Design of novel melatonin receptor ligands with neuroprotective activity

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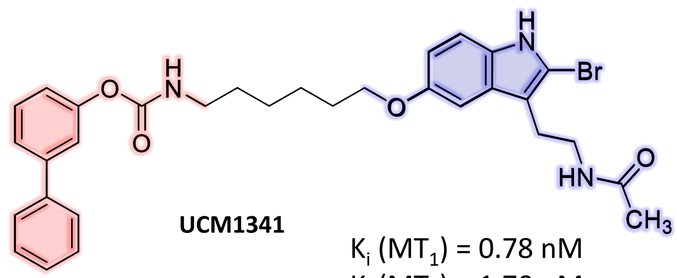
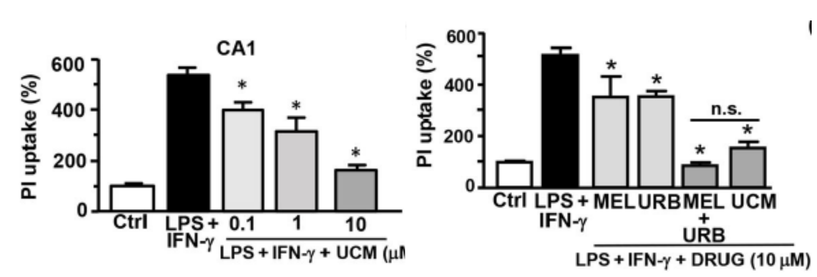
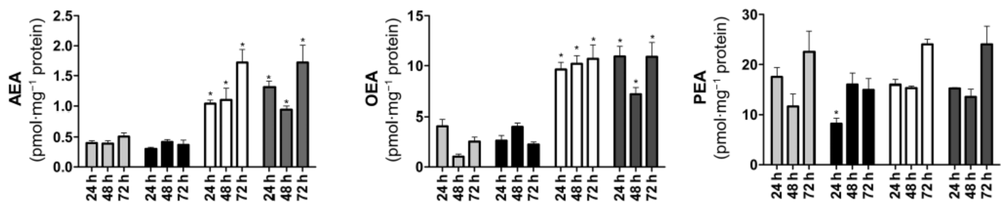
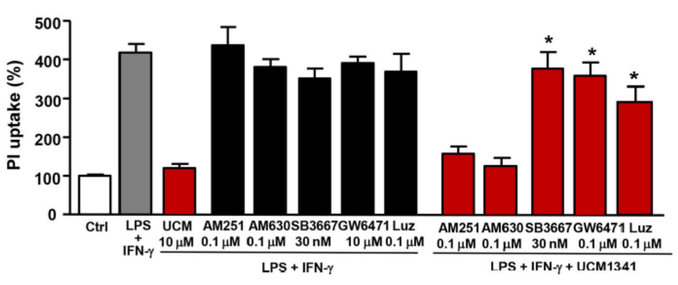
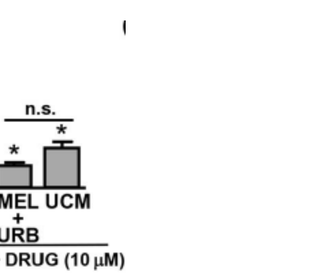
- Melatonin, the neurohormone mainly secreted by the pineal gland, binds and activates two GPCRs, MT_1 and MT_2, exerts antioxidant and radical scavenging effects and has neuroprotective activity.[1]
- Fatty acid amide hydrolase (FAAH) is responsible for the inactivating hydrolysis of N-acylethanolamines, including the endocannabinoid anandamide (AEA), and the lipid modulators oleoylethanolamide (OEA) and palmitoylethanolamide (PEA).[2]
- Enhancing the endocannabinoid and melatonergic tone has therapeutic potential to treat neuroinflammatory diseases.
- UCM1341 is a dual-acting compound with FAAH inhibitory action and agonist activity on melatonin receptors.[3]
- Aim: to evaluate the protective effects of UCM1341 against neuroinflammation-induced degeneration.[4]

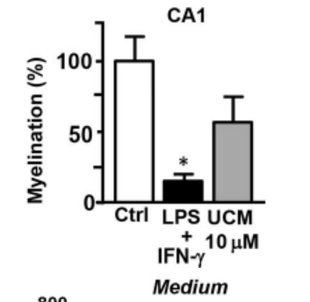


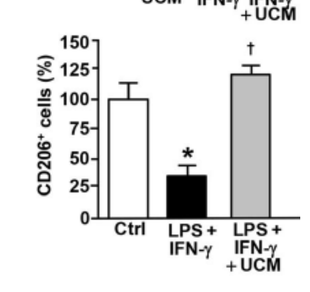


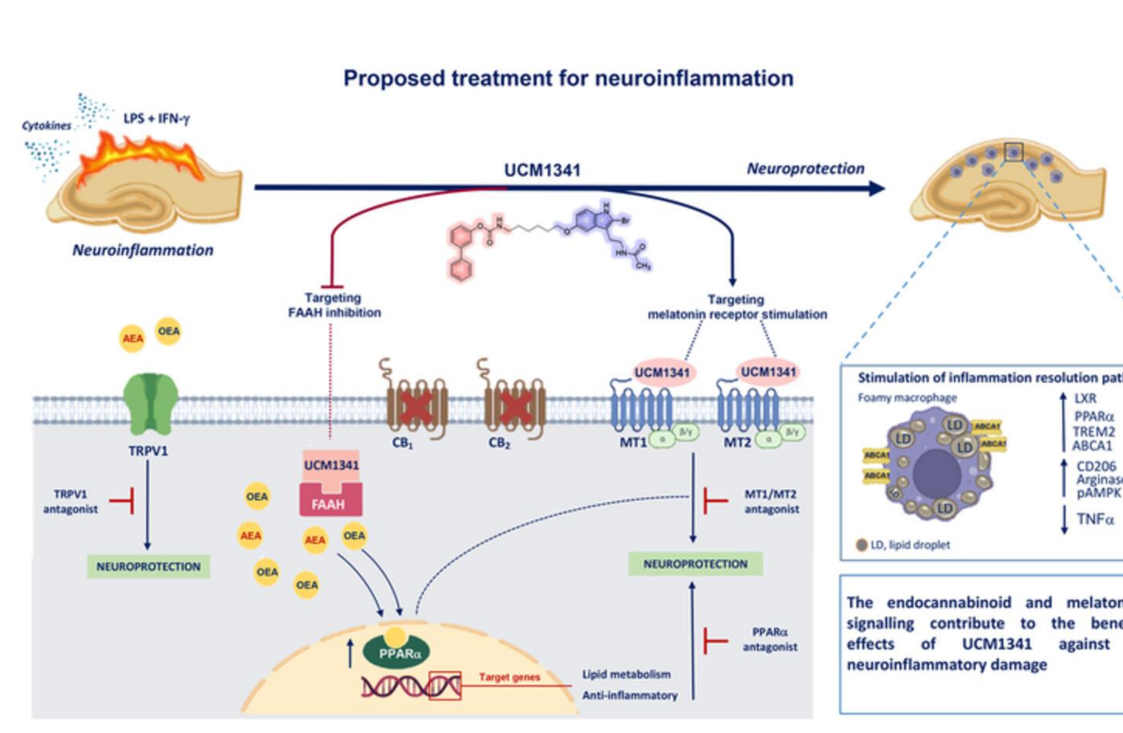






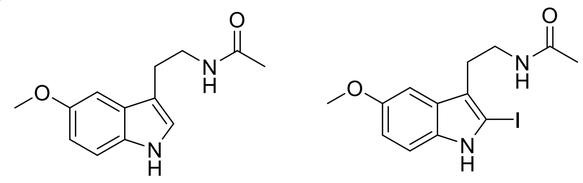






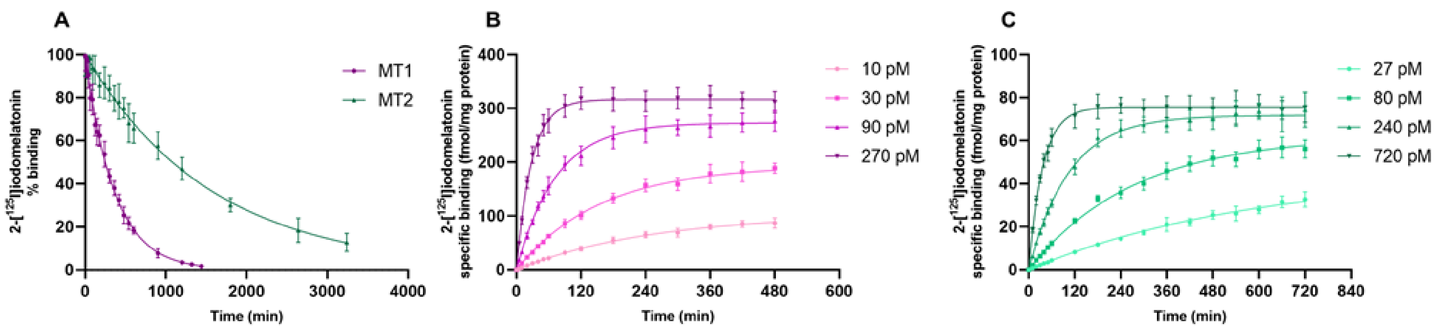
Unbinding simulations of 2-iodomelatonin from MT_1 and MT_2 receptors

- Determination of ligand binding affinity to melatonin receptors relies on displacement binding assays with the radioligand 2-[^{125}I]iodomelatonin (2-[^{125}I]IMLT) which is characterized by slow dissociation rate.
- Aim: to evaluate the impact of the slow dissociation of 2-[^{125}I]IMLT on K_i values obtained for ligands in standard experimental conditions;
  to provide a mechanistic explanation of the different dissociation half-life observed for 2-iodomelatonin.[5]



melatonin
pK_i (MT_1) = 9.65
pK_i (MT_2) = 9.27

2-iodomelatonin
pK_i (MT_1) = 10.71
pK_i (MT_2) = 9.83



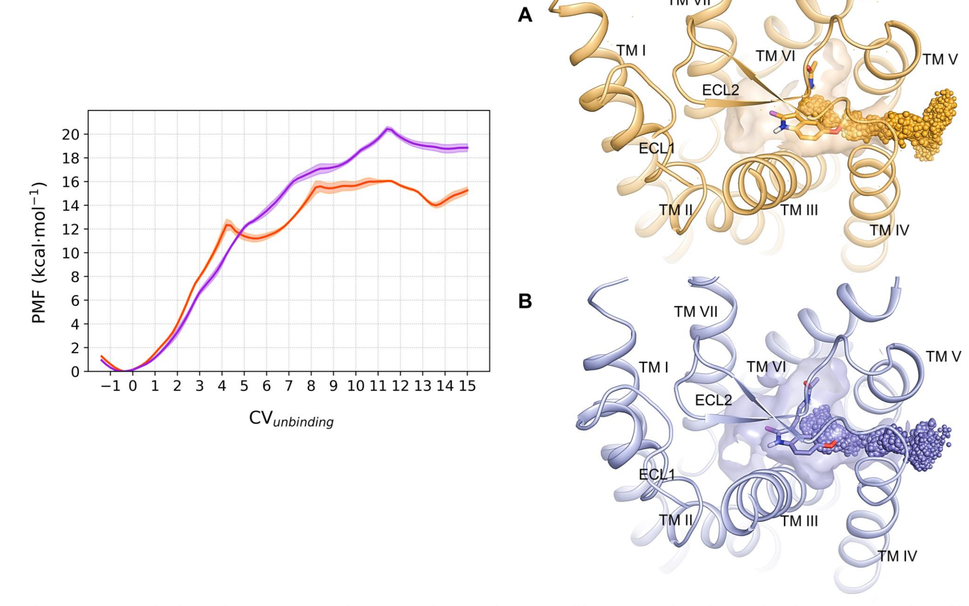
Dissociation curves (**A**) of 2-[^{125}I]IMLT for MT_1 and MT_2 receptors. Association curves of 2-[^{125}I]IMLT for MT_1 (**B**) and MT_2 (**C**) receptors.

	k_{on} (M^{-1} min^{-1})	k_{off} (min^{-1})	Dissociation $t_{1/2}$ (min)
MT_1	1.2 ± 0.1 x 10^8	0.0028 ± 0.0002	248 ± 20
MT_2	3.7 ± 0.3 x 10^7	0.000639 ± 0.000054	1085 ± 98

Receptor	Incubation time	K_D (pM)	Bmax (fmol mg^{-1} protein)
MT_1	2 h	26 ± 2	342 ± 26
MT_1	20 h	19 ± 2	329 ± 31
MT_2	2 h	78 ± 5	76 ± 7
MT_2	20 h	65 ± 4	74 ± 6

Results

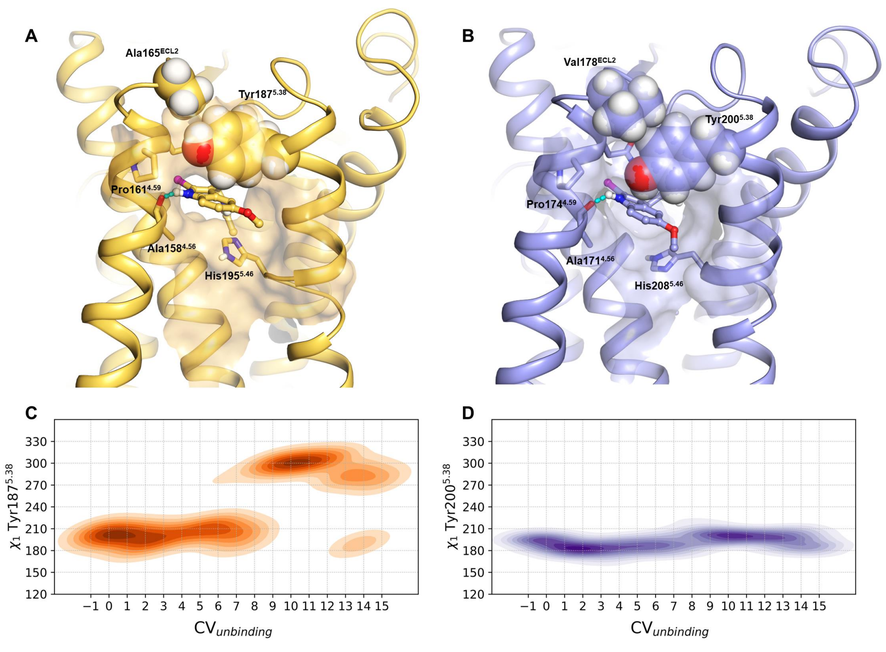
- Incubation time affected only weakly the binding affinity constants.
- Structure-activity relationships are conserved when binding data are collected at shorter incubation times.



Left: potential of mean force (PMF) profiles calculated from umbrella sampling simulations for 2-iodomelatonin unbinding from the MT_1 (red) and MT_2 receptor (purple). Right: the unbinding pathway of 2-iodomelatonin at the MT_1 (A, orange) and MT_2 (B, purple) receptor is represented through the position of the center of mass of the ligand.

Results

- Energy barriers consistent with the longer dissociation half-life at the MT_2 receptor.
- Restricted mobility of a gatekeeper tyrosine along a lipophilic path at the MT_2 receptor.



Top: 2-Iodomelatonin unbinding from the MT_1 (**A**) and MT_2 (**B**) receptors (snapshot corresponding to CV_{unb} =6 Å). Bottom: density estimation plots showing χ1 dihedral angle of Tyr187/200$^{5.38}$ in US simulations at the MT_1 (**C**) and MT_2 (**D**) receptors (χ1~180°, closed conformation; χ1~300°, open conformation).

References

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