The Effects of Ayahuasca on the Neural Proliferation and Maturation

Riba J, Morales-García J, Rodriguez-Franco MI, Pérez-Castillo A, de la Fuente Revenga M, Feilding A. *Manuscript In Preparation*

Beckley / Sant Pau Research Programme

What is this study about?

This is the first study to examine the effects of ayahuasca, a psychedelic beverage from the Amazon, on neurogenesis – the birth of new brain cells. Ayahuasca is made with plants containing DMT (a classical psychedelic compound) and beta-carbolines, such as harmine, harmaline and tetrahydroharmine (monoamine oxidase inhibitors making DMT orally active).

What did we do?

- Neural stem cells (NSC) were extracted from the hippocampus and lateral ventricles of adult mice.
- NSC were induced to proliferate into neurospheres (clusters of NSC)
- 1 µM test compounds were added: saline (control); harmine; tetrahydroharmine; harmaline; and harmol
- Assessed the capacity of compounds to promote:
  - Early stages of Neurogenesis (**young neurons**): TuJ1 staining (**green**)
  - Neuronal Maturation (**mature neurons**): MAP-2 staining (**red**)

Why did we do this study?

- Experimental evidence since the late 1990's has challenged the old 'immutable brain' paradigm by showing that neurogenesis occurs in the hippocampus and around the ventricles of the adult mammal brain.
- The hippocampus plays a key role in important cognitive tasks such as learning and memory. Its function declines with the normal aging process, and more dramatically so in certain neurodegenerative disorders such as Alzheimer's disease.
- **We wanted to know: Do the components of ayahuasca have an effect on neurogenesis?**

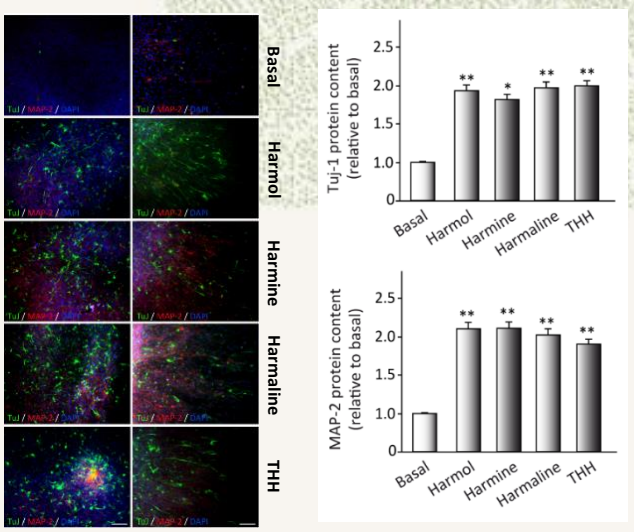
About the research team

Amanda Feilding is the Founder and Director of the Beckley Foundation. She and Jordi Riba are Co-Directors of the Beckley/Sant Pau Research Programme. The study has been done in collaboration with researchers from the Spanish National Research Council (CSIC): Jose Morales-García, María Isabel Rodriguez-Franco, Ana Pérez-Castillo and Mario de la Fuente Revenga.

What did we find?

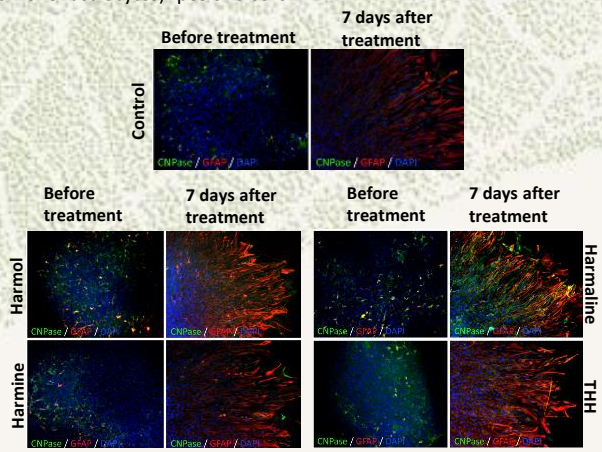
Effects of treatment with β-carbolines on neurospheres

1. Reduced expression of proteins that are markers of "stemness" of cultured neurospheres: musashi-1, nestin and SOX-2, indicating that the β-carbolines led the NSC to **lose their undifferentiated state**.
2. Increased number of Ki67- (marker of dividing cells) and PCNA- (marker of proliferation) positive cells, indicating a direct effect of these compounds on **proliferation**.
3. Increased **migration** capacity; neural stem cells moved long distances out of the neurosphere body in the presence of the β-carbolines, while cells in the control cultures remained close to the neurosphere core.



4. Increased the number of Tuj1- and MAP-2-positive cells, indicating **differentiation** of neural stem cells into mature neurons (illustrated in figures above).

5. Harmol- and harmaline-treated cultures increased the differentiation of neural precursors towards an oligodendrocyte phenotype, as shown by some scattered **CNPase** (marker of oligodendrocytes)- positive cells (illustrated in figures below); all β-carbolines increased differentiation into astroglial cells or astrocyte-like radial cells, as shown by an increase in the number of **GFAP** (marker of astrocytes)- positive cells.



Conclusion: We found that major alkaloids in ayahuasca – harmol, harmine, harmaline, and tetrahydroharmine – have potent neurogenic properties. The addition of these β-carbolines to cultures containing neural stem cells dramatically increased the stem cells' proliferation, migration, differentiation, and maturation into neurons.

What is coming next?

We plan to replicate these experiments in vivo (in animal models).

Why is this important?

- The replication of the present findings in vivo would open a **new avenue of research** for ayahuasca and its active principles.
- **Potential applications** could range from treating brain damage associated with stroke or trauma to psychiatric and neurodegenerative disorders like Alzheimer's and Parkinson's disease.

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