Epibatidine

Epibatidine is a putative alkaloid that is secreted by the Ecuadoran frog Epipedobates anthonyi.

It was discovered by John W. Daly in 1974, but its structure was not fully elucidated until 1992. Whether epibatidine is the first observed example of a chlorinated alkaloid remains controversial, due to challenges in conclusively identifying the compound from the limited samples collected by Daly. By the time that high-resolution spectrometry was used in 1991, there remained less than one milligram of extract from Daily's samples, raising concerns about possible contamination. Samples from other batches of the same species of frog failed to yield epibatidine.

Epibatidine is toxic. Its toxicity stems from its ability to interact with nicotinic and muscarinic acetylcholine receptors. These receptors are involved in the transmission of painful sensations, and in movement, among other functions. Epibatidine then causes numbness, and, eventually, paralysis. Doses are lethal when the paralysis causes respiratory arrest. Originally, it was thought that epibatidine could be useful as a drug. However, because it can be deadly even at very low doses, it is no longer being researched for potential therapeutic uses.

Results suggest a possibility that a brain endocannabinoid, probably 2-AG, plays an inhibitory role in (±)-epibatidine-induced activation of central adrenomedullary outflow through brain CB1 receptors in the rat [1)].

Receptor autoradiography shows a reduction in number of epibatidine binding sites following capsaicin treatment. The reduction is particularly marked in the dorsal horn and primarily affects the class of high affinity epibatidine binding sites thought to modulate nociceptive responses. Accompanying the loss of terminals and nicotinic binding sites were significant reductions in the expression of alpha 3, alpha 4, alpha 5, beta 2 and beta 4 nicotinic receptor subunits in the superficial layers of the spinal cord as determined by antibody staining and confocal microscopy. The loss of nicotinic receptors that follows capsaicin treatment results in attenuation of the nociceptive responses to both spinal cytisine and epibatidine. Capsaicin treatment also diminishes the capacity of cytisine to desensitize nicotinic receptors mediating nociception, but it shows little effect on intrathecal nicotinic agonist elicited pressor and heart rate responses. Hence, our data suggest that alpha 3, alpha 4, alpha 5, beta 2 and beta 4 subunits of nicotinic receptors are localized in the spinal cord on primary afferent terminals that mediate nociceptive input. A variety of convergent data based on functional studies and subunit expression suggest that alpha 3 and alpha 4, in combination with beta 2 and alpha 5 subunits, form the majority of functional nicotinic receptors on C-fiber primary afferent terminals. Conversely, spinal nicotinic receptors not located on C-fibers play a primary role in the spinal pathways evoking spinally coordinated autonomic cardiovascular responses [2)].

1)

Shimizu T, Tanaka K, Shimizu S, Higashi Y, Yawata T, Nakamura K, Taniuchi K, Ueba T, Yuri K, Saito M. Possible inhibitory role of endogenous 2-arachidonoylglycerol as an endocannabinoid in (±)-epibatidine-induced activation of central adrenomedullary outflow in the rat. Neuropharmacology. 2015 Aug;95:278-89. doi: 10.1016/j.neuropharm.2015.03.034. Epub 2015 Apr 14. PubMed PMID: 25882827.

2)

Khan IM, Wennerholm M, Singletary E, Polston K, Zhang L, Deerinck T, Yaksh TL, Taylor P. Ablation of primary afferent terminals reduces nicotinic receptor expression and the nociceptive responses to nicotinic agonists in the spinal cord. J Neurocytol. 2004 Sep;33(5):543-56. PubMed PMID: 15906161.