Scale Up Isolation of Aaptamine for In Vivo Evaluation Indicates Its Neurobiological Activity is Linked to the Delta Opioid Receptor

Nicole L. McIntosh  
*Dominican University of California*

Eptisam Lambo  
*Dominican University of California*

Laura Millan-Lobo  
*University of California - San Francisco*

Fei Li  
*University of California - San Francisco*

Li He  
*University of California - San Francisco*

See next page for additional authors

Follow this and additional works at:  [https://scholar.dominican.edu/ug-student-posters](https://scholar.dominican.edu/ug-student-posters)

Part of the Analytical Chemistry Commons, Biochemistry Commons, Marine Biology Commons, and the Organic Chemistry Commons

Survey: Let us know how this paper benefits you.

Recommended Citation

McIntosh, Nicole L.; Lambo, Eptisam; Millan-Lobo, Laura; Li, Fei; He, Li; Crews, Phillip; Whistler, Jennifer L.; and Johnson, Tyler, "Scale Up Isolation of Aaptamine for In Vivo Evaluation Indicates Its Neurobiological Activity is Linked to the Delta Opioid Receptor" (2015). *Student Research Posters*. 9.  
[https://scholar.dominican.edu/ug-student-posters/9](https://scholar.dominican.edu/ug-student-posters/9)

This Presentation is brought to you for free and open access by the The Dominican Experience at Dominican Scholar. It has been accepted for inclusion in Student Research Posters by an authorized administrator of Dominican Scholar. For more information, please contact michael.pujals@dominican.edu.
Authors
Nicole L. McIntosh, Eptisam Lambo, Laura Millan-Lobo, Fei Li, Li He, Phillip Crews, Jennifer L. Whistler, and Tyler Johnson
Scale up isolation of aaptamine for in vivo evaluation indicates its neurobiological activity is linked to the delta opioid receptor

Eptisam Lambo†, Nicole L. McIntosh†, Laura Millan-Lobo3, Fei Li3, Li-He3, Phillip Crews2, Jennifer L. Whistler3 and Tyler A. Johnson1,2

1Department of Natural Sciences & Mathematics, Dominican University of California
2Department of Chemistry & Biochemistry, University of California, Santa Cruz
3Department of Neurology, University of California, San Francisco

†These authors contributed equally to this work

Introduction

Opioid receptors belong to the large superfamily of seven transmembrane spanning (7TM) G protein-coupled receptors (GPCRs). As a class, GPCRs are of fundamental physiological importance mediating the actions of the majority of known neurotransmitters and hormones. The Mu, Delta and Kappa (MOR, DOR, KOR) opioid receptors are particularly intriguing members of this receptor family as they are the targets involved in many neurobiological diseases such as addiction, pain, stress, anxiety, and depression. To date few marine natural products have been investigated for their neurobiological activities.1

One noteworthy example involves ziconotide (1) from the cone snail Conus magnus.2 Compound 1 was the first marine natural product approved by the FDA and is used for the treatment of pain, marketed under the trade name Prialt® (2004).3 More recently Hamman reported that aaptamine (2) is the first marine natural product to show in vivo antidepressant activity; however no mechanism of action was proposed.4 During a separate collaborative screening project we profiled 96 sponge-derived extracts and discovered demethyl-aaptamine (3) and demethyl (oxy) – aaptamine (4) were selective DOR agonists as shown in Figure 1. We speculated that the in vivo activity for 2 could thus be linked to the DOR target and to test this hypothesis we conducted the following experiments below.

Experimental and Results

Our first step involved obtaining a source of aaptamine (2) for in vitro and in vivo evaluation. Compounds 3-4 were obtained from the sponge Aaptos aaptos (coll. no. 92553) but were devoid of 2. LC-MS analysis of sponge coll. no. 11308 (A. aaptos) indicated m/z ions of 229 [M+H]+ consistent with that of 2 (not shown). We extracted coll. no. 11308 using a partition scheme shown in Figure 2. The WB extract was enriched with 2 based on LC-MS data in Figure 3a and used to scale up its isolation by HPLC shown in Figure 3b. Chemical validation of pure 2 was confirmed by LC-MS and 1H NMR data in Figure 4. This allowed us to screen 2 alongside 3 and confirm its DOR activity in vitro. In vivo evaluation indicated 2 was an antidepressant in wild type mice in the forced swim test (Figure 5a, black bars) while having no effect on general locomotion (Figure 5b). We further found that the antidepressant activity was abolished in genetically modified mice where the DOR gene was knocked out (Figure 5c).

Conclusions

1) Scale up isolation of aaptamine (2) is best achieved through purification of water soluble extracts.
2) The mechanism of action for the in vivo anti-depressant-like and anxiolytic-like activity of 2 is mediated by it’s activity on the delta opioid receptor (DOR).
3) These data suggest that 2 can represent a novel chemical scaffold for the development of new DOR ligands in neurobiological research.

Acknowledgements

Financial support was provided by NIH grants RO1 CA 47135 (PC), RO1 AA 020401 (JW), International Cooperative Biodiversity Group (ICBG) grant 1191TW000160 (JW, TJ), and by the Fletcher Jones Endowment Fund of Dominican University of California (TJ).

References

1. Lambo, E; McIntosh, N; Millan-Lobo, L; Li, F; He, L; Crews, P; Johnson, T; Forster, S; Whistler, J; Rodriguez, A; Hamman, J; El-Alfy, A; Matsumoto, R; Harno, M; Hamann, M; Stoker, J; Hamann, M. Chemical diversity of marine invertebrates from the Philippines: Preclinical evaluation of a marine sponge extract for in vivo antidepressant activity. Phytomedicine 2009, 16, 101-107.