



LEEDS
BECKETT
UNIVERSITY

Citation:

Milton, NG (2018) Effects of the CB1 cannabinoid receptor antagonist AM281 on kissorphin protection against amyloid- neurotoxicity. In: 8th European Workshop on Cannabinoid Research, 31 August 2017 - 02 September 2017, London.

Link to Leeds Beckett Repository record:

<https://eprints.leedsbeckett.ac.uk/id/eprint/4985/>

Document Version:

Conference or Workshop Item (Published Version)

Conference Paper Abstract

The aim of the Leeds Beckett Repository is to provide open access to our research, as required by funder policies and permitted by publishers and copyright law.

The Leeds Beckett repository holds a wide range of publications, each of which has been checked for copyright and the relevant embargo period has been applied by the Research Services team.

We operate on a standard take-down policy. If you are the author or publisher of an output and you would like it removed from the repository, please [contact us](#) and we will investigate on a case-by-case basis.

Each thesis in the repository has been cleared where necessary by the author for third party copyright. If you would like a thesis to be removed from the repository or believe there is an issue with copyright, please contact us on openaccess@leedsbeckett.ac.uk and we will investigate on a case-by-case basis.

Effect of the CB₁ cannabinoid receptor antagonist AM251 on kissorphin protection against amyloid- β neurotoxicity

N. G. Milton. School of Clinical & Applied Sciences, Leeds Beckett University, Leeds, United Kingdom.

Introduction: Previous *in vitro* and *in vivo* studies demonstrate protective properties of kissorphin (KSO) peptides against amyloid- β (A β) 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 A β 25-35, but not A β 31-35 peptides^{1,4}. The KiSS-1 gene expression is regulated by endocannabinoids⁵. The aim of this study was to determine whether endocannabinoids contribute to KSO protection against A β toxicity using a CB₁ cannabinoid receptor antagonist.

Method: This study employed MTT cell viability assays to investigate the effects of the CB₁ antagonist AM281 on KSO 1-6 protection against A β 25-35 neurotoxicity in human neuroblastoma SH-SY5Y cells. The effects of AM281 on A β 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 CB₁ antagonist AM281 (0.01-10 μ M) promoted a concentration dependent increase in 10 μ M A β 25-35 induced neurotoxicity in SH-SY5Y cells in the presence of 10 μ M KSO 1-6 (Figure 1A). The PKiSS protection against 10 μ M A β 25-35 was reversed by the CB₁ antagonist AM281 (10 μ M) and anti-KSO antibody (1 μ g/ml). In the presence of anti-KSO antibody 10 μ M 2-AG was protective against 10 μ M A β 25-35.

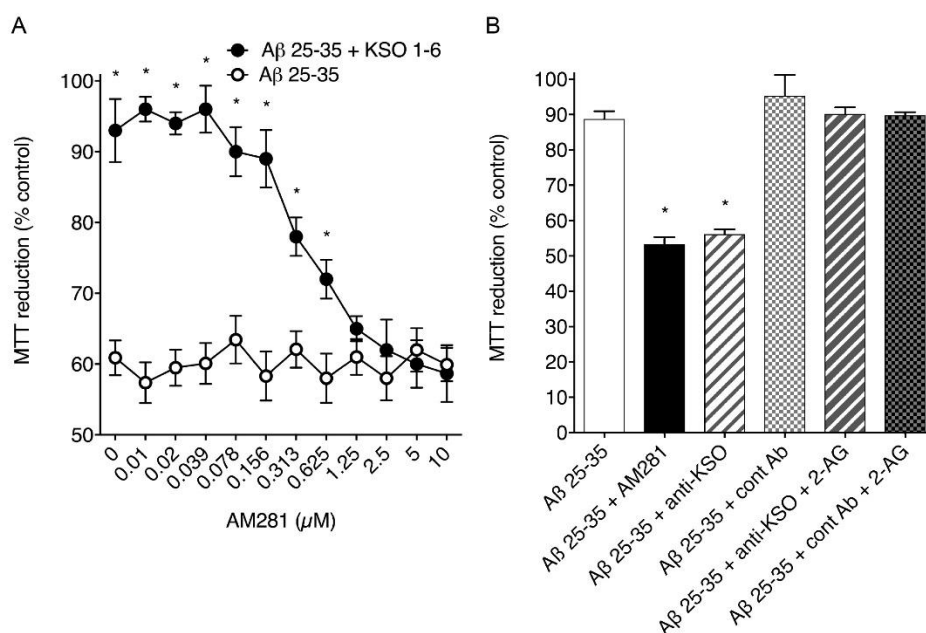


Figure 1. (A) Dose-response curves for AM281 in the presence of 10 μ M A β 25-35 with or without 10 μ M KSO 1-6, on MTT reduction in SH-SY5Y cells. (B) PKiSS SH-SY5Y cells were exposed to 10 μ M A β 25-35 alone; 10 μ M A β 25-35 plus 10 μ M AM281; 10 μ M A β 25-35 plus 1 μ g/ml anti-KSO antibody; 10 μ M A β 25-35 plus 1 μ g/ml control antibody; 10 μ M A β 25-35 plus 1 μ g/ml anti-KSO antibody with 10 μ M 2-AG; 10 μ M A β 25-35 plus 1 μ g/ml control antibody with 10 μ 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 β 25-35 alone (one-way ANOVA).

Conclusion: In conclusion, protection against A β 25-35 induced neurotoxicity by KSO and KiSS-1 overexpression in SH-SY5Y cells is reversed by the AM281 CB₁ antagonist. Anti-KSO antibodies prevent neuroprotection by KiSS-1 overexpression and 2-AG restores neuroprotection. This suggests KSO neuroprotection against A β involves activation of endocannabinoids.

References:

- (1) Milton NGN *et al.* (2012). *ACS Chem Neurosci* **3**: 706-719.
- (2) Jiang JH *et al.* (2015). *Neurobiol Learn Mem.* **123**: 187-95.
- (3) Chilumuri A & Milton NGN (2013). *ISRN Neuroscience* **2013**: 253210.
- (4) Milton NGN (2002). *Neurosci Letts* **332**: 127-130.
- (5) Karamikheirabad M *et al.* (2013). *Clin Exp Reprod Med* **40**: 155-162.