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LETTER TO THE EDITOR

CHLOROQUINE'S PATHO-TOXICOLOGICAL EFFECT ON THE RETINA – A NITRIC OXIDE AND CAMP MEDIATED MECHANISM

Sir,

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Chloroquine is used, particularly in the third world, as a cheap antimalarial and for the treatment of rheumatoid arthritis, lupus erythematosus and various inflammatory conditions. Chloroquine promotes attenuation of cAMP and an increase in nitric oxide (NO) production (1). Renal function, mediated through these factors, is compromised by chloroquine when ingested in combination with ethanol (2). Chloroquine's toxicological consequences on the retina are multifactorial including lysosomal dysfunction (3), aberrations in serum proteins and free amino acids (4), and various lipidemic effects (5).

The eye is an extremely complex and efficient sense organ. Within its orbit the eye is endowed with a layer of receptors, a metabolically active lens and cornea that focus light onto retinal receptors, and an optic nerve that conducts nerve impulses to the visual cortex in the brain (6). Incident light is captured by a sequence of events, collectively phototransduction, and converted into action potentials in bipolar cells and neural elements within the optic nerve (7).

I propose that chloroquine damages the retina via stimulation of NO production and indirectly via a reduction of cAMP concentration. With attenuation of cAMP, there is a decrease in associated allosteric signals normally involved in an increase in the rate of catabolic reactions. Activation of phosphorylase and glycogenolysis drops (8). NO, a free radical, causes damage to living cells, resulting in morphological and nuclear alterations in the retina (9). Although NO activity decreases during retinal ischemia-reperfusion, it increases the thickness of the inner plexiform layer of the retina (10) and contributes to capillary degeneration (11).

Hypothesis

I hypothesise that chloroquine-mediated attenuation of cAMP decreases the sensitivity of phosphofructokinase-1 to small alterations in the energy status of a cell. Consequently, there is a diminished control of the amount of carbohydrate undergoing glycolysis before it enters the Tricarboxylic Acid Cycle (TCA). Ultimately, as there is less ATP produced, there is no longer a sparing action of fatty acid oxidation on glucose metabolism. Additionally, an attenuated Pasteur effect results in a drop in glucose-6-phosphate and a stimulated glucose uptake transporter into extrahepatic tissues. This is likely to elevate intracellular

concentrations of glucose and subsequently increase intraocular pressure.

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