Neurobiology of Learning and Memory 145 (2017) 1–6

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Invited review

Histamine regulates memory consolidation

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ARTICLE INFO

Article history:
Received 22 April 2017
Revised 14 August 2017
Accepted 20 August 2017
Available online 23 August 2017

Keywords:
Histamine
Consolidation
Retrieval
Basolateral amygdala
Dorsal hippocampus

ABSTRACT

Recent findings have reasserted the role of histamine in the regulation of memory consolidation first proposed in 1986 in an inhibitory avoidance task in rats. They indicate that histamine is indeed a major regulator of memory consolidation in various tasks, through H2 receptors in the dorsal hippocampus and through H3 receptors in the basolateral amygdala, depending on the task. In the object recognition task, the memory enhancing effect is mediated by the three receptors (H1, H2, H3) in the dorsal hippocampus. In social recognition, the consolidation effect is mediated by H2 receptors in both amygdala and dorsal hippocampus. Data have suggested, in addition, influences on retrieval; this has been best studied in the dorsal hippocampus in step-down inhibitory avoidance task. Depending on the recent history of the conditioned stimulus (i.e., whether it has been recently reinforced or not), histamine acts on hippocampal H1 receptors, facilitating retrieval, or on H2 receptors, inhibiting it.

1. Early data suggesting a role for histamine in memory consolidation: inhibitory avoidance learning

Histamine is synthetized in neurons whose cell bodies are in the tuberomamillary nucleus of the hypothalamus (Panula, Yang, & Costa, 1984). These cells project to multiple brain areas involving different histamine receptor types, which suggests that histaminergic neurons are probably organized into functionally distinct circuits, impinging on different brain regions and displaying selective control mechanisms (Munari, Provensi, Passani, & Blandina, 2013). This could imply separate and independent functions of subsets of histamine neurons according to their respective origin and terminal projections (Blandina, Munari, Provensi, & Passani, 2012). Histaminergic fibers from the tuberomamillary nucleus projects to the septum/diagonal band nucleus (Wouterlood, Gaykema, Steinbusch, Watanabe, & Wada, 1988), and to the dorsal hippocampus and the basolateral amygdala, regions critically involved in memory consolidation and retrieval (Izquierdo, Furini, & Myskiw, 2016; Myskiw, Furini, & Izquierdo, 2016).

The first suggestion that histamine may play a role in memory consolidation was from Almeida and Izquierdo (de Almeida & Izquierdo, 1986) who showed that the immediate posttraining intracerebroventricular (i.c.v.) administration of 1–10 ng of the drug were found to enhance the retention of one-trial inhibitory avoidance in rats (Table 1). This was then (Gold, 1986) and probably still is now (Izquierdo et al., 2016), the task most widely used for studies of memory mechanisms, particularly memory consolidation (McGaugh, 2004, 2015). It relies on hippocampal CA1 long-term potentiation, as ascertained by measurement of cellular biochemical changes (Izquierdo et al., 2006) and by electrophysiological observations (Whitlock, Heynen, Shuler, & Bear, 2006; see Izquierdo et al., 2016) and is strongly modulated by the basolateral amygdala (McGaugh, 2004, 2015). The trace is stored in parallel in hippocampal CA1 and in basolateral amygdala (Fabbri et al., 2016; Izquierdo et al., 1992, 2016).

2. Generalization of the effects to other tasks, including extinction memory consolidation

In the thirty-one years that followed the original report on memory facilitation by i.c.v. histamine infusion, many authors

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http://dx.doi.org/10.1016/j.nlm.2017.08.007
1074-7427/

Table 1
Drugs that act on the histaminergic system and effect on memory.

Drug	Brain structure	Animal	Behavioral task	Effect on memory	Reference
Histamine	Lateral ventricle	Rats	One-trial inhibitory avoidance	Facilitates consolidation	de Almeida and Izquierdo (1986)
Histamine + Promethazine (H1 receptor antagonist)	Lateral ventricle	Rats	One-trial inhibitory avoidance	Prevent the histamine effect	de Almeida and Izquierdo (1986)
Histamine + Cimetidine (H1 receptor antagonist)	Lateral ventricle	Rats	One-trial inhibitory avoidance	Prevent the histamine effect	de Almeida and Izquierdo (1986)
Histamine	CA1 of hippocampus	Rats	One-trial inhibitory avoidance	Facilitates consolidation	Da Silva et al. (2006)
SKF-91488 (N-methyltransferase inhibitor)	CA1 of hippocampus	Rats	One-trial inhibitory avoidance	Facilitates consolidation	Da Silva et al. (2006)
Dimaprit (H2 receptor agonist)	CA1 of hippocampus	Rats	One-trial inhibitory avoidance	Facilitates consolidation	Da Silva et al. (2006)
Histamine + Ranitidine (H2 receptor antagonist)	CA1 of hippocampus	Rats	One-trial inhibitory avoidance	Prevents the histamine effect	Da Silva et al., 2006
SKF-91488 + Ranitidine (H2 receptor antagonist)	CA1 of hippocampus	Rats	One-trial inhibitory avoidance	Prevents the SKF-91844 effect	Da Silva et al. (2006)
Histamine	Basolateral amygdala	Rats	One-trial inhibitory avoidance	Facilitates consolidation	Benetti and Izquierdo (2013)
SKF-91488	Basolateral amygdala	Rats	One-trial inhibitory avoidance	Facilitates consolidation	Benetti and Izquierdo (2013)
SKF-91488 + Thioperamide (H3 receptor antagonist)	Basolateral amygdala	Rats	One-trial inhibitory avoidance	Prevents the SKF-91844 effect	Benetti and Izquierdo (2013)
Histamine + Thioperamide (H3 receptor antagonist)	Basolateral amygdala	Rats	One-trial inhibitory avoidance	Prevents the histamine effect	Benetti and Izquierdo (2013)
Imetit (H3 receptor agonist)	Basolateral amygdala	Rats	One-trial inhibitory avoidance	Facilitates consolidation	Benetti and Izquierdo (2013)
Histamine	CA1 of hippocampus	Rats	One-trial inhibitory avoidance	Facilitates extinction	Bonini et al. (2011)
Dimaprit (H2 receptor agonist)	CA1 of hippocampus	Rats	One-trial inhibitory avoidance	Facilitates extinction	Bonini et al. (2011)
Ranitidine (H2 receptor antagonist)	CA1 of hippocampus	Rats	One-trial inhibitory avoidance	Impairs extinction	Bonini et al. (2011)
Histamine + Ranitidine (H2 receptor antagonist)	CA1 of hippocampus	Rats	One-trial inhibitory avoidance	Prevents the histamine effect	Bonini et al. (2011)
SKF-91488	CA1 of hippocampus	Rats	One-trial inhibitory avoidance	Facilitates extinction	Bonini et al. (2011)
Ranitidine (H2 receptor antagonist)	Cerebellar vermmis	Mice	One-trial inhibitory avoidance	Impairs consolidation	Gianlorenço et al. (2015)
Dimaprit (H2 receptor agonist)	Cerebellar vermmis	Mice	One-trial inhibitory avoidance	Facilitates consolidation	Gianlorenço et al. (2015)
Histamine	Cerebellar vermmis	Mice	One-trial inhibitory avoidance	Facilitates consolidation	Silva-Marques et al. (2016)
Pyrilamine (H1-receptor antagonist)	CA1 of hippocampus	Rats	Object recognition	Impairs consolidation	da Silveira et al. (2013)
Ranitidine (H2 receptor antagonist)	CA1 of hippocampus	Rats	Object recognition	Impairs consolidation	da Silveira et al. (2013)
Imetit (H3 receptor agonist)	CA1 of hippocampus	Rats	Object recognition	Impairs consolidation	da Silveira et al. (2013)
Ranitidine (H2 receptor antagonist)	CA1 of hippocampus	Rats	Social recognition	Impairs consolidation	Garrido Zinn et al. (2016)
Ranitidine (H2 receptor antagonist)	Basolateral amygdala	Rats	Social recognition	Impairs consolidation	Garrido Zinn et al. (2016)
Ranitidine (H2 receptor antagonist) + Dimaprit (H2 receptor agonist)	CA1 of hippocampus	Rats	Social recognition	Dimaprit prevents the ranitidine effect	Garrido Zinn et al. (2016)
Ranitidine (H2 receptor antagonist) + Dimaprit (H2 receptor agonist)	Basolateral amygdala	Rats	Social recognition	Dimaprit prevents the ranitidine effect	Garrido Zinn et al. (2016)
a-FMHis (suicide inhibitor of histidine-decarboxylase)	Lateral ventricle	Rats	One-trial inhibitory avoidance	Impairs consolidation	Benetti et al. (2015)
a-FMHis + histamine	Lateral ventricle + CA1 of hippocampus	Rats	One-trial inhibitory avoidance	Histamine prevents the a-FMHis effect (until 6 h after training)	Benetti et al. (2015)
a-FMHis + histamine	Lateral ventricle + Basolateral amygdala	Rats	One-trial inhibitory avoidance	Histamine prevents the a-FMHis effect	Benetti et al. (2015)
a-FMHis	Lateral ventricle	Rats	One-trial inhibitory avoidance	Impairs retrieval	Fabbri et al. (2016)
a-FMHis + histamine	Lateral ventricle + CA1 of hippocampus	Rats	One-trial inhibitory avoidance	Histamine prevents the a-FMHis effect on retrieval	Fabbri et al. (2016)
a-FMHis + 2-(2-pyridyl)ethylamine (H1 receptor agonist)	Lateral ventricle + CA1 of hippocampus	Rats	One-trial inhibitory avoidance	2-(2-pyridyl)ethylamine prevents the a-FMHis effect on retrieval	Fabbri et al. (2016)
Pyrilamine (H1 receptor antagonist)	CA1 of hippocampus	Rats	One-trial inhibitory avoidance	Impairs retrieval	Fabbri et al. (2016)
Histamine	CA1 of hippocampus	Rats	One-trial inhibitory avoidance	Facilitates memory consolidation in a maternal deprivation protocol	Benetti et al. (2009)
a-FMHis	Lateral ventricle	Rats	Fear conditioning	Prevents the procognitive effects of oleoylethanolamide	Provensi et al. (2017)
Pyrilamine (H1 receptor antagonist)	Basolateral amygdala	Rats	Fear conditioning	Prevents the procognitive effects of oleoylethanolamide	Provensi et al. (2017)
Zolantidine (H2 receptor antagonist)	Basolateral amygdala	Rats	Fear conditioning	Prevents the procognitive effects of oleoylethanolamide	Provensi et al. (2017)