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Actions of octocoral and tobacco cembranoids on nicotinic receptors

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ABSTRACT

Nicotinic acetylcholine receptors (AChRs) are pentameric proteins that form agonist-gated cation channels through the plasma membrane. AChR agonists and antagonists are potential candidates for the treatment of neurodegenerative diseases. Cembranoids are naturally occurring diterpenoids that contain a 14-carbon ring. These diterpenoids interact with AChRs in complex ways: as irreversible inhibitors at the agonist sites, as noncompetitive inhibitors, or as positive modulators, but no cembranoid was ever shown to have agonistic activity on AChRs. The cembranoid eupalmerin acetate displays positive modulation of agonist-induced currents in the muscle-type AChR and in the related gamma-aminobutyric acid (GABA) type A receptor. Moreover, cembranoids display important biological effects, many of them mediated by nicotinic receptors. Cembranoids from tobacco are neuroprotective through a nicotinic anti-apoptotic mechanism preventing excitotoxic neuronal death which in part could result from anti-inflammatory properties of cembranoids. Moreover, tobacco cembranoids also have anti-inflammatory properties which could enhance their neuroprotective properties. Cembranoids from tobacco affect nicotine-related behavior: they increase the transient initial ataxia caused by first nicotine injection into naive rats and inhibit the expression of locomotor sensitization to repeated injections of nicotine. In addition, cembranoids are known to act as anti-tumor compounds. In conclusion, cembranoids provide a promising source of lead drugs for many clinical areas, including neuroprotection, smoking-cessation, and anti-cancer therapies.

1. Introduction

The octocorals are a subclass of anthozoans that feature polyps with eight-fold symmetry. The octocorallia currently include 3 orders, 45 families and close to 4000 estimated species. The order *Alcyonacea* is the most abundant and contains about two-thirds of the octocoral families. *Alcyonacea* include the so-called "soft" corals and two suborders of sea fans or "gorgonians". The octocorals are ideal organisms to search for bioactive metabolites that could be used by them for chemical defense. Octocorals are immobile, apparently defenseless organisms without the rigid carbonate skeletons that protect their cousins, the scleractinian or "hard" corals. Therefore, without chemical defenses the octocorals would seem to be easy nutrient sources for marine predators. In addition, some octocorals are brightly colored. In the words of the biologist Edward O. Wilson: "…if a small and otherwise unknown organism is strikingly beautiful, it is probably poisonous; and if it is not only beautiful, but also easy to catch, it is probably deadly" (Wilson, 2003). The role of octocoral secondary metabolites in defensive mechanisms has been documented (Sammarco and Coll, 1992). Among these metabolites are many examples of terpenoids. This review will limit itself to a subgroup of diterpenoids known as cembranoids.

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Cembranoids are diterpenoids that contain a 14-carbon or "cembrane" ring that has varying degrees of oxygenation (Fig. 1). More than 300 naturally occurring cembranoids have been described (Wahlberg and Eklund, 1992). Although cembranoids have been isolated from plants, including tobacco, insects and even vertebrates, marine invertebrates have been, by far, the richest source of cembranoids. Most of these compounds have been isolated from Caribbean or Pacific gorgonians in which cembranoids comprise up to 25% of their identified secondary metabolites (Rodríguez, 2001). The occurrence of cembranoids in octocorals was discovered nearly 50 years ago by the Ciereszko lab (Ciereszko et al., 1960), where they successfully isolated and characterized eunicin (Fig. 1) from the Caribbean gorgonian *Eunicea mammosa*.

Nicotinic acetylcholine receptors (AChRs) are pentameric transmembrane proteins that form agonist-gated cation channels through the plasma membrane (Karlin, 2002). They are members of the ligand-gated ion channel superfamily that also includes gamma-aminobutyric acid (GABA) type A, glycine and serotonin (5HT) type 3 receptors. Each AChR subunit features a large extracellular N-terminal segment followed by 4 transmembrane segments, M1–M4, with M2 lining the transmembrane ion channel. The large extracellular segments form the agonist sites at their subunit interfaces where agonists and competitive antagonists bind. Noncompetitive AChR antagonists bind outside the agonist cavity thereby and prevent conformational changes of the protein necessary for channel opening.

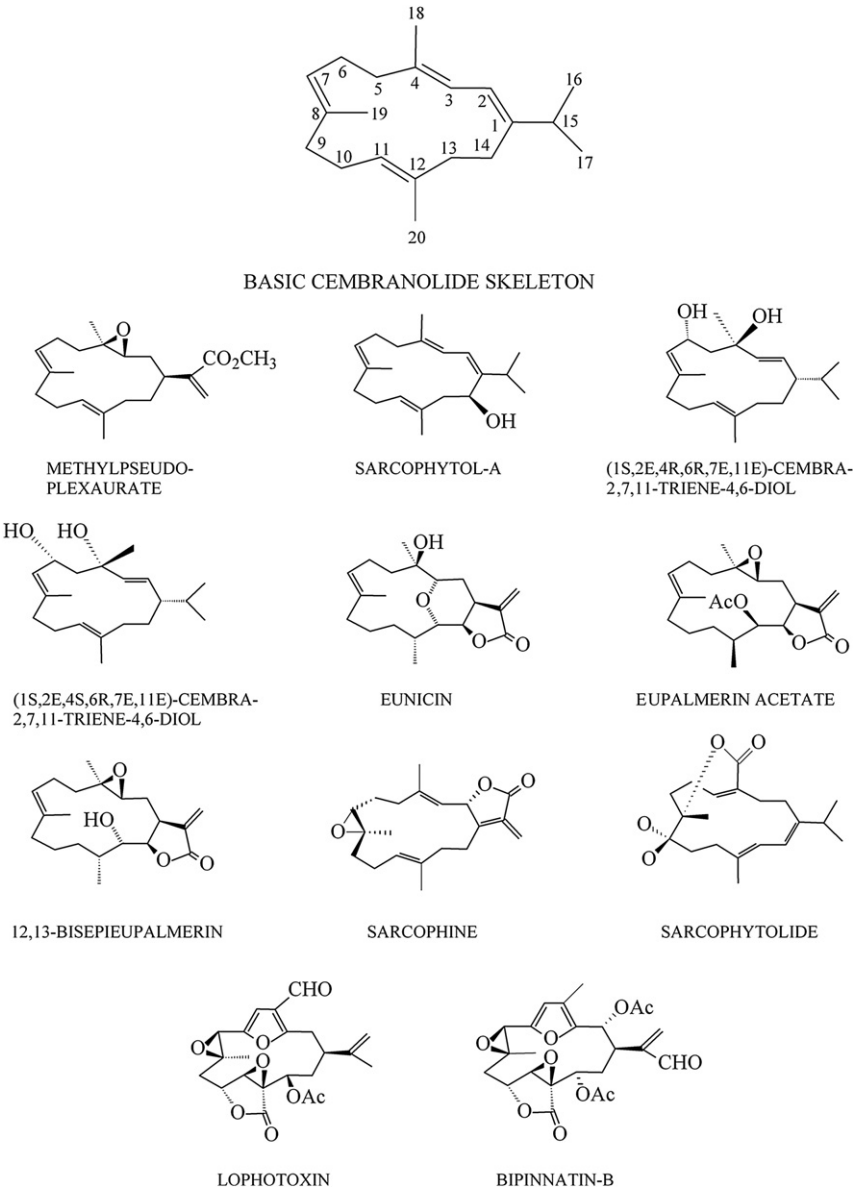

Fig. 1. Cembranoid structures.