BIO201: a new drug candidate for the treatment of dry AMD

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PURPOSE

Dry AMD is a major cause of visual impairment associated with aging, and no drug treatment is presently available. In collaboration with the Institut de la Vision, Biophytis develops a drug candidate (BIO201) based on norbixin, a di-apo-carotenoid, as API. We describe here the effects of norbixin on retinal pigmented epithelium (RPE) and retina photoprotection in vitro and in vivo.

MATERIALS AND METHODS

The photo-protective effect of norbixin, bixin, lutein, zeaxanthin and crocetin was evaluated on primary cultures of porcine RPE cells challenged with 30 nM A2E and illuminated with blue light (470 nm, 50 min) (N=16).

In vivo experiments measured the photo-protective effect of norbixin one week after blue light damage in the Abca4 deficiency transgenic mouse model by intravitreal injections and in a standard rat blue light model of photodamage by repeated intraperitoneal injections. Twenty-eight 7-week-old mice were injected intra-retinally in one eye with 120 µM norbixin (in 0.3% DMSO) or with DMSO alone, dark-adapted during 24 hours and exposed to blue light (4000 lux) for one hour. Ten mice were used as non-illuminated controls. Groups of 6-12 rats were injected intraperitoneally with either norbixin (10, 50, 100 mg/kg), bixin (5 mg/kg) or 5 mg/kg light damage and eyes were removed for histology and full field scotopic electroretinogram was measured one week after BLD.

RESULTS

High protection of RPE cells by bixin and norbixin

Bixin and norbixin were highly protective even at 5 µg/mL inducing 80.75 and 72.5 % RPE survival respectively whereas lutein, zeaxanthin and crocetin showed no protection at this concentration. At the different concentrations tested norbixin was always slightly less efficient than bixin.

Norbixin bioavailability is much better than that of bixin

Blood was collected at various intervals and plasma levels were measured by HPLC-MS/MS. Ingested Bixin (A) bioavailability is quite low (ca. 2%) and this compound is rapidly converted into norbixin by esteras. Norbixin bioavailability (B) is much better and may become close to 100% with a suitable dosage form.

CONCLUSIONS

1-Bixin and norbixin are more active than xanthophylls (lutein, zeaxanthin) in vitro

2-Norbixin has a much better oral bioavailability than bixin and was therefore selected for further studies

3-Norbixin provides an efficient photoprotection when injected intravitreally in Abca4 deficiency mice

4-Norbixin is at least as efficient as PBN by intraperitoneal injections in the blue light rat model

5-Chronic oral treatment of Abca4 deficiency mice with norbixin is presently under investigation and appears to (1) reduce A2E accumulation and (2) prevent the degradation of ERG.

Norbixin protects the retina of Abca4-deficiency mouse against blue light induced phototoxicity

In the eyes injected with norbixin we observed a partial but clear protection of photoreceptor cells and outer segments compared to the non-induced control (9-10 rows compared to 10-11 rows).

Norbixin protects the rat retina against blue light induced phototoxicity

BLD induced a massive photoreceptor degeneration in vehicle-treated rats (4-6 rows remaining) compared to non-treated rats (10-11 rows). At 10 and 50 mg/kg norbixin induced a partial photoreceptor protection similar to that obtained with PBN (7-9 rows) whereas at 100 mg/kg the protection was very close to the non-induced control (9-10 rows compared to 10-11 rows).