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Conference Paper Abstract

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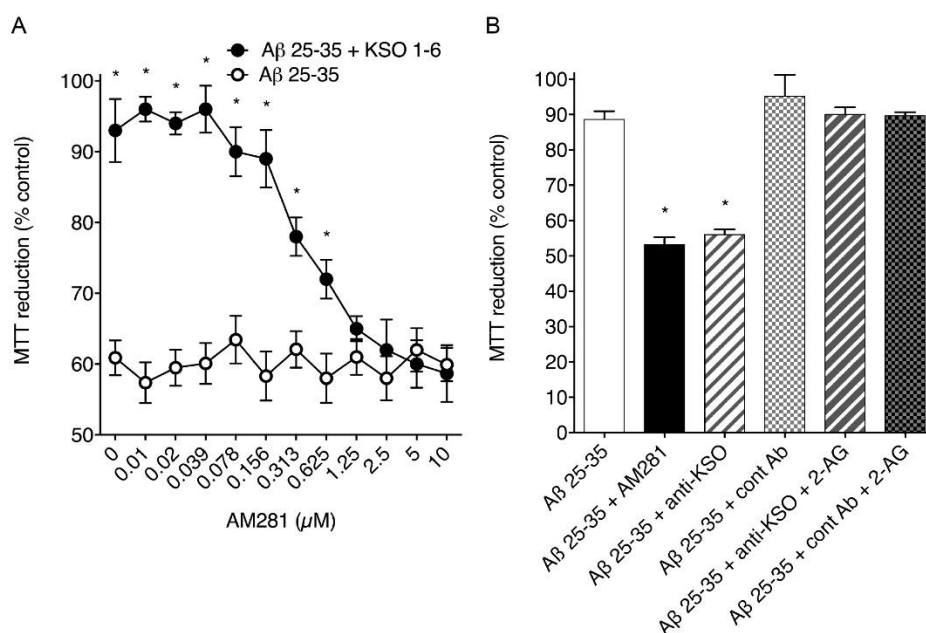
## Effect of the CB<sub>1</sub> cannabinoid receptor antagonist AM281 on kissorphin protection against amyloid- $\beta$ neurotoxicity

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**Introduction:** Previous *in vitro* and *in vivo* studies demonstrate protective properties of kissorphin (KSO) peptides against amyloid- $\beta$  (A $\beta$ ) neurotoxicity<sup>1,2</sup>. Overexpression of the KiSS-1 gene, that encodes the KSO peptides, is also neuroprotective<sup>1,3</sup>. Endocannabinoids and KSO peptides are neuroprotective against A $\beta$  25-35, but not A $\beta$  31-35 peptides<sup>1,4</sup>. The KiSS-1 gene expression is regulated by endocannabinoids<sup>5</sup>. The aim of this study was to determine whether endocannabinoids contribute to KSO protection against A $\beta$  toxicity using a CB<sub>1</sub> cannabinoid receptor antagonist.

**Method:** This study employed MTT cell viability assays to investigate the effects of the CB<sub>1</sub> antagonist AM281 on KSO 1-6 protection against A $\beta$  25-35 neurotoxicity in human neuroblastoma SH-SY5Y cells. The effects of AM281 on A $\beta$  25-35 induced neurotoxicity in KiSS-1 gene overexpressing SH-SY5Y cells (PKiSS)<sup>1,3</sup> was also investigated<sup>1,3</sup>. Data was analyzed by one-way analysis of variance (ANOVA).

**Results:** The CB<sub>1</sub> antagonist AM281 (0.01-10 $\mu$ M) promoted a concentration dependent increase in 10 $\mu$ M A $\beta$  25-35 induced neurotoxicity in SH-SY5Y cells in the presence of 10 $\mu$ M KSO 1-6 (Figure 1A). The PKiSS protection against 10 $\mu$ M A $\beta$  25-35 was reversed by the CB<sub>1</sub> antagonist AM281 (10 $\mu$ M) and anti-KSO antibody (1 $\mu$ g/ml). In the presence of anti-KSO antibody 10 $\mu$ M 2-AG was protective against 10 $\mu$ M A $\beta$  25-35.



**Figure 1.** (A) Dose-response curves for AM281 in the presence of 10 $\mu$ M A $\beta$  25-35 with or without 10 $\mu$ M KSO 1-6, on MTT reduction in SH-SY5Y cells. (B) PKiSS SH-SY5Y cells were exposed to 10 $\mu$ M A $\beta$  25-35 alone; 10 $\mu$ M A $\beta$  25-35 plus 10 $\mu$ M AM281; 10 $\mu$ M A $\beta$  25-35 plus 1 $\mu$ g/ml anti-KSO antibody; 10 $\mu$ M A $\beta$  25-35 plus 1 $\mu$ g/ml control antibody; 10 $\mu$ M A $\beta$  25-35 plus 1 $\mu$ g/ml anti-KSO antibody with 10 $\mu$ M 2-AG; 10 $\mu$ M A $\beta$  25-35 plus 1 $\mu$ g/ml control antibody with 10 $\mu$ M 2-AG; and cell viability determined by MTT reduction. Results are mean  $\pm$  SEM (n=8 for each data point); \* = P < 0.05 vs A $\beta$  25-35 alone (one-way ANOVA).

**Conclusion:** In conclusion, protection against A $\beta$  25-35 induced neurotoxicity by KSO and KiSS-1 overexpression in SH-SY5Y cells is reversed by the AM281 CB<sub>1</sub> antagonist. Anti-KSO antibodies prevent neuroprotection by KiSS-1 overexpression and 2-AG restores neuroprotection. This suggests KSO neuroprotection against A $\beta$  involves activation of endocannabinoids.

**References:**

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