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Endocannabinoid Signaling Regulates Sleep Stability.

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Abstract

The hypnogenic properties of cannabis have been recognized for centuries, but endogenous cannabinoid (endocannabinoid) regulation of vigilance states is poorly characterized. We report findings from a series of experiments in mice measuring sleep with polysomnography after various systemic pharmacological manipulations of the endocannabinoid system. Rapid, unbiased scoring of vigilance states was achieved using an automated algorithm that we devised and validated. Increasing endocannabinoid tone with a selective inhibitor of monoacyglycerol lipase (JZL184) or fatty acid amide hydrolase (AM3506) produced a transient increase in non-rapid eye movement (NREM) sleep due to an augmentation of the length of NREM bouts (NREM stability). Similarly, direct activation of type 1 cannabinoid (CB1) receptors with CP47,497 increased NREM stability, but both CP47,497 and JZL184 had a secondary effect that reduced NREM sleep time and stability. This secondary response to these drugs was similar to the early effect of CB1 blockade with the antagonist/inverse agonist AM281, which fragmented NREM sleep. The magnitude of the effects produced by JZL184 and AM281 were dependent on the time of day this drug was administered. While activation of CB1 resulted in only a slight reduction in gamma power, CB1 blockade had dramatic effects on broadband power in the EEG, particularly at low frequencies. However, CB1 blockade did not significantly reduce the rebound in NREM sleep following total sleep deprivation. These results support the hypothesis that endocannabinoid signaling through CB1 is necessary for NREM stability but it is not necessary for sleep homeostasis.

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