Conference Paper Abstract

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Effect of the CB_1 cannabinoid receptor antagonist AM251 on kissorphin protection against amyloid-β neurotoxicity

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Introduction: Previous *in vitro* and *in vivo* studies demonstrate protective properties of kissorphin (KSO) peptides against amyloid-β (Aβ) neurotoxicity[1,2]. Overexpression of the KiSS-1 gene, that encodes the KSO peptides, is also neuroprotective[1,3]. Endocannabinoids and KSO peptides are neuroprotective against Aβ 25-35, but not Aβ 31-35 peptides[1,4]. The KiSS-1 gene expression is regulated by endocannabinoids[5]. The aim of this study was to determine whether endocannabinoids contribute to KSO protection against Aβ toxicity using a CB_1 cannabinoid receptor antagonist.

Method: This study employed MTT cell viability assays to investigate the effects of the CB_1 antagonist AM281 on KSO 1-6 protection against Aβ 25-35 neurotoxicity in human neuroblastoma SH-SY5Y cells. The effects of AM281 on Aβ 25-35 induced neurotoxicity in KiSS-1 gene overexpressing SH-SY5Y cells (PKiSS)[1,3] was also investigated[1,3]. Data was analyzed by one-way analysis of variance (ANOVA).

Results: The CB_1 antagonist AM281 (0.01-10μM) promoted a concentration dependent increase in 10μM Aβ 25-35 induced neurotoxicity in SH-SY5Y cells in the presence of 10μM KSO 1-6 (Figure 1A). The PKiSS protection against 10μM Aβ 25-35 was reversed by the CB_1 antagonist AM281 (10μM) and anti-KSO antibody (1μg/ml). In the presence of anti-KSO antibody 10μM 2-AG was protective against 10μM Aβ 25-35.

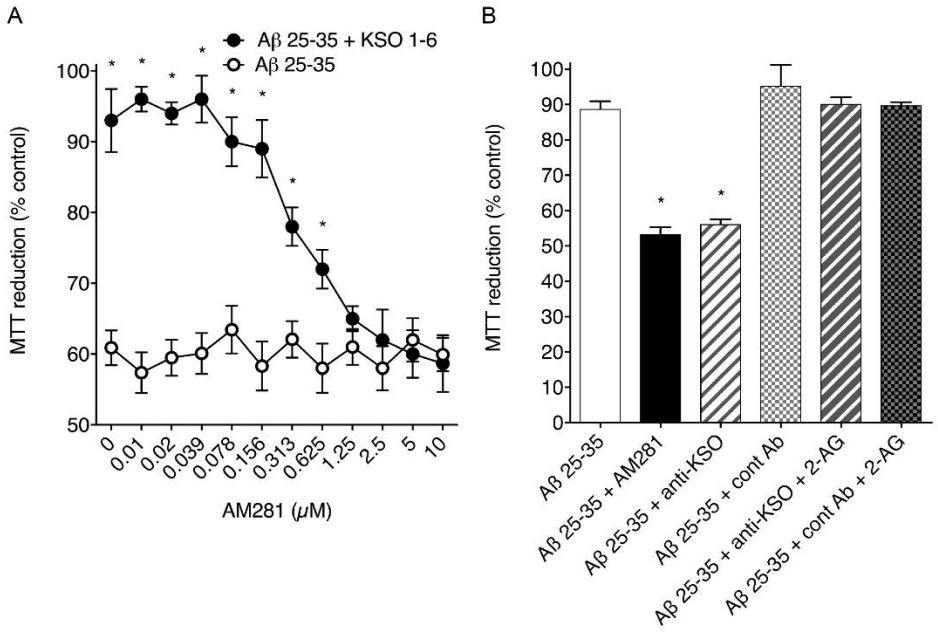

Figure 1. (A) Dose-response curves for AM281 in the presence of 10μM Aβ 25-35 with or without 10μM KSO 1-6, on MTT reduction in SH-SY5Y cells. **(B)** PKiSS SH-SY5Y cells were exposed to 10μM Aβ 25-35 alone; 10μM Aβ 25-35 plus 10μM AM281; 10μM Aβ 25-35 plus 1μg/ml anti-KSO antibody; 10μM Aβ 25-35 plus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

Conclusion: In conclusion, protection against Aβ 25-35 induced neurotoxicity by KSO and KiSS-1 overexpression in SH-SY5Y cells is reversed by the AM281 CB_1 antagonist. Anti-KSO antibodies prevent neuroprotection by KiSS-1 overexpression and 2-AG restores neuroprotection. This suggests KSO neuroprotection against Aβ involves activation of endocannabinoids.

References:

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