

## 11-cis-retinal Analogs for the Treatment of Age-Related Retinopathies

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**Purpose:** To describe the effects of aging on the retinoid cycle and the effects of exogenously delivered synthetic 11-*cis* retinoid analogs (SCR) on the aging murine retina.

**Methods:** First, 10-month old C57BL/6 mice were treated with a single oral dose of SCR, *all-trans*-retinyl acetate (vitamin A) or vehicle (control) (short-term therapy). In the second experiment (long-term therapy), 4-month old mice were treated monthly with oral doses of SCR or vehicle for either 6 or 10 months. The vehicle treated arm of this experiment served as a model for aging in the wild type mouse. In both experiments, the mice were housed in 12 hr light/dark cycles and had normal diets. The levels of retinoids, rhodopsin, isorhodopsin (opsin+ SCR) and dark-adapted ERGs (DA-ERG) were measured before and after treatment. In the long-term experiment, histology and changes in retinal gene expression in all mice were analyzed.

**Results:** After short-term therapy, the mice treated with SCR showed a significant increase in DA-ERG amplitudes ( $p < 0.01$ ) as compared to control animals. The Vitamin A group responded identically to the control group. In the long-term experiment, the vehicle control group showed an age-related decrease in DA-ERG amplitudes and in amount of rhodopsin available as well as an increase in the opsin:rhodopsin ratio at 10 and 14 months of age. The SCR treated mice had higher DA-ERG amplitudes at the same time points ( $P < 0.001$ ).

**Conclusions:** Deteriorating photoreceptor function documented in mice at 10 and 14 versus 4 months of age was improved significantly by long-term, monthly administration of SCR. These findings suggest a potential therapeutic approach to prevent age-related retinal dysfunction.