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An entourage effect: inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity.

Ben-Shabat S[1], Fride E, Sheskin T, Tamiri T, Rhee MH, Vogel Z, Bisogno T, De Petrocellis L, Di Marzo V, Mechoulam R.

Author information

Abstract

2-Arachidonoyl-glycerol (2-Ara-Gl) has been isolated from various tissues and identified as an endogenous ligand for both cannabinoid receptors, CB1 and CB2. Here we report that in spleen, as in brain and gut, 2-Ara-Gl is accompanied by several 2-acyl-glycerol esters, two major ones being 2-linoleoyl-glycerol (2-Lino-Gl) and 2-palmitoyl-glycerol (2-Palm-Gl). These two esters do not bind to the cannabinoid receptors, nor do they inhibit adenylyl cyclase via either CB1 or CB2; however, they significantly potentiate the apparent binding of 2-Ara-Gl and its apparent capacity to inhibit adenylyl cyclase. Together these esters also significantly potentiate 2-Ara-Gl inhibition of motor behavior, immobility on a ring, analgesia on a hot plate and hypothermia caused by 2-Ara-Gl in mice. 2-Lino-Gl, but not 2-Palm-Gl, significantly inhibits the inactivation of 2-Ara-Gl by neuronal and basophilic cells. These data indicate that the biological activity of 2-Ara-Gl can be increased by related, endogenous 2-acyl-glycerols, which alone show no significant activity in any of the tests employed. This effect ('entourage effect') may represent a novel route for molecular regulation of endogenous cannabinoid activity.