HA-Ction: Hypothalamic histaminergic modulation of brain regions involved in fear memory

Main area: Subcortical structures: from cognition to action
Keywords: amygdala; hypothalamus; cortical loop
Duration: 36 months
Total project funding: € 549.969

Abstract

Memory determines the uniqueness of our personal history, and is decisive for each individual to survive and prosper. It is a multistate process that includes consolidation and retrieval. Impairment of memory processing may result in intrusive ideation, triggering maladaptive responses that are key symptoms of psychiatric disorders such as generalized anxiety, obsessive-compulsive disorders, post-traumatic stress disorder and phobias. Insights leading to better treatments of these diseases can be gained by understanding the neurobiology of emotional memory. Several neurotransmitters contribute to memory formation and in particular, the integrity of the hypothalamic histamine (HA) system is necessary for the different phases of emotional memory formation and retrieval. HA neurons are organized into functionally distinct circuits, display selective control mechanisms and impinge on different brain regions involved in memory, including amygdala, prefrontal cortex and hippocampus. HA neurotransmission is critical to provide the brain with the plasticity necessary to store and retrieve memories through recruitment of alternative circuits. Despite the extensive literature reporting the importance of brain HA in learning and memory, a detailed map of HA pathways that are activated at different time points during memory formation and retrieval is currently not available. HA-CTion aims at elucidating how brain HA networks and selected ligands of HA receptors modulate emotional memory formation. The project poses particular emphasis on H1 receptor (H1R) ligands, as antagonists of this receptor are among the most used drugs worldwide, and on new H3R compounds. These ligands have memory impairing or memory enhancing effects that could be exploited to modulate emotional memory processing. In this respect, animals are crucial to bridge the translational gap between preclinical and clinical research, as the basic architecture of emotional memory and its mechanisms are conserved across species. HA-CTion will use a validated preclinical model, the inhibitory avoidance test, to establish a strong emotional memory in mice. HA-CTion will analyse the architecture and function of circuits that link hypothalamic HA neurons to its target neurons (e.g., in the cortex, hippocampus or amygdala) implicated in the processing of emotional memory consolidation and retrieval. The proposal is built on close cooperative actions of 4 partners from 3 EU countries. The combined use of new neuroanatomical, chemogenetic and photo-pharmacological tools will uncover previously unidentified HA brain circuitries and mechanisms involved in emotional memory consolidation and retrieval with unprecedented temporal and spatial resolution. HA-Ction will provide experimentally testable hypotheses to guide future research in humans, offering possible targets for a novel pharmacotherapy to treat dysfunctional aversive memories and increase the efficacy of exposure psychotherapies.

Consortium

Beatrice Passani – Universitá di Firenze –Italy – Funded by: MIUR
Ludovico Silvestri – Laboratorio Europeo di Spettroscopie Non-lineari – Italy – Funded by: With own funds
Guillaume Ferreira – Nutrition et Neurobiologie intégrée – France – Funded by: ANR
Rob Leurs – Vrije Universiteit Amsterdam – The Netherlands – Funded by: NWO