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Dual BACE1/2 inhibitor treatment-induced changes in hair pigmentation in mice confirms a role for BACE-2 in melanin production

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Beta secretase 1 (BACE-1) is the first enzyme in the metabolic pathway converting the amyloid precursor protein (APP) to amyloid beta peptide (Aβ), and is currently considered the most promising therapeutic approach to test the amyloid hypothesis of Alzheimer's disease (AD). The development of BACE inhibitors was dogged for a number of years by difficulties in generating potent molecules with drug-like properties. Newer compounds have overcome many of these issues, including selectivity over closely related aspartyl peptidases such as pepsin, renin and cathepsin D. Gaining selectivity for BACE-1 over the close homology BACE-2, however, has remained challenging. Furthermore, the functions of BACE-2 have remained elusive until recently. Perhaps consequently, the majority of clinically tested BACE inhibitors have limited selectivity for BACE-1 over BACE-2, or are counter-selective. BACE-2 is expressed at lower levels, predominantly in the periphery. Evidence exists for a role of BACE-2 in APP metabolism (albeit controversially), and in pancreatic beta-cell function and glucose homeostasis. BACE-2 is also highly expressed in pigment-producing cells, and recent investigations using knock out and silencing techniques indicate that BACE-2 is implicated in melanogenesis via proteolytic cleavage of the membrane-bound form of pigment cell-specific melanocyte protein (PMEL) (1). The consequences of chronic BACE-2 blockade by dual inhibitors, however, have not been well investigated. We therefore set out to investigate the influence of BACE-1/2 inhibition on melanogenesis in pigmented mice, and to dissect the contribution of BACE-2 in hair depigmentation.

C57Bl/6 male mice were dosed *per os* with NB-360, a novel, brain penetrating 3-amino-dihydro-oxazine dual BACE-1/2 inhibitor which potently reduces Aβ in the brains and CSF of animal models (2). At doses effective in lowering central Aβ, NB-360 induced dose- and exposure-dependent patches of depigmented (grey) hair within a few weeks of treatment initiation. Reduction of melanin pigments was observed in anagen (growing) hairs but not in skin melanocytes, telogen (resting) hairs or in other pigmented organs, including retina. Compound levels were ~ 10-fold higher in skin than in the blood. Hair depigmentation did not reverse after treatment cessation unless hair was plucked from affected regions, indicating long-lasting effects on existing melanocytes or affected hairs. In vitro investigations with human MNT-1 and mouse B16-F0 melanocyte cells confirmed that BACE-2 but not BACE-1 inhibition altered PMEL processing and melanin content. These data underscore the importance of BACE-2 in the pigmentation process and suggest that improving the selectivity of dual BACE inhibitors for BACE-1 over BACE-2 may mitigate effects on melanocytes and melanogenesis.

1. Rochin L et al. (2013). *Proc Natl Acad Sci U S A***110**:10658-10663.

2. Neumann U et al. (2014). *Alzheimer's Association International Conference, Copenhagen, Denmark*, **July**: P4-363.