BRAIN HISTAMINE IS ESSENTIAL FOR LONG-TERM BUT NOT SHORT-TERM SOCIAL MEMORY

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Background and aim: Histamine neurons are a phylogenetically old group of cells localized in the tuberomamillary nucleus (TMN) of the posterior hypothalamus sending broad projections organized in distinct circuits impinging on different brain regions. Within these neurons, histamine is synthesized from the amino acid histidine through oxidative decarboxylation by histidine decarboxylase (HDC). So far, four different histaminergic receptors have been identified and among these the histamine H3receptor (H3R) is largely confined to the nervous system where it acts as an autoreceptor to restricts histamine synthesis and release, and as a heteroreceptor modulating the release of several other neurotransmitters. Neuronal histamine by activating its specific receptors is involved in the regulation of autonomic functions (e.g. energy balance, sleep, body temperature) and is crucial in controlling arousal and cognition. Evidence provided by us and others indicates that brain histamine plays a fundamental role in different phases of the mnemonic process in several behavioural paradigms. In this study we investigated whether the central histaminergic system was involved in sociability as well as short and long-term social recognition memory.

Materials and methods: Normal and histamine-deficient adult male mice were used. Reduction of brain histamine levels was achieved using three different approaches: (i) mice lacking the HDC gene ($HDC^{-/-}$); (ii) injection of the HDC inhibitor alpha-fluoromethylhistidine (α-FMH, i.c.v.) and (iii) administration of the brain permeant H_3receptor agonist VUF16839(5mg/kg, i.p). These mice and their respective controls were evaluated in the social discrimination paradigm. This task relies on the animal's innate tendency to explore a novel social stimulus with respect to a familiar, previously encountered congener. During training the subject is placed in an open field arena and time spent in the proximity of an empty wire cage or one containing a juvenile mouse was measured as an index of sociability. During the test, the experimental mouse was placed in the same arena and the time spent in the proximity of the familiar mouse or the cage containing a novel juvenile mouse was assessed. Retention tests were performed after 1h or 24h after training to evaluate short- and long-term memory, respectively.

Results: During the training session, both normal and histamine-deprived mice spent more time exploring the cage containing the juvenile social stimulus compared to the empty cage, indicating that the presence of an intact brain histaminergic system is not essential for animals' sociability. When the test session was performed 1h after the training (short-term memory), control animals spent more time exploring the novel mice with respect to the familiar one. Similar results were observed with mice genetically or pharmacologically unable to synthesize histamine. On the other hand, mice receiving injections of the H_3receptor agonist 1h before training did not discriminate between social stimuli. When the inter-trial interval was increased to 24h, control animals were still able to recognize the familiar stimulus, therefore spent more time exploring the new one. On the contrary, histamine-depleted (either $HDC^{-/-}$, or α-FMH-induced) mice spent similar amount of time exploring both social stimuli, indicating social memory impairment.

Conclusions: Although the integrity of the central histaminergic is apparently not required for the arousing effects caused by the presence of a social stimulus, brain histamine plays a pivotal role in social memory processing with a pronounced impact on long-term memory.