PB-03

SR144528 as Inverse Agonist of CB2 Cannabinoid Receptor

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We examined the role of SR 144528 (N-[-(1S-endo-1,3,,3-trimethyl-bicyclo[2, 2, 1] heptan-2-yl]-5-(-4-chloro-3-methyl-phenyl)-(4-methylbenzyl)-pyrazole-3-carboxamide) in the modulation of certain AC isoforms in transiently transfected COS-7 cells. We found that CB2 in COS cells has a constitutive activity, and thus leading to inhibition of AC-V activity even in the absence of agonist. In addition, this constitutive modulation of AC is reversed by SR144528.

It is now well established that several G protein-coupled receptors can signal without agonist stimulation(constitutive receptors). Inverse agonists have been shown to inhibit the activity of such constitutive G protein-coupled receptor signaling.

Agonist activation of the $G_{i/o}$-coupled peripheral cannabinoid receptor CB2 normally inhibits adenylyl cyclase type V and stimulates adenylyl cyclase type II. Using transfected COS cells, we show here that application of SR144528, an inverse agonist of CB2, leads to a reverse action (stimulation of adenylyl cyclase V and inhibition of adenylyl cyclase II).

This inverse agonism of SR144528 is dependent on the temperature, as well as on the concentration of the cDNA of CB2 transfected. Pertussis toxin blocked the regulation of adenylyl cyclase activity by SR 144528.

Key Words) ***Cannabinoids, CB2 cannabinoid receptor, SR144528, Inverse agonism, G protein Adenylyl cyclase.***