Marine Cyanobacterial Fatty Acid Amides Acting on Cannabinoid Receptors

R. Montaser (UF, Medicinal Chemistry); V. J. Paul (Smithsonian Marine Station); H. Luesch (UF, Medicinal Chemistry)

Introduction

The endocannabinoid system is represented by two G-protein coupled cannabinoid receptors CB_1 and CB_2 and their endogenous lipid ligands known as the endocannabinoids. Importantly, this system has been implicated in various pathophysiologies, including neurodegenerative diseases, eating disorders, pain, inflammation and cancer. Therefore, a better understanding of this system has become of significant interest, and the cannabinoid receptors have been viewed as possible targets for different diseases. Anandamide (*N*-arachidonoyl-ethanolamine) was the first endogenous ligand to be identified among the endocannabinoid family. Influenced by its structure, the discovery of this fatty acid amide suggested that other natural and synthetic fatty acid amides might function as cannabinoid receptor ligands as well. In that context, marine cyanobacteria of the genus *Lyngbya* have a characteristic metabolic profile that is rich in fatty acid amides (in addition to peptides), and therefore represent a potential source of new model compounds acting on the cannabinoid receptors. Exploring a *Lyngbya* sample from Piti Bomb Holes from Guam led us to isolate and characterize the new fatty acid amide serinolamide B, a closely related analogue to the recently reported cannabimimetic lipid serinolamide A. We evaluated the ability of serinolamide B to bind to both human cannabinoid receptors CB_1 and CB_2 with a functional outcome.

Experimental

^{1}H and 2D NMR spectra were recorded on a Bruker Avance II spectrometer (600 MHz, 5 mm TXI cryogenic probe).

Results and Discussion

A population of the cyanobacterium *Lyngbya majuscula* from Piti Bomb Holes from Guam was extracted with organic solvents. This organic extract was subjected to solvent partitioning followed by NMR-guided fractionation using silica gel chromatography. Further purification of one silica fraction by reversed-phase HPLC yielded the new fatty acid amide serinolamide B. The planar structure was elucidated using 1D/2D NMR and MS experiments. The stereochemistry of the serinol derived moiety was established using oxidation and enantioselective HPLC-MS analysis. Serinolamide B can bind to both CB_1 and CB_2 receptors with moderate to weak binding affinities with higher selectivity to CB_2 (K_i = 5.2 μM) over CB_1 receptor (K_i = 16.4 μM). Additionally, serinolamide B was able to inhibit forskolin-stimulated cAMP accumulation through both CB_1 (EC_{50} = 11.8 μM) and CB_2 (EC_{50} = 1.8 μM) receptors with moderate potencies, which proves that this metabolite acts as cannabinoid receptor agonist. Intriguingly, serinolamide B appeared to be more CB_2 receptor selective in the binding as well as the functional assays.

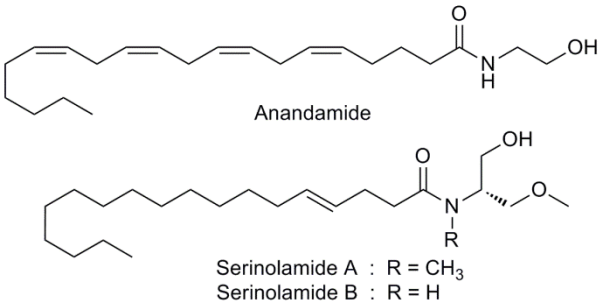

Figure. Structures of anandamide, serinolamide A and serinolamide B.

Conclusions

Marine cyanobacteria continue to be a prolific source of bioactive secondary metabolites with interesting biological activities.

Acknowledgements

National Institutes of Health, NIGMS Grant P41GM086210 and J. R. Rocca.

References

[1] Wenk, M. R., *Nat. Rev. Drug Discov.*, **4**, 594-610 (2005).
[2] Di Marzo, V., *Nat. Rev. Drug Discov.*, **7**, 438-455 (2008).
[3] Gutiérrez, M. *et al*., *J. Nat. Prod.*, **74**, 2313-2317 (2011).
[4] Montaser, R. *et al*., ChemBioChem, (2012).