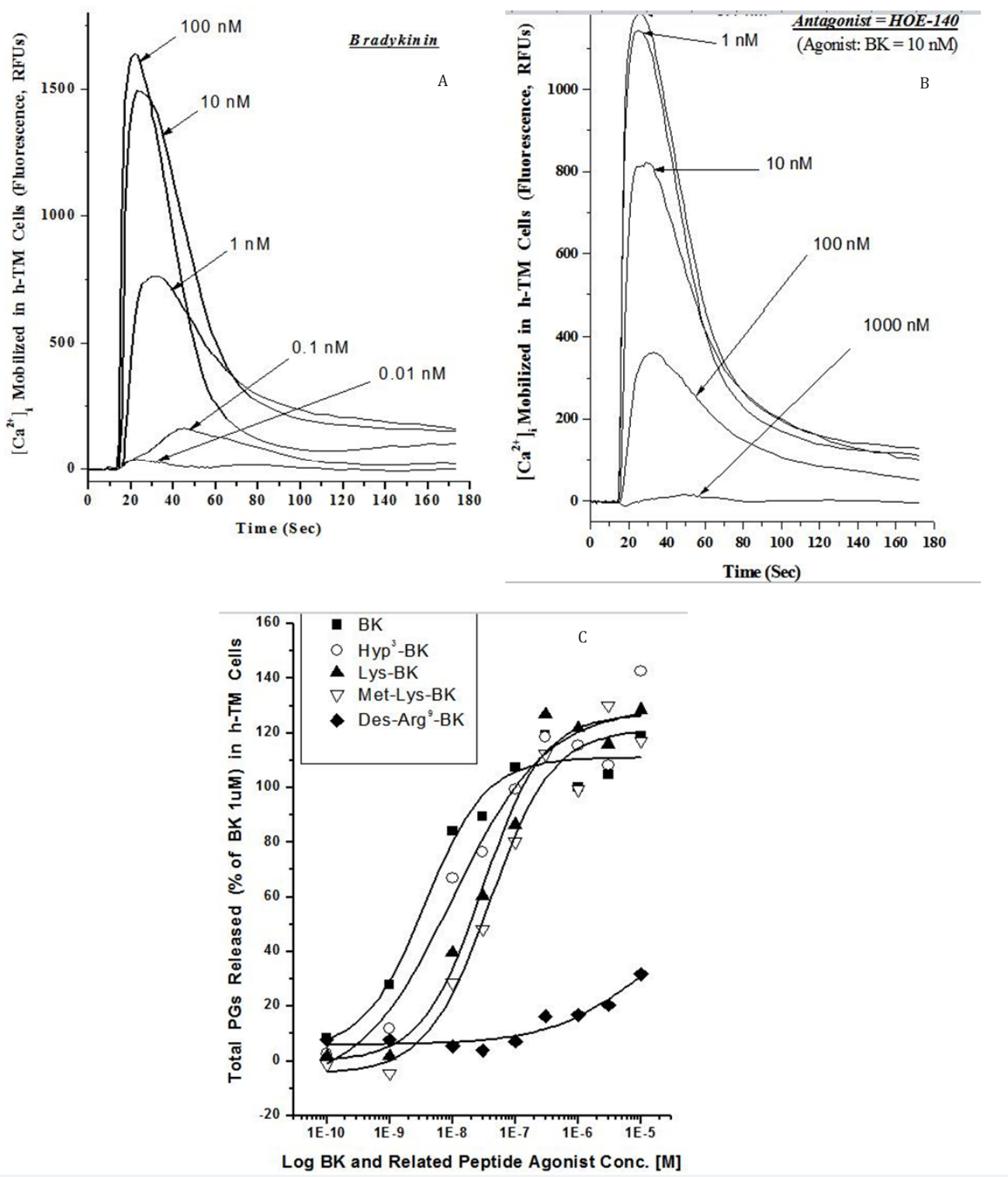

Figure 5: $[Ca^{2+}]_i$ mobilization in h-TM cells by BK (panel A) and its blockade by the B_2-receptor antagonist HOE-140 (panel B). Panel C shows concentration-response curves for various kinins stimulating $[Ca^{2+}]_i$ mobilization in h-TM cells. Modified from Ref.[146].

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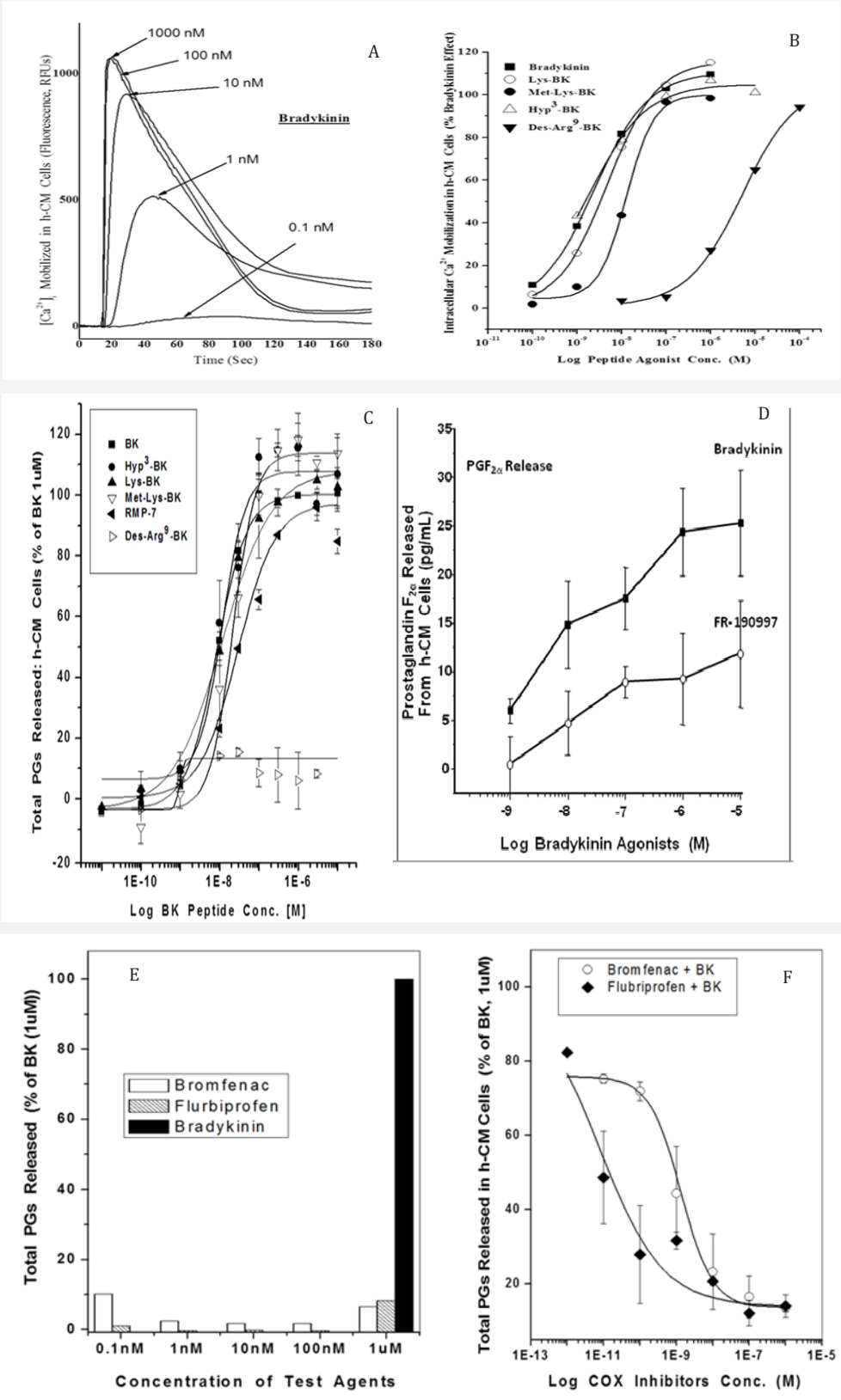

Figure 6: Mobilization of [Ca^{2+}]i in primary h-CM cells in response to BK and various BK analogs (Panel A and B). Concentration-response curves for kinins inducing the production and secretion of total PGS in h-CM cells in shown in panel C. Ability of various concentrations of BK and FR-190997 to generate and release PGF2α from h-CM cells is depicted in panel D. In panels E and F, the inhibition of PG synthesis and release in h-CM cells by two synthetase inhibitors is shown. Modified from Ref. [145].

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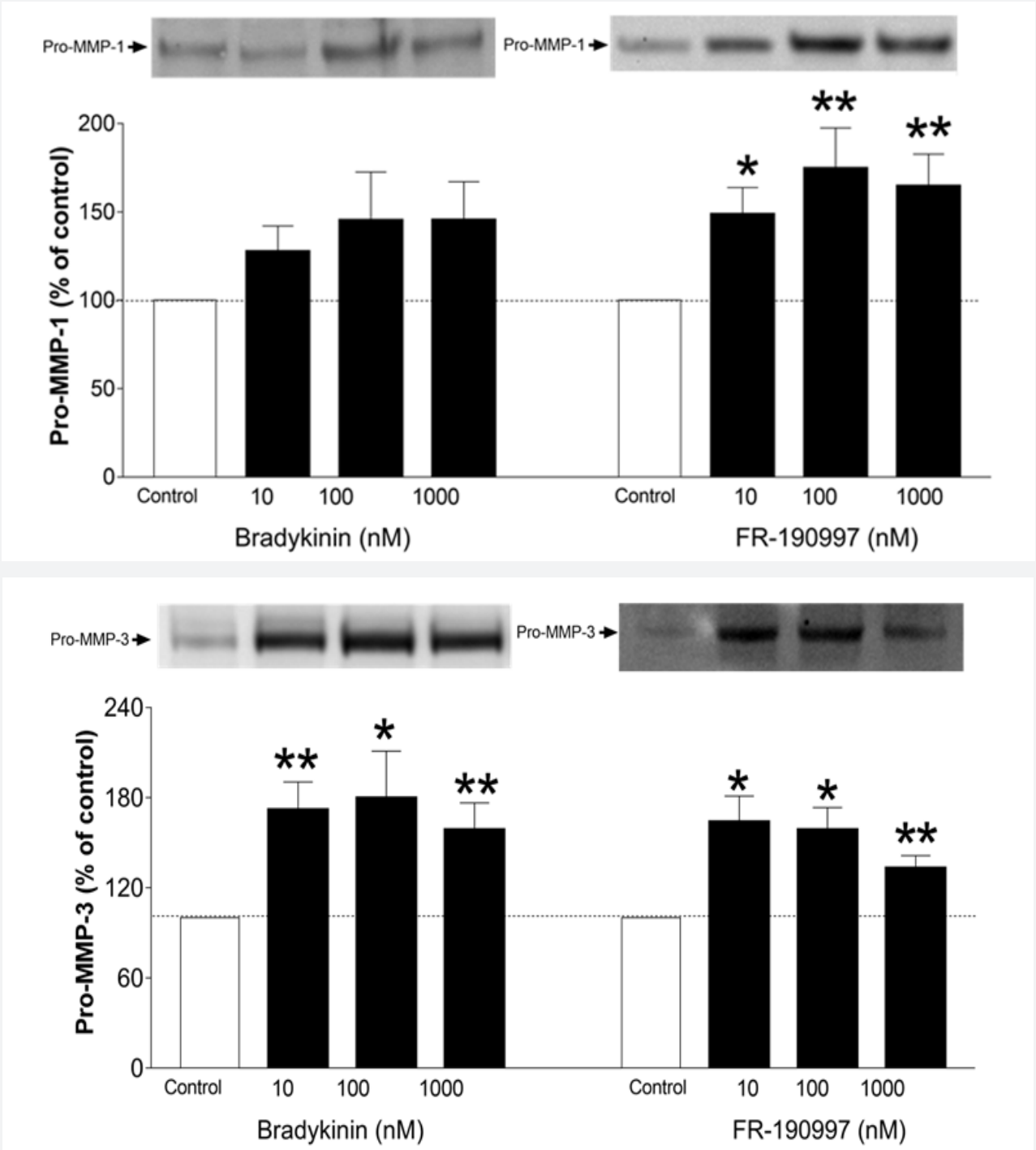

Figure 7: The induction of pro-MMP-1 and pro-MMP-3 generation and secretion by BK and FR-190997 from h-CM cells is shown. Modified from Ref.[158].

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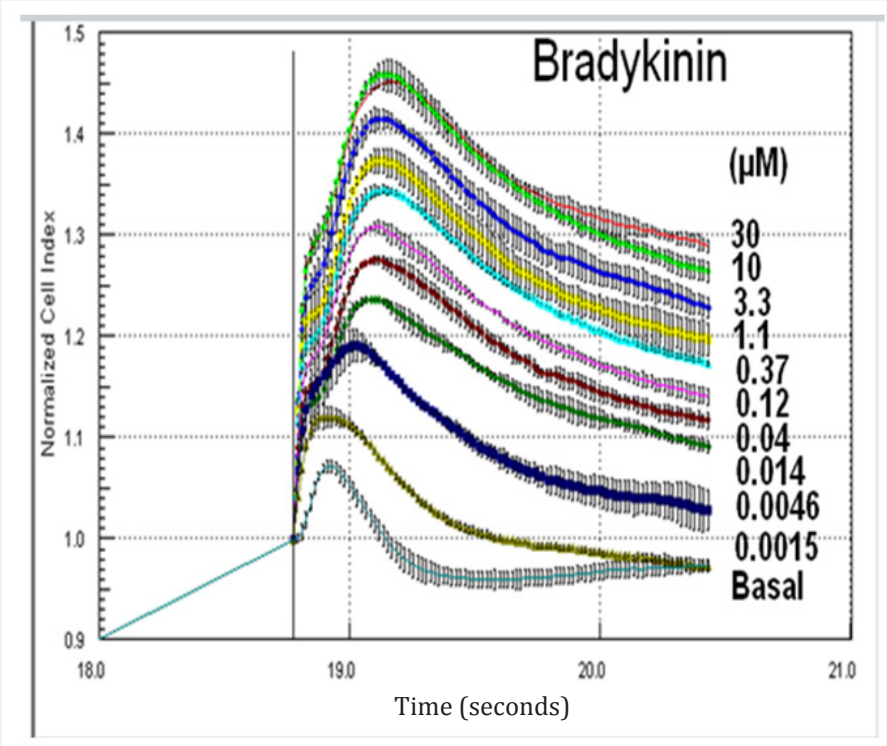

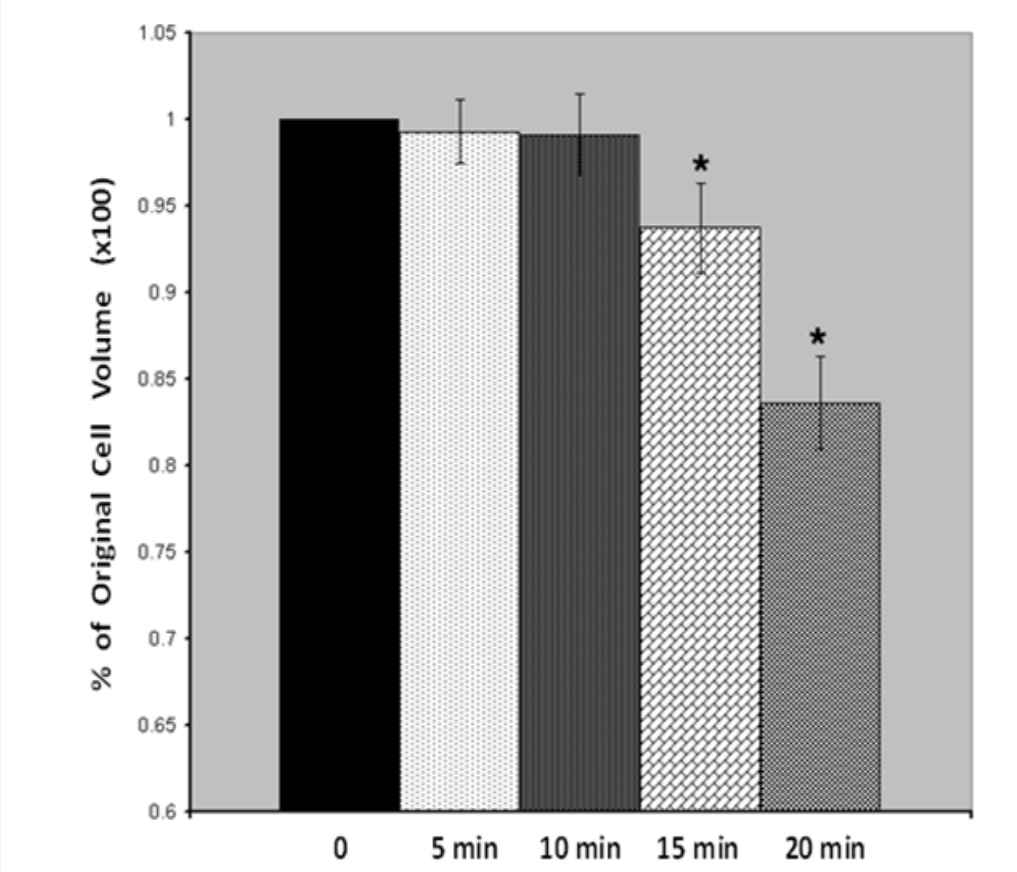

Figure 8: BK-induced change in cell-impedance (index of relaxation as shown) (top panel) and reduction of cell volume (bottom panel) in h-TM cells is shown. * p< 0.05 relative to baseline time-zero. Modified from Ref. [146].

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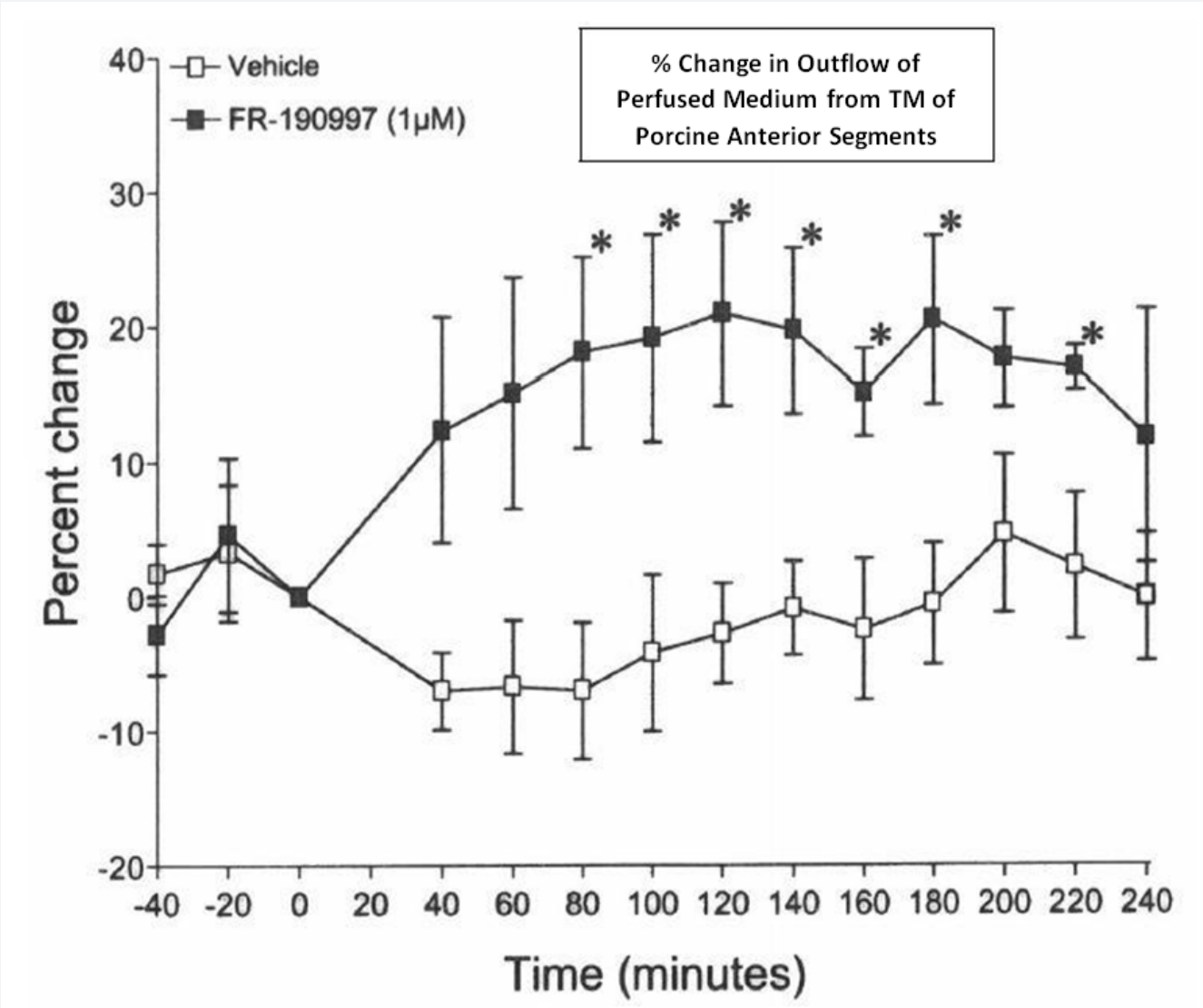

Figure 9: The enhancement of outflow of perfused fluid via the TM/SC pathway in porcine anterior eye segments by FR-190997 is shown. * p< 0.05 relative to baseline time-zero. Modified from Ref.[155].

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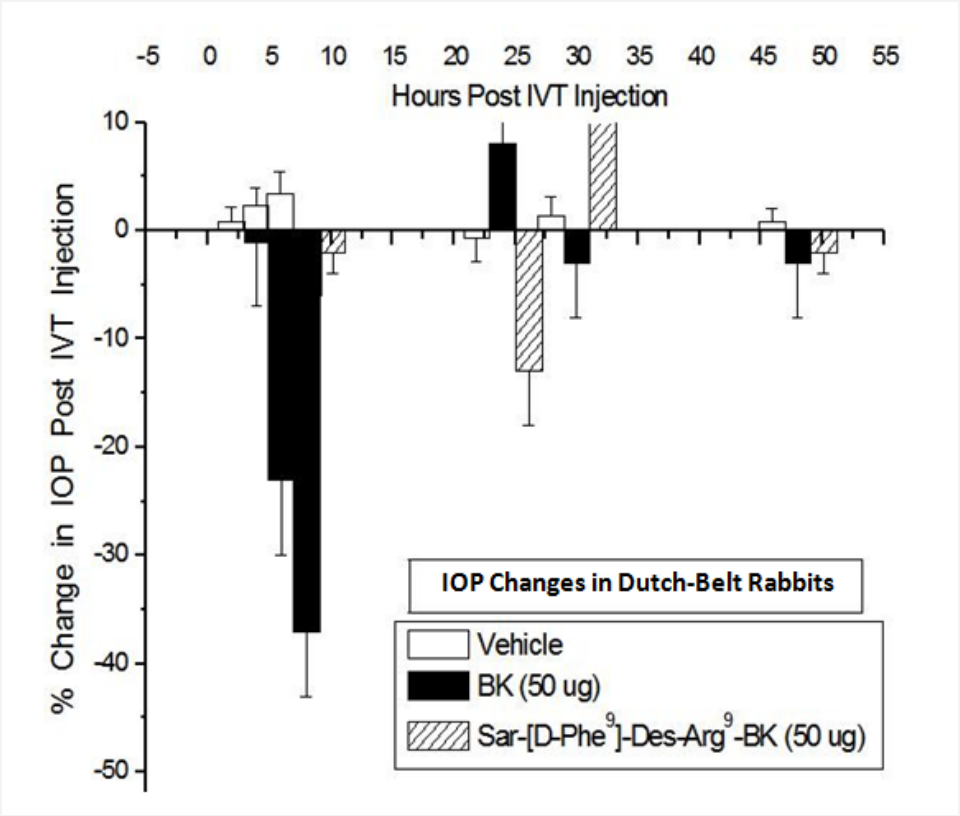

Figure 10

In order to ascribe a role of BK in ocular functions, early researchers administered BK either systemically or topical ocularly (t.o.) or via injections into the anterior chamber of the eye of different species [147-153].. BK either increased or decreased IOP accompanied by local inflammation and/or miosis [147-153]..Using ex-vivo isolated bovine [154,161] and porcine [155,156] eye anterior segments, perfused BK was shown to induce disparate results, either causing decreased outflow or increasing outflow of AQH, thereby adding to the overall confusion. The known metabolic instability of BK in the presence of fluids or exposed tissues/cells [136,144,156,161]., and possible species differences potentially contributed to these contradictory observations. The need for metabolically stabilized BK analogs or non-peptide BK mimetics was soon realized (see below). The rather paucity of information regarding the ocular BK receptor family in human ocular cells and tissues was slowly overcome by research in the early 80s-90s, including the work of Igic [139], Ma et al. [140], Sharif et al. [141], Wiernas et al. [143,144], and by Webb et al.[144,156,161].

The work of Ma et al. [140] using reverse transcription-polymerase chain reaction (RT-PCR) and Southern blot analyses, and in situ hybridization to localize components of the KNK system in human ocular tissues was affirmed using immunohistochemistry (IHC) [145-146]. For the current subject matter of this review article, it was important to demonstrate the specific distribution and localization of the B2-BK receptor proteins. Accordingly, the presence of B2-BK receptors in human TM [146],ciliary muscle (CM) [145] and non-pigmented ciliary epithelial (NPE) [157]cells was demonstrated by IHC techniques (Figure 4). These are all key tissues involved in the drainage (CM and TM) and production (NPE) of AQH respectively. Importantly, these IHC observations were extended to the cynomolgus monkey anterior chamber tissues [144,156,157] in order to help correlate functional in vivo data (IOPlowerig; AQH dynamics) with these in vitro observations (see ahead). Next, it was important to determine whether the IHC of B_2-receptors bore any linkage to functionality of these proteins in the respective human ocular cells mentioned above. To this end, primary h-NPE, h-CM and h-TM cells were isolated and challenged with BK, its many peptide analogs and two non-peptide BK-mimetics, FR-190997 and BK2A78. Many of these kininergic compounds stimulated the production of intracellular inositol phosphates [141,145,147,156,157], and all peptide and non-peptide agents liberated endogenous intracellular Ca^{2+} ((Ca^{2+}) i) from the endoplasmic reticulum in normal h-NPE, h-CM and h-TM cells [145,146,157] Figures 5-7 (and in bovine TM cells [156]) to varying degrees and with different relative potencies, a feature also observed in cells transfected with a cloned human B_2-receptor. Additionally, these BK agonists also activated

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extracellular-regulated kinases-1/2 in h-TM [144] and h-CM [158] cells, and promoted the synthesis and secretion of PGE2 and PGF2α in the latter cells Figure 5,6. Since Des-Arg^9-BK (a selective B_1-agonist) was always a very weak agonist in all these biochemical assays, and since two B_2-receptor antagonists (HOE-140 and WIN-64338) potently blocked the responses induced by BK, RMP-7 (a stabilized peptide analog of BK), FR-1909997 and BK2A78 [146,147,156,158,160,161], the functionality and pharmacological identification of B_2-receptors in these cells were completely confirmed. Additional studies in h-CM and h-TM cells indicated that BK and FR-190997 could also activate intracellular signal transduction pathways to cause the release of various matrix metalloproteinases [156,158,161] Figure 7 that are known to digest extracellular matrix components such as collagen and thus aid in the efflux of AQH from the anterior chamber to lower IOP, a mechanism previously associated with ocular hypotensive FP-class PGAs [1-6,53-55,70-71]. Interestingly, BK enhanced the production of cAMP induced by PGE2 in h-TM cells [162], indicating that additional control of TM function by kinins was possible through activation of adenylyl cyclase. The next exciting phase of investigations tried to link these diverse biological actions of kinins in isolated cells of an almost intact organ, in this case enucleated porcine and bovine anterior segments of the eye. While one study initially showed a somewhat decrease in perfused fluid outflow in response to BK in the bovine eye [154], other studies by Webb et al. [161] showed that BK actually robustly stimulated outflow in bovine eyes as did the BK mimetic FR-190997 in other independent experiments using porcine eyes [155,159] (Figure 9). Mechanistically Webb et al. [106] also showed that this increased outflow by BK was mediated by B_2-receptor-induced secretion of MMP-9 since a B_2-antagonist and an MMP inhibitor abolished the effects of BK [161].

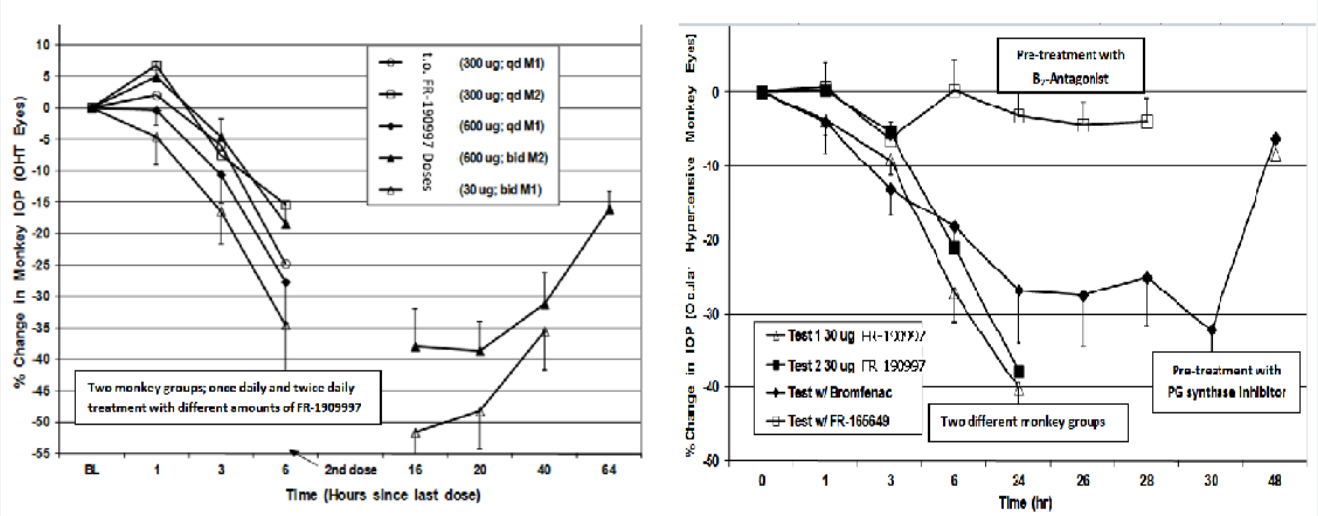

Figure 11

The role of BK in modulating IOP was investigated in a number of species.Topical ocular (t.o.) instillation of BK (50-100µg in a 30µl drop) to Dutch-belted rabbits, mixed breed cats, mice, rats, guinea pigs and cynomolgus monkeys (ocularly normotensive or hypertensive) failed to consistently influence IOP to any significant extent. However, intravitreal injection (ivt) of BK (50µg) in eyes of Dutch-Belted rabbits induced a robustdecrease in IOP up to 8 hrs post-injection [146]. Interestingly, both B_1-receptor-agonists, Des-Arg^9-BK and Sar(D-Phe9)-Des-Arg^9-BK injected ivt, did not alter IOP at all [145,146] (Figure 10). These data further substantiated the fact that only B_2-receptors are involved in lowering and controlling IOP without any contribution from B_1-receptors, at least in the rabbit. Since ethically and economically, we could not repeat IVT injection studies using BK in higher animals, and since topical ocular BK was without effect, a different approach was necessitated. Also, even though a metabolically stabilized peptide mimetic of BK (RMP-7) is available, it is still too polar a molecule to be used t.o. For such IOP modulation studies. However, a non-peptidic hydrophobic BK-mimetic, FR-190997 formulated in a standard vehicle was bioavailable when administered topically, and it potently and efficaciously reduced IOP in the conscious ocular hypertensive monkey eyes [155,159]. As little as 1µg total t.o. Dose induced a 25% IOP reduction for up to 24-hrs after dosing, and dose-dependent reductions out to 48hrs post-t.o. Dosing were possible with a 10µg dose [156,160]. The ocular hypotensive effects of FR-190997 and BK2A78 were in the realm of what the t.o. PG FDA-approved drugs like TRAVATAN® and Xalatan® produce in the monkey-model and in humans, but only to 24hrs post-dose. The fact that a non-peptide B_2-receptor antagonist (FR-165649) completely prevented the IOP-lowering actions of FR-190997 in the OHT monkey eyes strongly suggested that the B_2-receptor was mediating the IOP-lowering actions of FR-190997 (Figure 11). Furthermore, since FR-190997's ocular

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hypotensive effects were significantly attenuated by prior treatment with a PG-synthesis inhibitor (bromfenac) PGs were involved in mediating at least some of the IOP-lowering activities of this BK-mimetic, this being akin to the in vitro observations with FR-190997 [155,159] and BK [145-147,162]. In ascribing possible mechanisms activated by FR-190997 in its ability to reduce IOP in mildly-sedated OHT monkeys, it was discovered that a predominant enhancement of uveoscleral outflow of AQH was triggered by FR-190997 [155,159]. However, it would appear that in the porcine isolated anterior chamber model, this compound (and BK in bovine) promoted fluid egress via the TM/SC conventional outflow pathway [155,159]. It remains to be seen whether such observations of robust ocular hypotensive activity of FR-190997 and BK2A78, along with other non-peptide BK-mimetics, can be reproduced in OHT human patients. Since FR-190997 [155,159] and BK2A78 [160] caused minimal ocular discomfort in conscious Dutch-belt rabbits, mixed breed cats, rats and monkeys after t.o. dosing, and produced no observable systemic or local side-effects, such compounds represent ideal new drug candidates worthy of pursuit in appropriate human clinical trials for determining ocular hypotensive activity. Two physiological observations noted that may limit the future utility of such BK-mimetics to treat OHT/POAG are the apparent tachyphylactic effects of FR-190997 in terms of IOP-lowering at relatively high doses, and a mild anesthetic activity observed on cat corneal surface [159]. However, whether these elements translate to the human ocular system requires further study. As long as low pharmacologically-relevant t.o. doses of FR-190997 and BK2A78 (and their analogs and derivatives [155,159,160,162-164] are used t.o. in other animal models and in human subjects, it is possible to avoid triggering the above-mentioned "adverse" effects. Further studies on the ocular roles of BK and its analogs and mimetics are eagerly awaited.

Conclusion

Clearly there are now several drugs approved for the treatment of OHT/POAG and a number of new AQH drainage devices either approved or on the horizon for the same purpose of lowering IOP. It is the issues of compliance, and the number and relative seriousness of the side-effects, or ineffectiveness and complications of the procedures, that continue to warrant hunt for newer more efficacious and more tolerable medications. The latter quest has resulted in the recent discovery of some new ocular hypotensive agents, including the first generation bradykinin non-peptide mimetics such as FR-190997, BK2A78 and their analogs [155,159,160,162-164]

The studies described in this review have clearly shown the presence of various components of the kininergic system in human and monkey ocular cells and tissues using a variety of techniques. Furthermore, functionally active sub-types of BKreceptor (B_1- and B_2) also are present in the ocular cells involved in AQH dynamics, Hence, BK and its analogs and mimetics are able to generate a variety of second messengers such as inositol phosphates and intracellular Ca^{2+} in h-NPE, h-CM and h-TM cells. Activation of this signal transduction pathway, then stimulates the production and secretion of PGs from these cells. These PGs are pivotal in promoting the generation and release of MMPs from CM and TM cells that digest extracellular matrix to create new pathways for AQH to drain from the anterior chamber of the eye leading to lowering of the IOP. Such duality of action of MMPs in response to BK receptor activation probably explains the elevated TM/SC outflow and increase of uveoslceral outflow observed after treatment with FR-190997and the profound IOP-lowering that this compound produces [155,159]. These new non-peptidic kinin mimetic drugs [155,159,160,163,164] will hopefully inspire other researchers to use these as templates for synthesizing next generation of ocular hypotensive agents, perhaps with some secondary neuroprotective activity on top of the ocular hypotensive properties. We all await the results of such new discoveries.

Conflict of Interest Statement

Author is an inventor or co-inventor of some granted patents related to the use of BK agonists (peptide and non-peptide) for treatment of glaucoma and the associated OHT, and these are cited in this article. The author, is an adjunct professor at Texas Southern University (Houston, TX) and at University of North Texas Health Science Center (Fort Worth, TX), and has no other conflicts of interest to declare. The intent of this review article is simply to share and expand the knowledge of the ocular roles of Kinins and thus inspire further research in this arena for the discovery of novel drugs and treatments to help combat blinding diseases of the eye, especially OHT/POAG.

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