Oxytocin-Cannabinoids Cross-Talk in the Social Gut-Brain-Axis

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Rationale & Hypothesis

The "**social brain**" refers to a network involved in social processes, where the prefrontal cortex (PFC) is considered to orchestrate a top-down control over social cognitive functions, including the ability to perceive, process and react to different affective states in others. This emotion recognition ability has profound implications in the everyday life of all social animals. Recently, knowledge concerning the complexity and size of the **gut microbiome** (the trillions of microorganisms within our intestine) has resulted in multiple associations linking the microbiome to health and disease, including diseases affecting the brain. The bidirectional communication between the central nervous system and gut microbiota, referred to as the gut-brain-axis, has increasingly been suggested to be an important factor in regulating brain and behavior. However, the involvement of the gut-brain communications in the context of social processes remains poorly understood.

Here, we propose to capitalize on a series of new findings that suggest a cross-talk between the **oxytocin** (OXT) and **cannabinoid** (CB) systems in social information processing and immune responses. OXT-related compounds are under intense scrutiny as potential pro-social drugs in immune-related neurodevelopmental disorders, whilst cannabinoid compounds (including marijuana), promote anti-inflammatory effects, but also increased vulnerability to social and psychiatric disorders. Given their therapeutic potential, and increasing recreational usage (CB), it is important to understand the network of mechanisms through which they elicit responses, including via immune/microbiota modulation. We will therefore follow a multi-disciplinary approach to disentangle how OXT and CB interaction influences social processes *in vivo*, through modulation of the gut-brain axis.

Aims:

1. We will characterize the effects of exogenous OXT and/or CB compounds on the microbiome composition and its relationship to their social effects. Specifically, we will try to understand the nature and directionality of the molecular messages (e.g. host vs microbial origin) by exploring how selective gnotobiotics manipulations might influence social processes in response to OXT and/or CB.

2. Immune responses within the brain are mainly mediated and modulated by glial cells like microglia and astrocytes. Here, we will investigate how selective manipulations of OXT-CB systems in microglia or astrocytes within the PFC can modulate microbiome and social processes. This will dissect the hierarchy of responses to OXT and/or CB.

Significance & Impact:

This collaborative project will explore new scientific paths related to the modulation of social processes by the gut-brain axis, with potential broad implications for life sciences and health.

Integration of Expertise of Partners:

The candidate will benefit of the integration of knowledge and approaches in the 3 partner laboratories. Francesco Papaleo (IIT) will contribute access to genetically modified mice, behavioral characterizations, in vivo mechanistic manipulations, providing fecal samples following pharmacological and brain manipulations. Rob Finn (EMBL-EBI) will provide the informatics capacity to characterize the mouse gut microbiota, and contextualize the functional and taxonomic repertoire against the human microbiome. Jamie Hackett (EMBL-Rome) will contribute access to gnotobiotic facilities for mechanistic studies into microbiota role, and multi-omics expertise (e.g. transcriptomics, metabolomics) for host characterization.