Multifunctional Redox Modulating Compounds for Treating Sensory Vision and Hearing Loss

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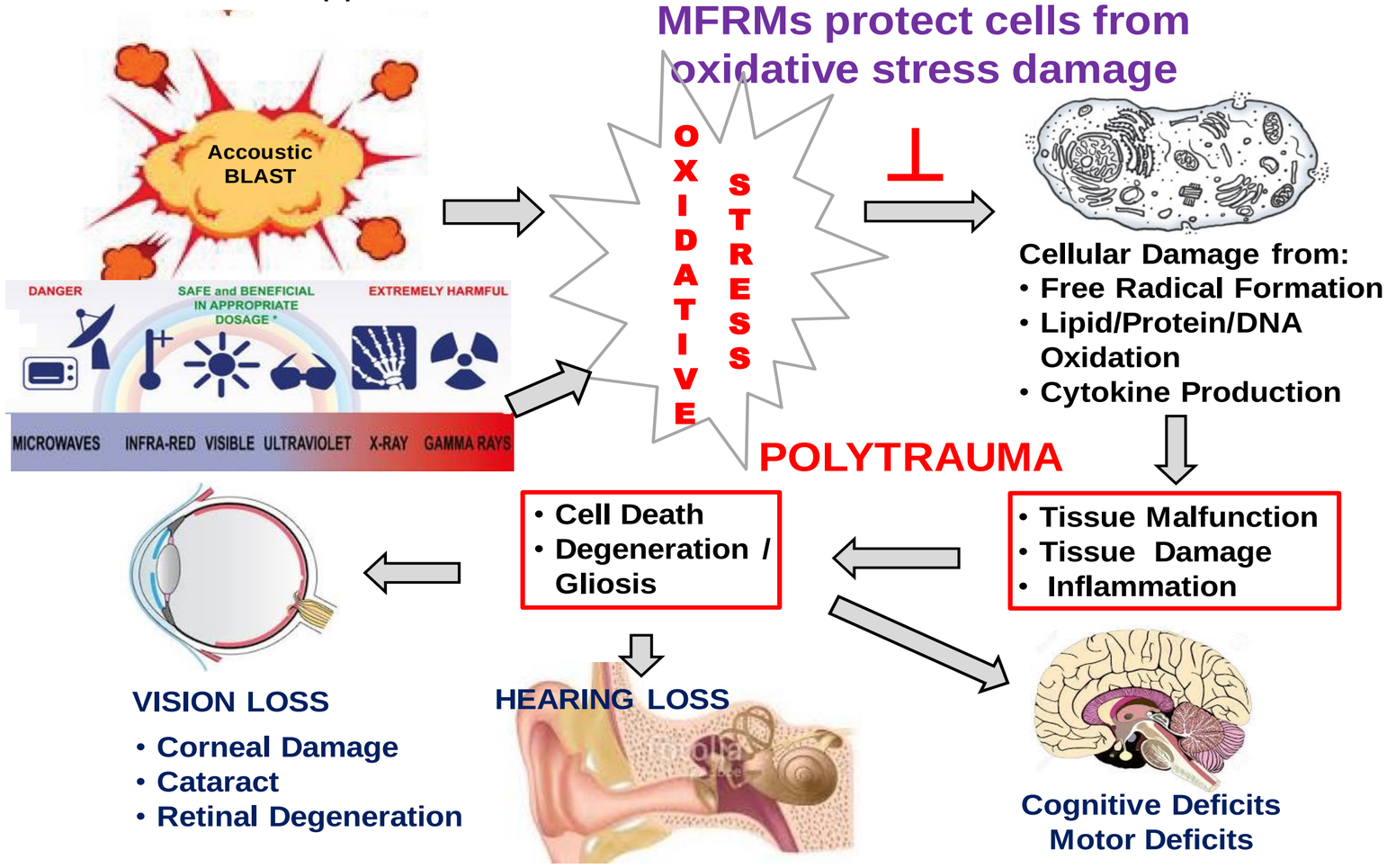
Introduction and Rationale

The eye and the ear are complex sensory organs that form part of the nervous system and polytrauma to their neurosensory tissues can lead to visual and hearing dysfunction. This trauma can occur in military personnel exposed to **high noise levels** from heavy military machinery, aircraft, weapon firings, blast wave overpressure from explosions or laser induced shock waves; **ionizing radiation** linked to nuclear reactors, nuclear weapons and depleted uranium; and **directed radiation** from bright lights, lasers, microwaves, particle beams and overexposure to UV light. Administration of **ototoxic medications** such as aminoglycoside antibiotics, antimalarials, and loop diuretics or exposure to **ototoxic materials** such as solvents, metals, and asphyxiants can also contribute to oxidative stress-linked polytrauma. As a result, hearing loss is the most common service-connected disability. Combat veterans also have a high rate of vision problems with gradual vision loss due to exposure to radiation, UV light, laser light, and after traumatic brain injury. Civilians are similarly at risk from work related industrial, construction and aircraft noise along with ‘recreational noise’ exposure during sport events in enclosed stadiums, bars, clubs, or concert venues, or from earphone or earbud use. Civilians are also exposed to environmental, industrial, and recreational radiation that include x-rays, microwaves, cell phones, lasers, UV light, and space radiation from cosmic rays by astronauts.

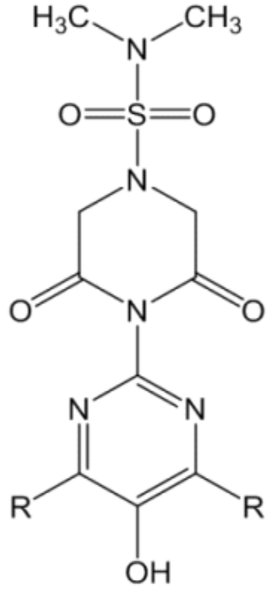
Hearing and vision loss are polytrauma-associated neurodegenerative injuries linked to oxidative stress from the generation of reactive oxygen and nitrogen species (ROS, RNS), mitochondrial dysfunction, and the release of iron, zinc and copper.

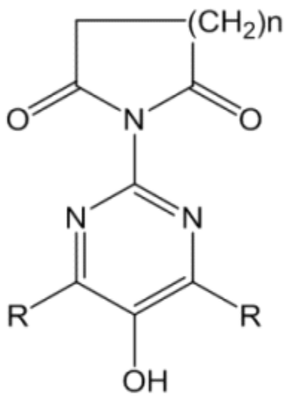


To counteract oxidative stress-induced polytrauma development, treatment with a number of natural antioxidants (nutraceuticals) or their precursors have been investigated. Although some of these nutraceuticals have shown promise in animal studies, none have shown efficacy in clinical trials. Therefore, **there is an urgent need for synthetic antioxidants with appropriate pharmacodynamics that prevent blast and radiation induced sensory loss.**

Multifunctional Redox Modulating Compounds (MFRMs)

It has been hypothesized that the clinical failure of oral nutraceutical antioxidants is due to their inability to adequately achieve therapeutic levels in target tissues and to their antioxidant radical scavenging activities being not adequately potent. **We have developed a new class of synthetic antioxidants called MFRMs*.** *These compounds use the innovative therapeutic strategy that multifunctional metal attenuating antioxidants targeting multiple mechanisms of radical action are superior to compounds that only bind transition metals or scavenge free radicals.* MFRMs not only reduce oxidative stress by scavenging free radicals but also independently by sequestering and redistributing the transition metals Cu, Fe, and Zn that participate in the Fenton generation of toxic hydroxyl radicals. The 2-amino-5-hydroxypyrimidine free radical scavenger (FRS) system (red dashed box) was chosen for the development of MFRMs because it is 50-fold chemically more reactive towards radicals than vitamin E. Carbonyls adjacent to the 2-amino group were introduced because the 2-N-succinamide-1,3-pyrimidine can complex transition metals (MB) (blue dashed box) such as Fe and Cu. By incorporating these chemical properties into the N,N-dimethylsulfamoyl-4-(2-pyrimidyl) piperazine ring, a first generation series JHX-4 and JHX-8 were developed. Replacing the piperazine ring with a piperidine ring (HK-6, HK-8) and a pyrrolidine ring (HK-2, HK-4) resulted in a second generation of MFRMs. MFRMs selectively bind in a 2:1 or 1:2 ratio with metals in the order $Cu^{1+} = Cu^{2+} > Fe^{2+} = Fe^{3+} > Zn^{2+}$. MFRMs also bind Mn^{2+} in a 2:1 ratio. These orally active compounds achieve therapeutic levels in the lens, neural retina, brain, and the inner ear.



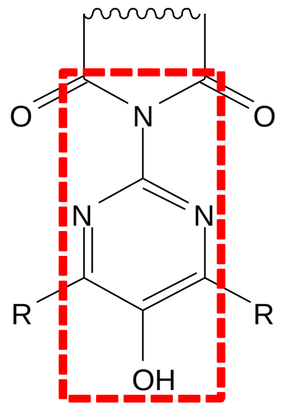


MFRMs Evaluated

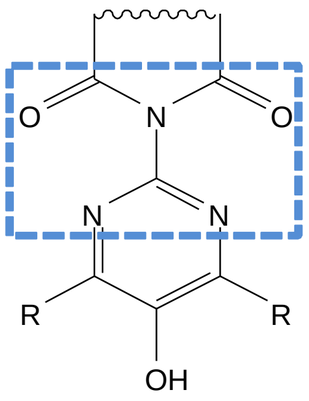
Compd.	R	$(CH_2)_n$
JHX-4	H	
JHX-8	OCH_3	
HK-2	H	1
HK-4	OCH_3	1
HK-6	H	2
HK-8	OCH_3	2

Groups Participating in

Free Radical Scavenger (FRS)



Metal Binding (MB)

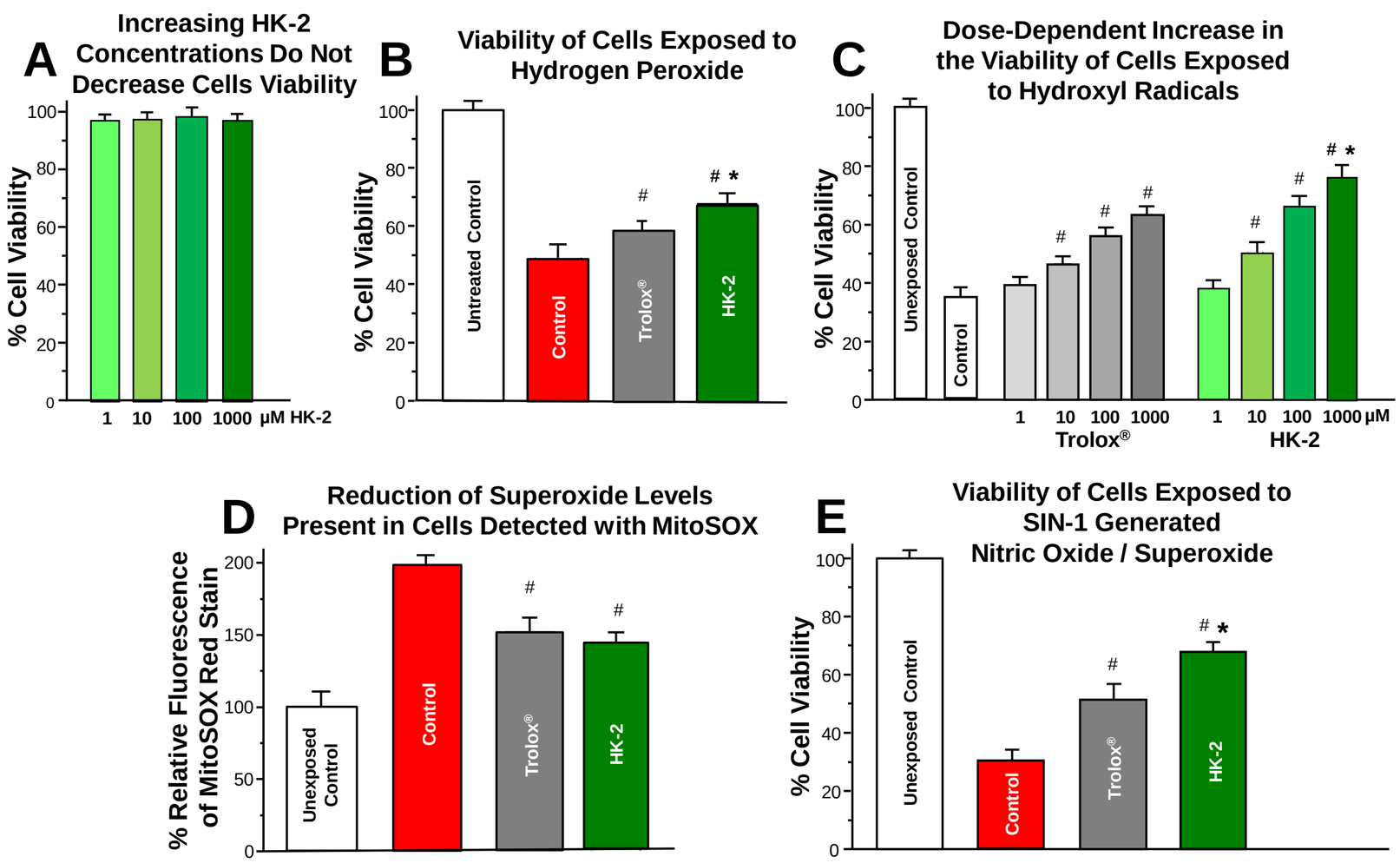


* MFRMs were initially called multifunctional antioxidants (MFAOs). They are now referred to as MFRMs because studies show that they possess distinct multiple properties that directly and indirectly modulate the cellular redox environment. These properties are distinct from natural FRS antioxidants such as α-tocopherol.

MFRMs Protect Cells From Oxidative Stress Generated by ROS / RNS and the Fenton Reaction

The Kador Lab has tested MFRMs in cell lines from the eye, brain and ear for their ability to protect against oxidative stress generated by hydrogen peroxide, hydroxyl radicals generated by the Fenton reaction, superoxide radicals, and nitric oxide. These include SRA-1 human lens epithelial cells, ARPE-19 human retinal pigmented epithelial (RPE) cells, HA-h human hippocampal astrocytes, RGC-5 rat retinal ganglion (RGC) cells, 661w photoreceptor cells, SH-SY5Y neuroblastoma cells (NB), and House Ear Institute-Organ of Corti 1 (HEI-OC1) cochlear hair cells. Protection was reflected in the reduced ROS staining of cells (H2DCF-DA stain), the maintenance of cell viability (MTS proliferation assay), the maintenance of reduced glutathione (GSH) levels (DTNB assay), and the reduction of cell death (apoptosis stain). Compared to the well-established antioxidant Trolox®, MFRMs provide superior protection against Fenton reaction generated hydroxyl radicals.

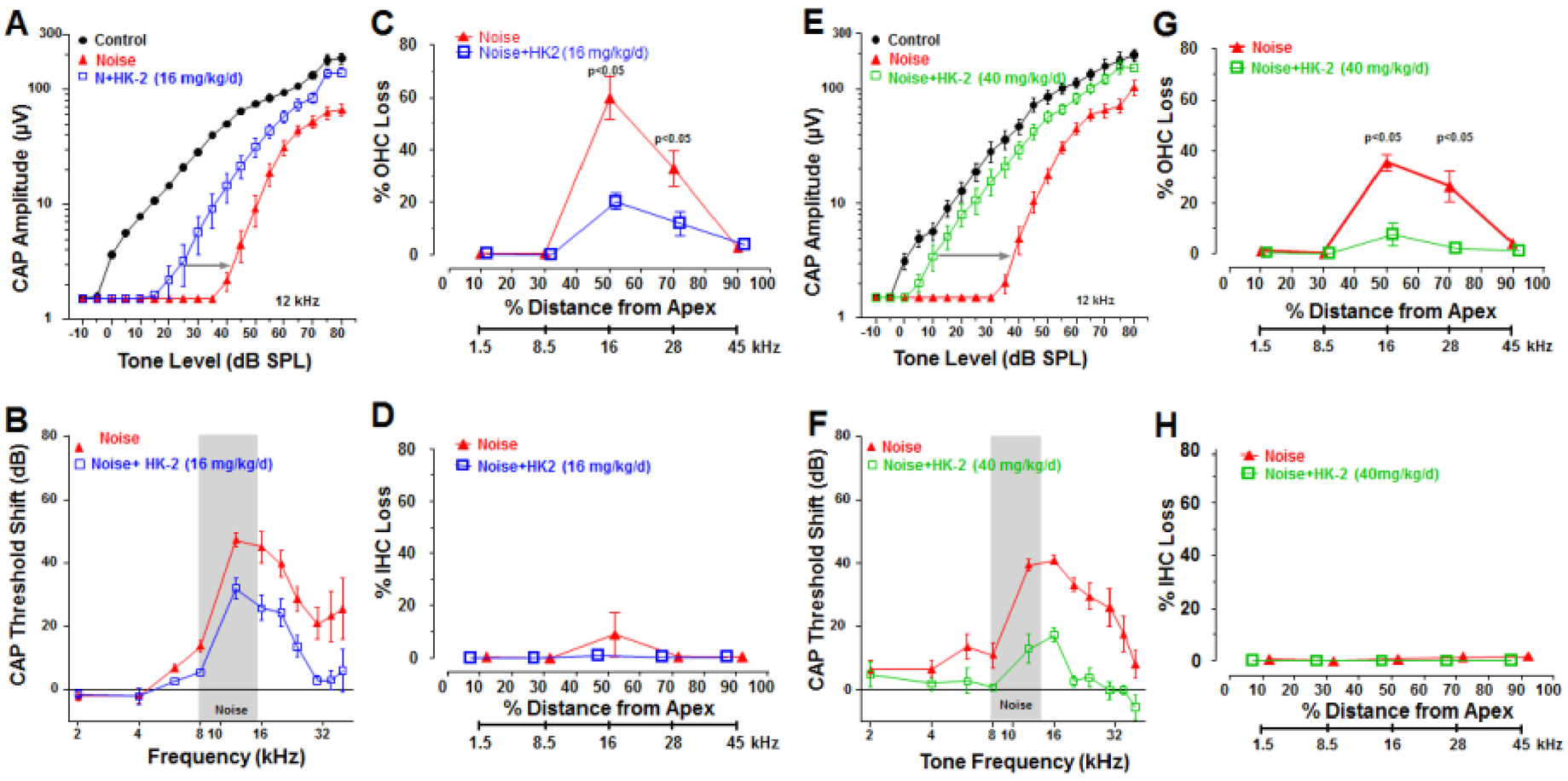
Using HEI-OC1 cells in the figures below, **A** shows that the cell viability was not adversely affected by 24 h exposure to HK-2 concentrations up to 1000 µM. In figures **B**-**E** below the response of untreated HEI-OC1 control cells (white) is compared to similar untreated cells exposed to various oxidants (red), and similar exposed cells preloaded for 1 h with 1 mM Trolox® (gray) or 1 mM HK-2 (green) before exposure in **B**-**D** or preloaded for 3 h before exposure in **E**. The cells were exposed for 2 h to 1 mM hydrogen peroxide in **B,** for 2 h to hydroxyl radicals generated by 1 mM Fenton reagent in **C**, for 2 h to superoxide radicals generated by xanthine oxidase (~100 µM/h) that can be fluorescently detected with mitoSOX staining, and for 24 h exposure to 3 mM 3-morpholinosydnonimine (SIN-1) which generates precursors of peroxynitrite, nitric oxide, and superoxide in cells in **E**. In each case, HK-2 provided significant protection of cell viability compared to the water soluble Vitamin E analog Trolox® in **B**, **C**, and **E**. **C** shows that this protection is dose-dependent while **D** shows that HK-2 reduced the levels of generated superoxide radicals present.



mean ± SD (n=4) # p < 0.05 compared to Control; * p < 0.05 compared to Trolox®

MFRMs Reduce Noise-Induced Hearing Loss

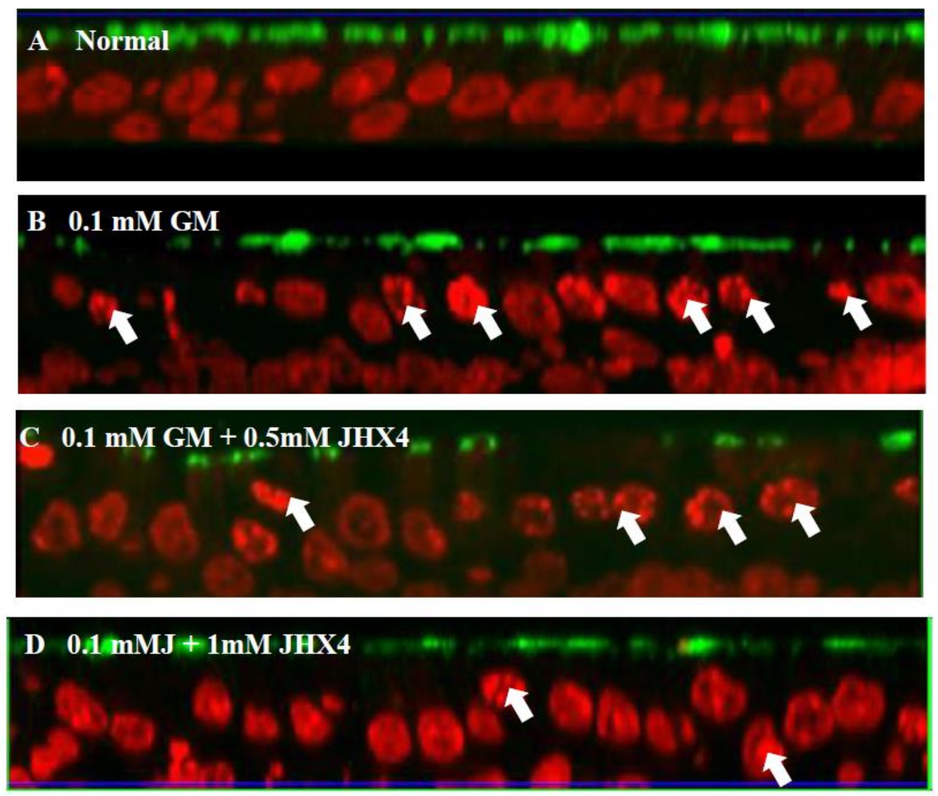
Noise-induced hearing loss (NIHL) that results in hair cell loss is linked to oxidative stress and an increase of iron. As shown below, studies conducted with the Salvi Lab demonstrate that oral HK-2 dose-dependently reduce NIHL in rats. Two doses of HK-2 (16 and 40 mg/kg/d) were administered to rats in a prevention study where rats were noise exposed (8 h/d; 8-16 kHz, 95 dB SPL). For the 21 d noise exposure study, HK-2 treatment began 5 d prior to the start of the noise exposure and continued for 10 d post-exposure. The compound action potential (CAP), which reflects the gross neural output from the cochlea, was measured to see the effect of noise on hearing loss. **A** below shows that the 12 kHz CAP input / output (I/O) functions in the untreated noise exposed group (red) significantly ($p<0.05$) shifted rightward by ~40 dB from the non-noise-exposed control group (black). This rightward shift of the I/O function was reduced to ~20 dB in the noise-exposed group treated with 16 mg/kg/d HK-2 (blue). CAP amplitudes in the noise group and noise+16 HK-2 group were significantly less than in controls and amplitudes in the noise group were significantly less than in the noise+16 HK-2 group ($p<0.05$). **E** shows that the 40 mg HK-2 dose (green) provided even greater protection against noise. These dose-dependent results were confirmed by measuring the loss of outer hair cells (OHC) shown in **C** and **G**, and inner hair cells (IHC) shown in **D** and **H** loss.

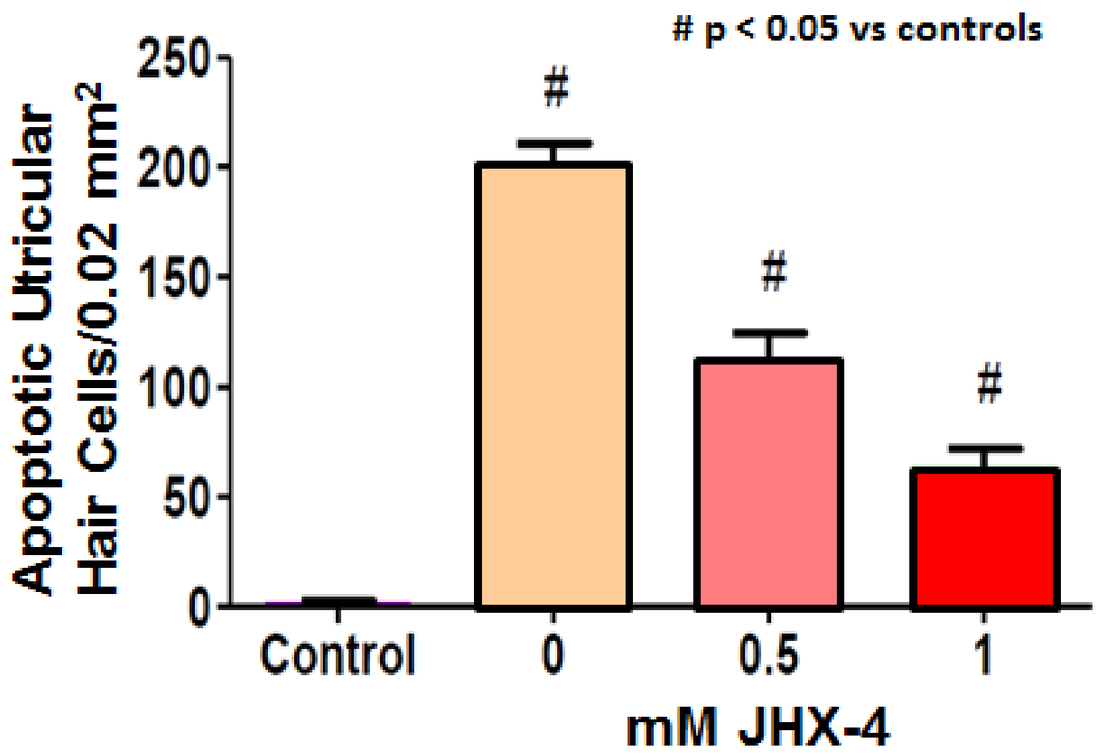


A preliminary intervention study (rescue study) was also conducted in which after 21 d of noise exposure, rats were orally administered HK-2 (125 mg/kg/d) for 10 d starting after the noise was turned off. HK-2 also significantly reduced the amount of hearing impairment, but the effect size was substantially less than in the prevention studies.

MFRMs Suppress Gentamycin-Induced Cochlear Hair Cell Loss

Gentamycin (GM) is a highly effective antibiotic whose use is limited by its ototoxic side effects which have been linked to the generation of ROS. To determine if MFRMs would protect the inner ear from ototoxic insult, the Salvi Lab treated postnatal day 3 (P3) cochlear and vestibular cultures with GM alone or in combination with JHX-4. The presence of 0.1 mM GM resulted in hair cell loss in the cochlear and vestibular cultures and this loss was reduced by JHX-4 at concentrations of 0.5 and 1.0 mM. The Z-plane images below show the apical surface (green) and nuclei (red) of the utricular hair cells (HC) in controls (**A**) and groups treated with (**B**), 0.1 mM GM, (**C**), 0.1 mM GM + 0.5 mM JHX-4, or 0.1 mM GM + 1.0 mM JHX-4 (**D**). The arrows indicate apoptotic hair cells with condensed / fragmented nuclei in treated groups (**B**-**D**). The graph shows the dose-dependent reduction (mean ± SEM) by JHX-4 of apoptotic utricular hair cells per 0.02 mm^2 in 0.01 mM GM cell cultures.

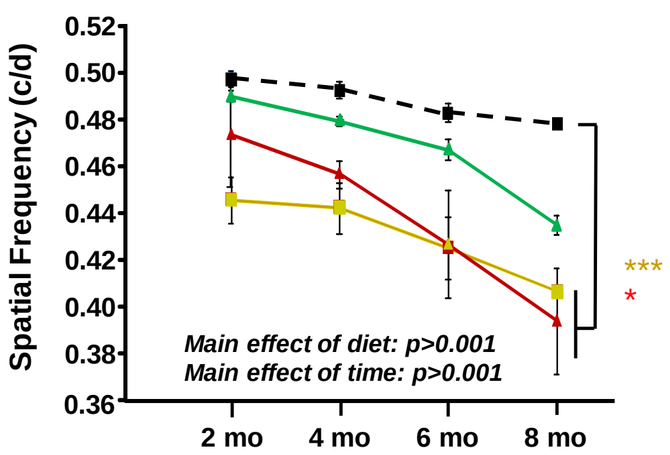




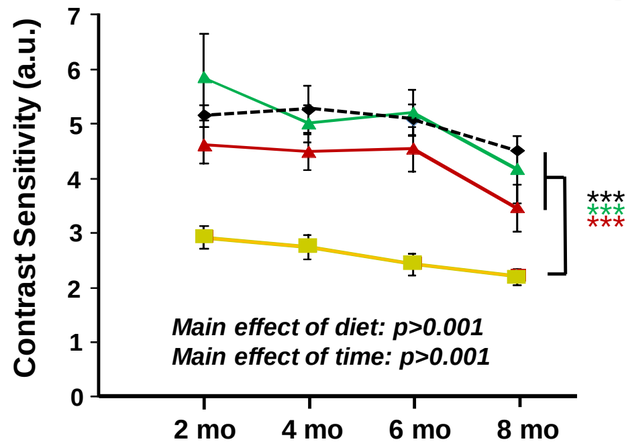
MFRMs Protect the Retina Against Acoustic Blast Overpressure (ABO)

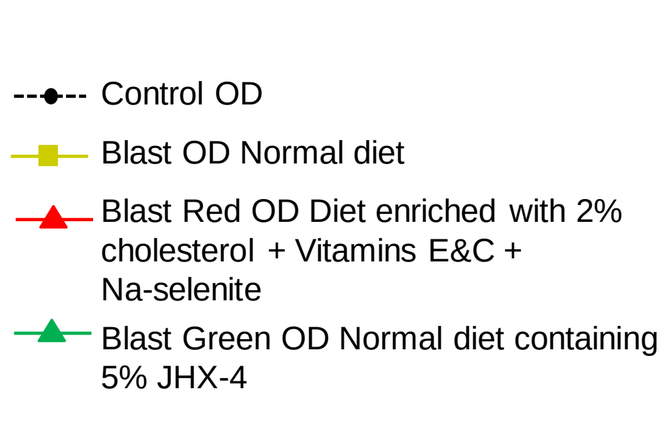
Primary blast injuries from acoustic blast overpressure cause long-term visual function and structure deficits. Initial studies conducted with the Fliesler Lab at the Buffalo VA Medical Center and the Pardue Lab at the Atlanta VA Medical Center suggest that MFRMs protect retinal function in rats exposed to either 1 blast or 2 blasts 1 mo apart. Exposed rats were fed either a standard rat chow (gold line), chow containing 0.05% of the MFRM JHX-4 (green line), or chow enriched with an antioxidant mixture of 2% a cholesterol, vitamin E and C, and sodium selenite (red line) for 1 mo prior to exposure to an ABO (63kPa, 190+ db-SPL). In a second study, similar groups of rats also received an additional blast exposure 30 d after the initial blast. The longitudinal follow-up data from 2-8 mo for all groups of rats after exposure to a single blast (**A**, **B**) or double blast (**C**, **D**, **E**) indicate that MFRM treatment significantly protected against vision functional changes which were measured as spatial frequency (**A**, **C**) and contrast sensitivity deficits (**B**, **D**). No correlations were observed between functional deficits and structure changes in any of the retinas among the different groups of rats. This possibly is due to differential affects of ABO on the brain versus retina and suggests that different mechanisms may underlie functional deficits associated with frequency of ABO exposure. **E** below shows that motor functions, assessed with Rotarod apparatus, significantly improved in 2x ABO exposed rats treated with JHX-4 and antioxidants diet treatment over the 4 mo post 2x blast period evaluated.

A **1x Blast Spatial Frequency**

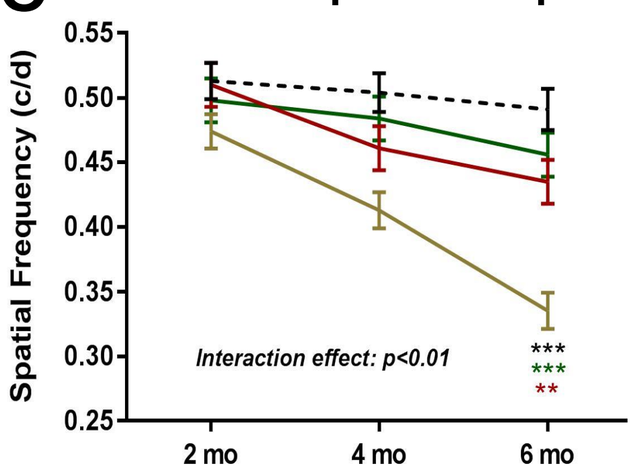


B **1x Blast Contrast Sensitivity**

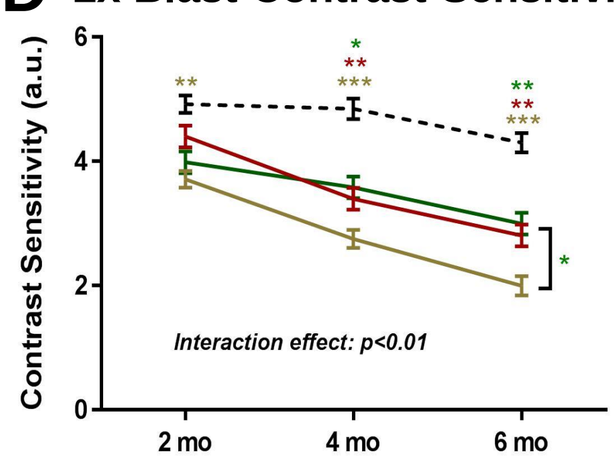




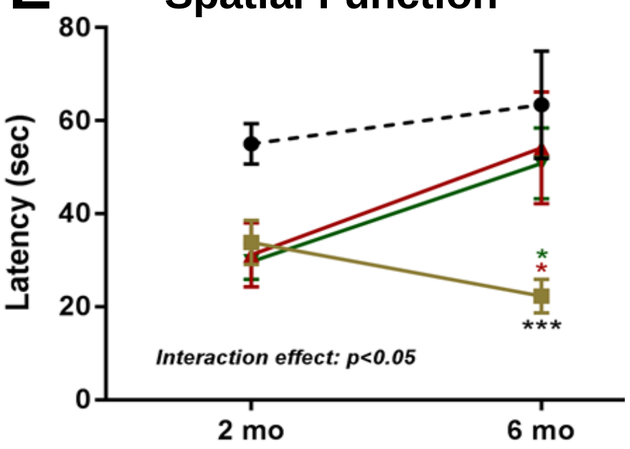
C **2x Blast Spatial Frequency**



D **2x Blast Contrast Sensitivity**

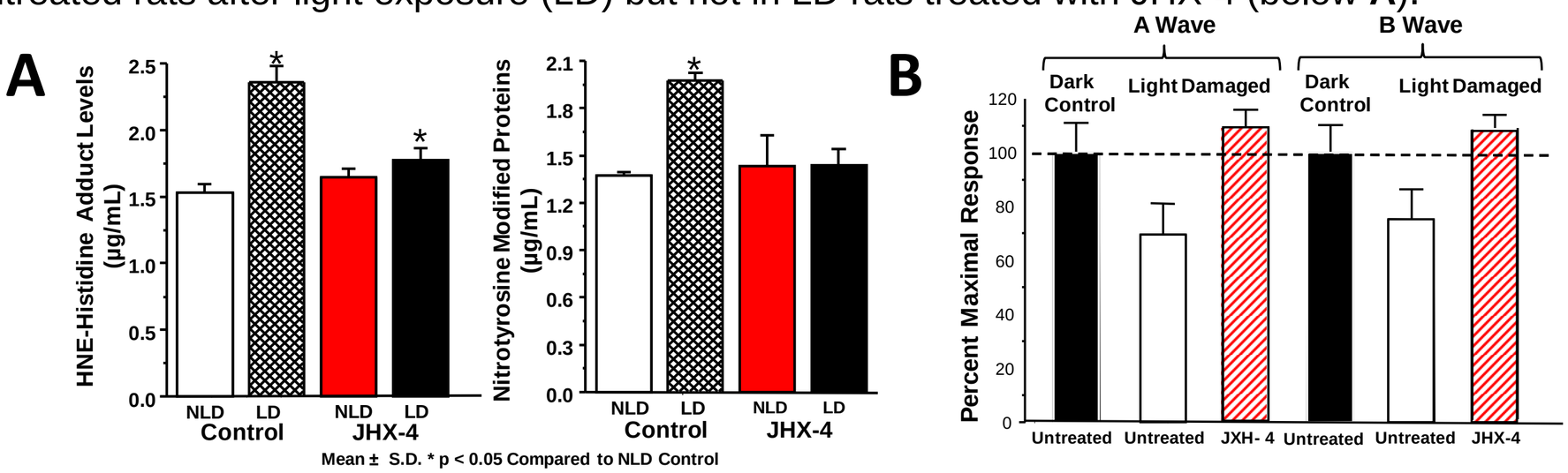


E **2x Blast Rotarod Spatial Function**



MFRMs Reduce Light-Induced Retinal Degeneration

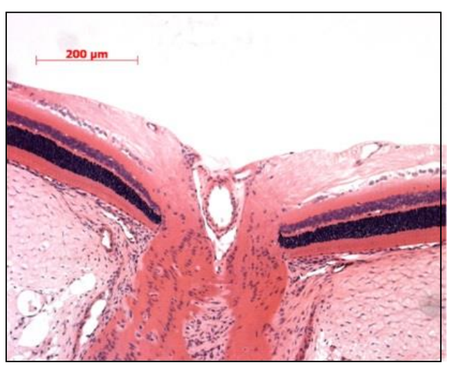
Exposure of dark adapted rats to light results in photoreceptor degeneration and other neural retinal changes that are initiated by the light-induced generation of ROS that is accompanied by iron dysregulation and the release of iron from ferritin. To determine whether MFRMs could ameliorate this light induced retinal degeneration, groups of Wistar rats were orally treated with or without diet containing 0.05% of MFRM JHX-4 beginning at the onset of 14 d dark adaption. Subsequent exposure of the rats to 1000 lx of light for 3 h resulted in an increase of oxidative stress markers in the neural retinas of these rats including hydroxynonenol (HNE) adducts that were formed with histidine and nitrotyrosine-modified proteins. Compared to the retinas in the non-light exposed (NLD) rats, these adducts were significantly increased in the untreated rats after light exposure (LD) but not in LD rats treated with JHX-4 (below **A**).



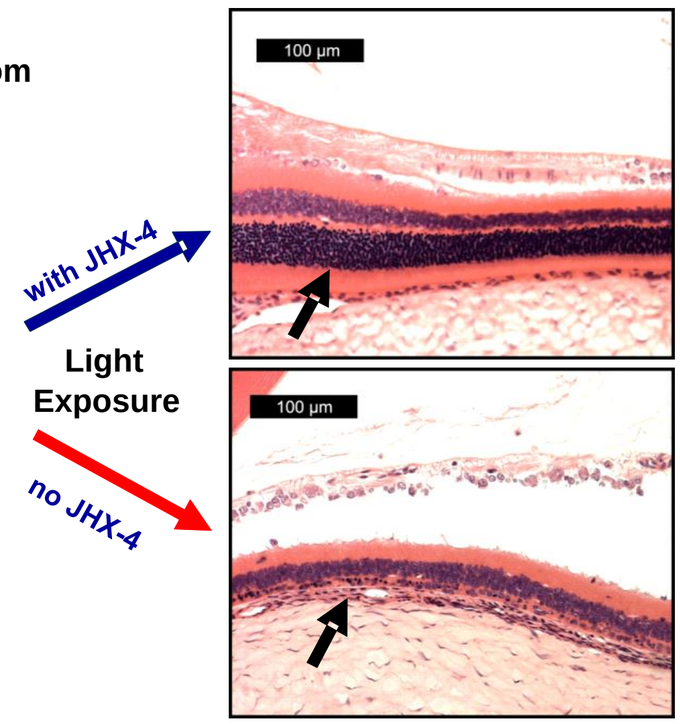
Mean ± S.D. * p < 0.05 Compared to NLD Control

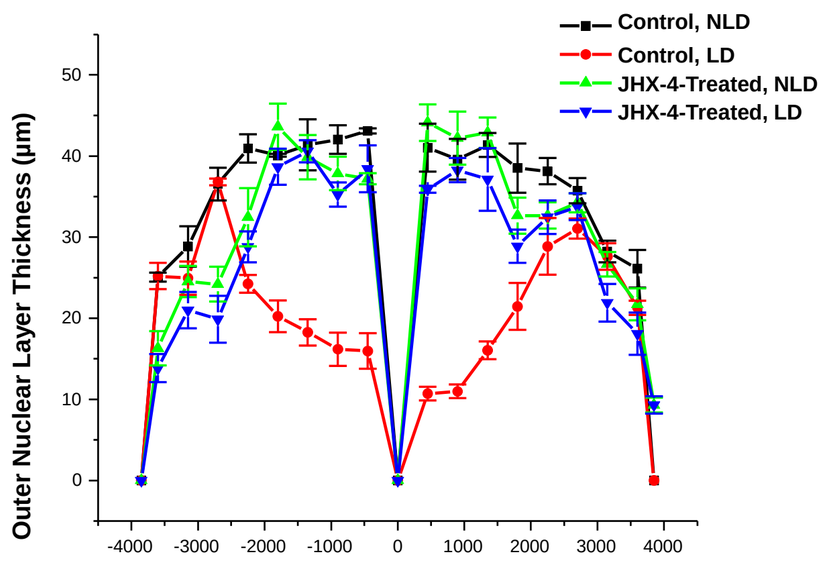
Intense light exposure also contributes to photoreceptor cell death by enhancing lipid peroxidation of the photoreceptor outer segments. Therefore, select dark-adapted rats after LD were returned to the dark for 5-7 d recovery. Their retinal neural functions were then evaluated by non-invasive electroretinography (ERG), a procedure that measures the function of photoreceptors (rods and cones), inner retinal cells (bipolar and amacrine cells), and ganglion cells through the measurement of electrical responses. As shown in the graph below, compared to untreated NLD control rats, the average scotopic maximum a- and b-wave amplitudes were significantly ($p<0.05$) reduced in the untreated LD rats. This reduction in the scotopic maximum a- and b-wave amplitudes was absent in LD rats treated with JHX-4 (above **B**). In addition to protecting the retina against light damage, these compounds demonstrated no toxic effects that damage the retina at the levels present. Histology (below), which shows that the photoreceptor layer was preserved by MFRM treatment, confirmed the ERG results.

JHX-4 Treatment Protects the Outer Nuclear Layer from Light Damage



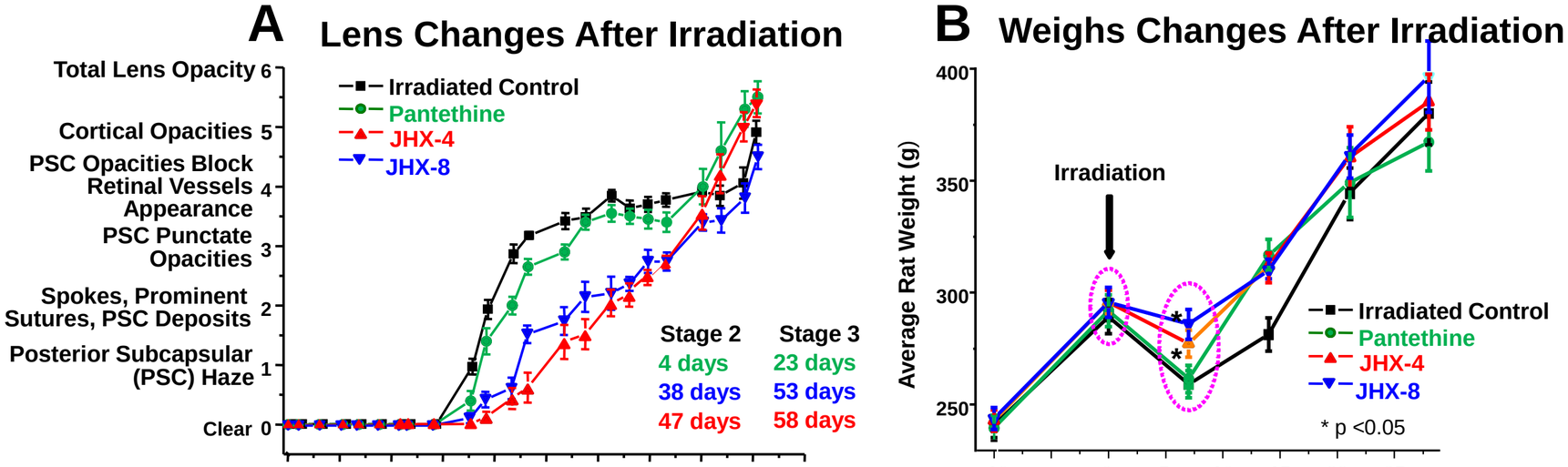
Normal Photoreceptor Layer
Exposure to light results in photoreceptor changes which are maximal 1 mm from the optic nerve toward the superior ora errata



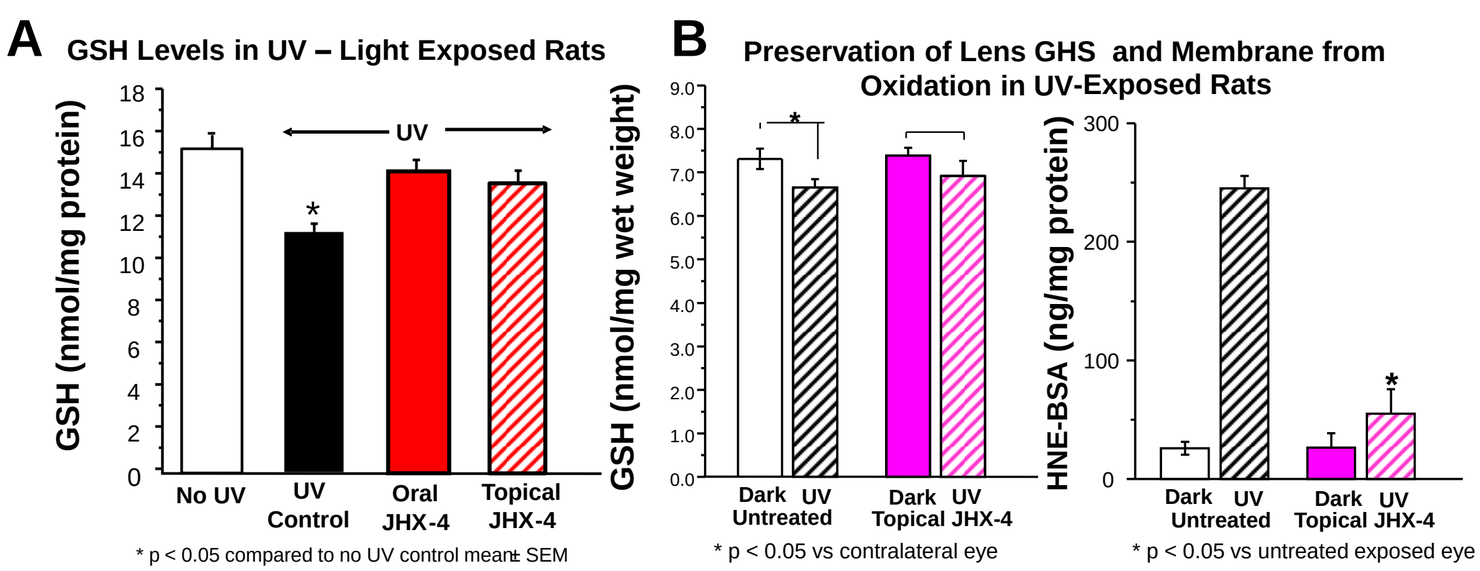


MFRMs Protect the Lens Against Radiation

The Kador Lab has observed that MFRMs are **radioprotective agents.** Long Evans rats were pretreated with either ~20 mg/kg/d of JHX-4 or JHX-8 for 14 d prior to 15 Gy whole head γ-irradiation. A 3rd group received a single 1 g /kg i.p. injection of pantethine 45 m prior to irradiation (pantethine has been reported[1] to be 3x more potent than radioprotective WR-77913). A 4th control group received only irradiation. Figure **A** below shows treatment with pantethine, JHX-4 and JHX-8 delayed initial lens changes by 4, 47, and 38 d, respectively, and posterior subcapsular opacities by 23, 53, and 58 d respectively. Irradiation also resulted in a transient reduction of salivary gland function which reduced food uptake and induced weight loss. Food uptake by the MFRM treated rats appeared less affected by the irradiation (**B**), since their weight loss was significantly less than either the pantethine or untreated controls. This suggests that MFRMs may also be beneficial for maintaining salivary function in patients receiving radiation therapy.



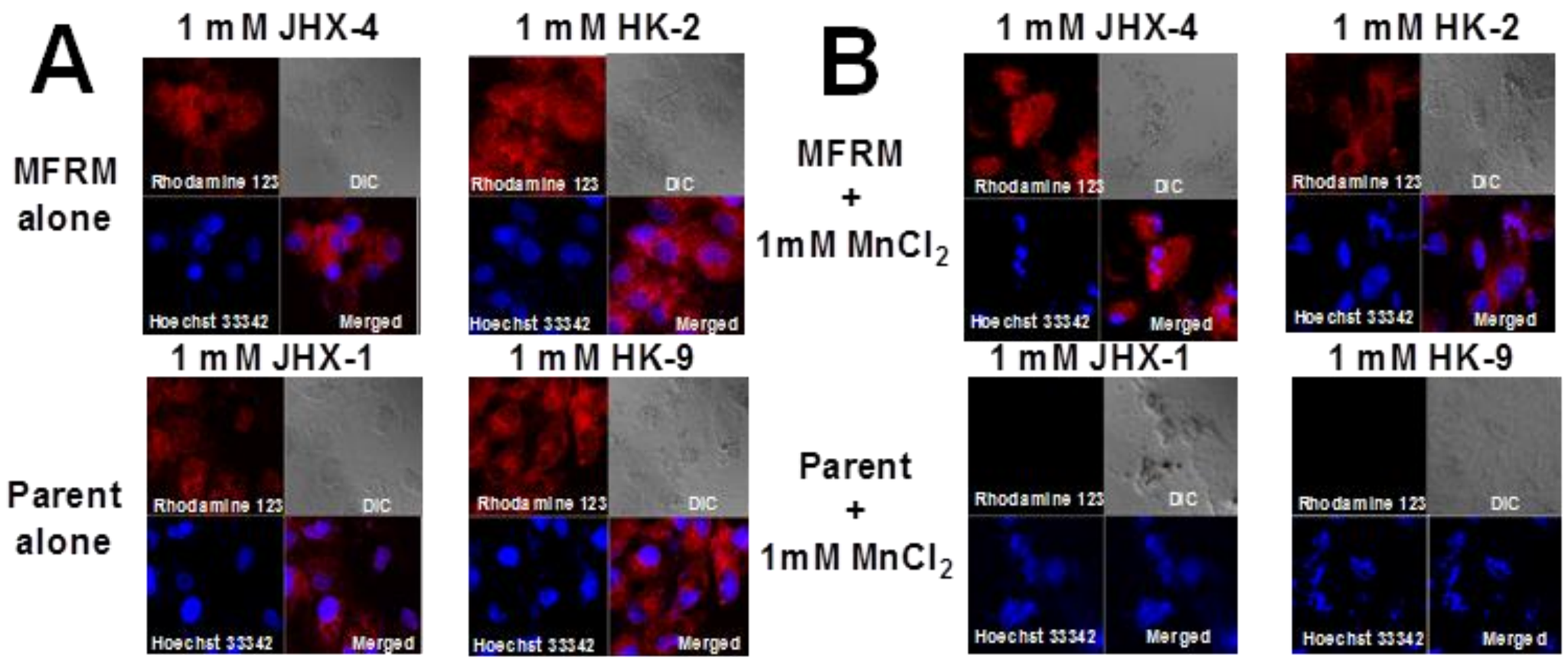
UV light radiation induces lens damage through generated ROS that leads to the rapid decrease of GSH and lens membrane oxidation. Figure **A** below shows that when young male albino rats were exposed to UV light (1600 μw/cm^2 of 280-360 nm, UV_{max} 306 nm for 15 m), a significant reduction of GSH occurs within 2-3 d post irradiation. This reduction was ameliorated by both oral (80 mg/kg) and topical (4%) administration of JHX-4. Figure **B** below shows that when UV exposure was limited to one eye with the contralateral eye serving as the unexposed control, similar UV exposure also resulted in significantly decreased GSH ($p < 0.05$) and increased 4-HNE lens membrane oxidation. This did not occur with JHX-4 treatment.



[1]Clark, J. I., Livesey, J. C. & Steele, J. E. Delay or Inhibition of Rat Lens Opacification using Pantethine and WR-77913. *Experimental Eye Research* **62**, 75-84, doi:https://doi.org/10.1006/exer.1996.0009 (1996)

MFRMs Provide Mitochondrial Protection

Mitochondria are key regulators of cell survival and cell death, and mounting evidence suggests that mitochondria have a central role in aging and the development of neurodegenerative diseases. A number of disease-specific proteins interact with mitochondria, including amyloid precursor protein (APP), presenilin (PS1) and presenilin 2 (PS2), which are associated with amyloid beta (Aβ) peptide, the primary component of Alzheimer's plaques. Metal concentrations in mitochondria are particularly important because they not only play essential roles in the production of ATP and detoxification of ROS, but metals such as iron and copper can also promote the formation of harmful radicals. Mitochondrial function can also be impaired by zinc, leading not only to excess ROS production, but also to the activation of a variety of extra-mitochondrial ROS-generating signaling cascades. Because MFRMs can transiently bind these transition metals, the possibility of MFRMs adversely affecting mitochondrial function has been investigated. As shown below, red fluorescent Rhodamine 123 staining which is indicative of mitochondrial function was not reduced in cultured ARPE-19 human RPE cells. Figure **A** shows that the addition of either 1 mM HK-2 or JHX-4 or their nonfunctional parent analogs HK-9 and JHX-1 that served as controls, did not reduce the cytoplasmic red fluorescent staining of Rhodamine 123. This indicates that MFRMs do not adversely affect mitochondrial function. Manganese overexposure, which has been implicated in Parkinson's disease, can lead to mitochondrial dysfunction. Figure **B** shows that after 1 h pre-incubation of cells with the nonfunctional HK-9 or JHX-1 or MFRM HK-2 or JHX-4, addition of 1 mM manganese chloride for 2 h resulted in the reduction of red Rhodamine 123 in the HK-9 or JHX-1 cells, indicating loss of mitochondrial function. The red fluorescent staining was retained in the presence of HK-2 or JHX-4 indicating that the MFRMs protected mitochondrial function by preventing Mn^{+2} ions from poisoning the mitochondria. Blue staining by Hoechst 33342 indicates the presence of cell nuclei.

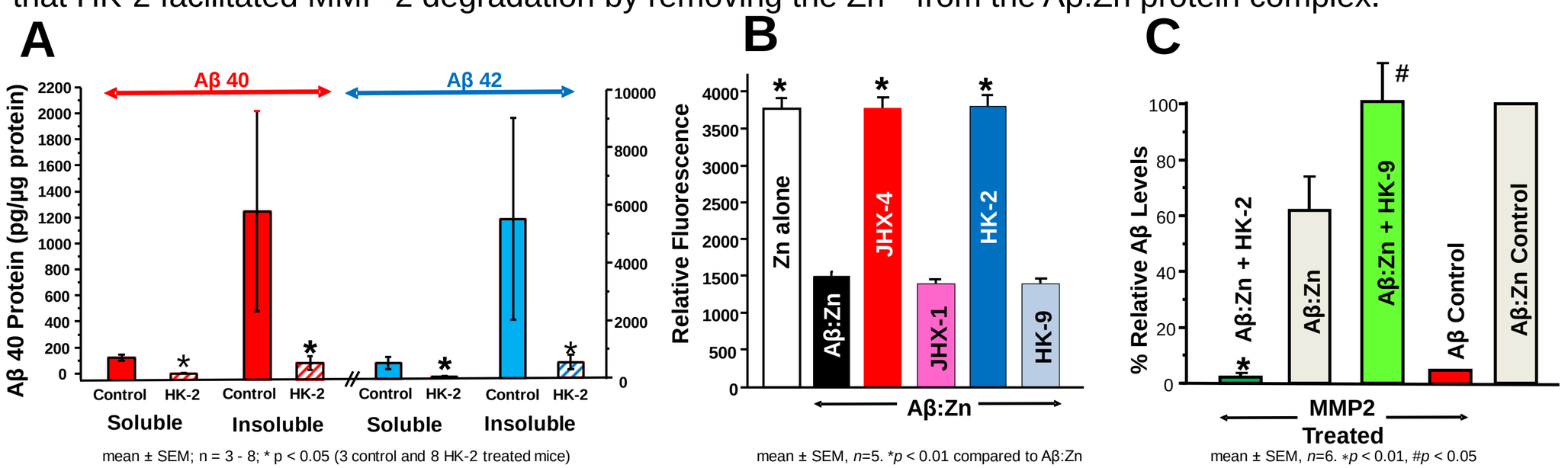


MFRMs Suppress Amyloid Beta Levels

Oxidative stress is a major factor in the development of Alzheimer's disease (AD) and other forms of dementia. Antioxidant therapy is proposed to slow this disease progression. MFRM HK-2, which crosses the blood brain barrier, has been investigated for its ability to reduce amyloid beta (Aβ) plaque formation in 2 mo old transgenic AD mice. As shown below, in graph **A**, 12 mo administration of HK-2 significantly reduced brain formation of Aβ40 and Aβ42 proteins in both SDS soluble (oligomeric Aβ) and insoluble (Aβ fibrils) fractions. Aβ plaque has also been reported to be present in cataracts of dementia patients and retinas demonstrating age related macular degeneration (AMD). Therefore, the eyes of these transgenic mice were also evaluated after 7 mo of HK-2 treatment showing a similar reduction of Aβ 40 and Aβ 42 protein levels in the soluble and insoluble protein fractions from the lens and retina.

The bioavailability of zinc is an important parameter in neuronal cells and zinc affects amyloid metabolism in the pathogenesis of AD. Zn^{2+} complexes Aβ peptide to form Aβ peptide aggregates, and the formed Aβ:Zn complexes increase protease-resistance, especially against matrix metalloprotease-2 (MMP2). As Zn^{2+} becomes co-localized with $Aβ_{1-42}$, the cellular bioavailability of cellular Zn^{2+} not only decreases, but the neurotoxicity of the Aβ:Zn complex increases. Using fluorescent zinquin to monitor cytoplasmic free Zn^{2+} levels in RPE cells cultured in media containing 10 μM zinc sulfate, the relative blue fluorescence indicative of the presence of labile Zn^{2+} was not significantly reduced by 1 h culture with 10 μM of the MFRMs JHX-4 or HK-2 (graph **B** below). This indicates that MFRMs do not adversely reduce the concentration of labile Zn^{2+}. However, the fluorescence zinquin was significantly decreased when cells were exposed for 1 h to 10 μM of Aβ:Zn. This decrease was not observed when the cells were pre-incubated for 1 h with 10 μM of JHX-4 or HK-2 prior to 1 h exposure to 10 μM of Aβ:Zn. Similarly, the reduction in zinquin fluorescence with Aβ:Zn was not ameliorated by preincubation with the nonfunctional analogs JHX-1 or HK-9. This indicates that the MFRMs are able to extract labile zinc from the Aβ:Zn complex and redistribute the Zn^{+2} back into the cytoplasm as labile Zn^{2+}.

Since MFRMs appear to extract Zn^{+2} from the Aβ:Zn complex, the ability of MFRMs to alter the degradation of the Aβ:Zn complex was examined using recombinant human MMP-2. *In vitro* studies were conducted in which 10 μM of Aβ:Zn or Aβ were incubated for 1 h with or without 10 μM of HK-2 or its nonfunctional analog together with 1.1 μL of recombinant human MMP-2. The samples were then denatured and evaluated by Western blot. As shown in figure **C**, the MMP-2 rapidly degraded Aβ by ~95% while the Aβ:Zn complex was only partially degraded by ~40%. Similar co-culture of the Aβ:Zn complex by MMP-2 in the presence of the HK-2 resulted in the rapid degradation of Aβ; however, co-culture in the presence of the nonfunctional analog HK-9 resulted in no degradation. The nearly complete degradation with HK-2 suggest that HK-2 facilitated MMP-2 degradation by removing the Zn^{+2} from the Aβ:Zn protein complex.



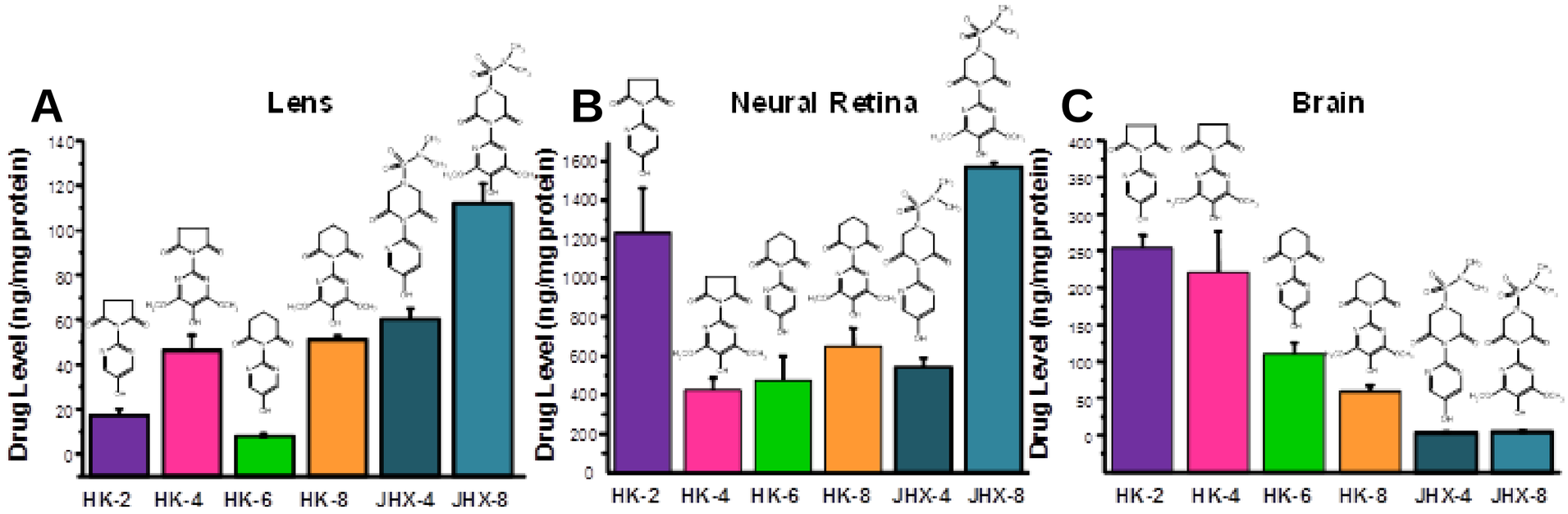
mean ± SEM; n = 3 - 8; * p < 0.05 (3 control and 8 HK-2 treated mice)

mean ± SEM, *n*=5. **p* < 0.01 compared to Aβ:Zn

mean ± SEM, *n*=6. ⁎*p* < 0.01, #*p* < 0.05

In Vivo Bioavailability and Safety Studies

To determine if MFRMs can adequately reach potential target tissues in the eye and brain after oral administration, MFRMs were orally administered to C57BL/6 mice in rodent chow containing 0.05% (wt/wt) MFRMs for 14 d. Feeding studies indicated that at this concentration, the mice received ~80 mg/kg/d of MFRM. After whole body perfusion at the time of sacrifice, MFRM levels in the lens (**A**), neural retina (**B**), and brain (**C**) were measured by HPLC-ESI-MS. As illustrated below, the JHX series achieved higher levels in the lens while the HK series achieved higher levels in the brain. In the neural retina, similar levels were achieved by both series. In general, HK-2 achieved highest concentrations in the brain and neural retina while JHX-8 achieved highest levels in the lens and neural retina. The results also indicate that distinct differences in the accumulation of MFRMs are linked to their structural/chemical characteristics. In correlating the calculated molecular descriptors for these MFRMs, inverse correlations between the uptake of MRFMs and their molecule parameters related to steric bulk, molar refractivity (estimate of polarizability of the molecule), polarity, and hydrophilic volume, were observed in the brain versus the lens. Although the retina is considered an extension of the brain, no correlations between the examined molecular parameters and accumulation of compound into the retina were observed.



Preliminary studies on determining the maximum tolerated dose were also conducted by administering escalating doses of HK-2 or JHX-4 by gavage to male and female C57BL/6 mice. Dosing started at 1000 mg/kg/d for 5 d and increased by 200 mg/kg/d increments every 5 d up to a maximum dose of 1800 mg/kg/d. Neither drugs caused any significant change in mortality, body weights, food consumption, signs of physical discomfort, or changes in behavior. Transgenic murine models of Alzheimer's disease were also fed diet containing 0.05% HK-2 corresponding to 80 mg/kg/d for 1 yr with no clinically adverse effects observed.

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Patents:

Patents licensed to the inventor

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