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Hippocampus, Ageing, and Taste Memories

Tatiana Manrique, Ignacio Morón, Mª Angeles Ballesteros, Rosa Mª Guerrero and Milagros Gallo

Institute of Neurosciences F. Oloriz, Department of Experimental Psychology and Physiology of Behavior, University of Granada, Campus Cartuja, Granada 18071, Spain

Correspondence to be sent to: M. Gallo, Institute of Neurosciences F. Olóriz, Department of Experimental Psychology and Physiology of Behavior, University of Granada, Campus Cartuja, Granada 18071, Spain. e-mail: mgallo@ugr.es

Abstract

Previous studies have shown that ageing may induce deficits in hippocampal-dependent learning and memory tasks, the spatial task being most extensively applied in rats. It is proposed that taste learning and memory tasks may assist in understanding the ageing of memory systems, giving access to a more complete picture. Taste learning tasks allow us to explore a variety of learning phenomena in safe and aversive memories using similar behavioral procedures. In demanding the same sensory, response, and motivational requirements, this approach provides reliable comparisons between the performance of hippocampal lesioned and aged rats in different types of memory. Present knowledge on the effect of both ageing and hippocampal damage in complex taste learning phenomena is reviewed. Besides inducing deficits in hippocampal-dependent phenomena, such as blocking of conditioned taste aversion, while at the same time leaving intact nonhippocampal-dependent effects, such as latent inhibition, ageing is also associated with an increased neophobia by previous aversive taste memories and enhanced taste aversion conditioning which cannot be explained by age-related changes in taste or visceral distress sensitivity. In all, the results indicate a peculiar organization of the memory systems during aging that cannot be explained by a general cognitive decline or exclusively by the decay of the hippocampal function.

Key words: ageing, conditioned blocking, context, hippocampal, latent inhibition, taste aversion, taste recognition memory, time of day, rat

Introduction

Ageing is a developmental process that offers a privileged opportunity to study the plasticity of the memory systems induced by both a long-life learning experience, together with changes in some body functions and new adaptive requirements. The cognitive decline related to ageing does not involve a general decay in the functioning of the memory systems. Some types of memories are spared, whereas others usually decay during normal ageing (Gallagher and Rapp 1997). This complex picture has arisen from research using a variety of different learning procedures that may involve different sensory modalities and different response requirements. Well-known changes in the hippocampal function (Rosenzweig and Barnes 2003; Wilson et al. 2005) have been related to a lower performance of aged rats in various memory tasks, there being the spatial tasks most extensively studied. However, the conventional behavioral tasks used to study the hippocampal functions have several pitfalls (Eichenbaum and Fortin 2003) that are magnified when applied to aged animals. The main criticism concerns the fact that some of these tasks may involve sensory, motor, and motivational requirements that may decline during ageing. Thus, a worse performance in a learning and memory task by old-age rats compared with young adult rats could have several interpretations, not necessarily related to the hippocampal involvement in learning and memory. For example, considerable research has focused on the use of the hidden platform water maze task on which performance is impaired in both aged and hippocampal-damaged young adult rats. Due to the visual component of the task, a worse performance of old rats in this task could be due to the well-described effects of visual system degeneration by ageing. Even if the aged rats behave as young adults in cued or visible platform control versions of the task, lower visual demands in the control tasks compared with those requiring processing of several environmental distal cues in the experimental task cannot be excluded. Motor deficits in aged rats can be another confounding variable if the escape latency is measured because swimming speed may decrease in aged rats. Even if path length is used to test learning and memory of the platform location, escape latency is a useful measure

to assess the potential motivational changes induced by aging. Motivational differences between old and young adult rats have been stressed as a major point of concern in ageing studies using the water maze task as poorer thermoregulation of aged rats may affect either the motivation to escape from the water or the emotional reactivity to the test situation (Van der Staay 2002). In all, cued or visible platform versions of the task proposed as the best control for motivational variables are only useful if the escape latencies of young adult and old rats are similar, which should not be expected in most of the cases.

We have previously proposed taste memory tasks as a suitable model for the study of hippocampal and nonhippocampal brain memory circuits in adult rats (Gallo et al. 1999). We also propose taste memory tasks as a choice paradigm for studying ageing-induced changes in different neural systems and cognitive domains. Taste recognition memory tasks allow us to study aversive and safe memories with dissociable neural, cellular, and molecular mechanisms (Bermúdez-Rattoni 2004). Aversive and safe taste memories have been widely studied in the laboratory using novel tastes which produce an innate response called neophobia. This consists of a tendency to reject a novel taste when it is first presented to the animal (Lubow 1989; Moron and Gallo 2006).

Safe taste memories are learned when a novel taste is presented without visceral malaise. As a consequence, there will be an increase in taste consumption in successive presentations of the taste. This learning process is called habituation of neophobia (Lubow 1989).

Conditioned taste aversions (CTAs) are learned when a taste is followed by aversive visceral consequences. The basic procedure for inducing aversive taste memories in the laboratory involves a single pairing of a novel taste (CS) and a malaise-inducing treatment (US). An intraperitoneal injection of lithium chloride (LiCl) is typically used as the US. As a consequence, the taste becomes aversive inducing orofacial aversive reactions and being avoided in later presentations.

Besides basic aversive and safe memories that depend on the consequences of ingesting novel tastes, the development of taste memories in daily life is profoundly modulated by previous and other ongoing experiences with the same or different tastes. Thus, understanding the effect of previous taste experience plays a major role in investigating taste memory and its role in diet selection at an advanced age. This can be investigated in the laboratory by using modified behavioral procedures that have been thoroughly studied in a variety of learning tasks. Contrary to early indications, CTA can access a variety of so-called complex learning phenomena, relying on the effect of previous experience, such as latent inhibition (LI), the US preexposure effect, and blocking, and also exhibits sensitivity to the context. LI refers to reduced conditioning if a familiar taste solution previously exposed without aversive consequences is used as the CS. The effect of the US exposure refers to a similar reduced conditioning if the US, LiCl injection for instance, was previously applied without being associated with the conditioned taste. Blocking consists of a reduced conditioning of a taste if it is presented during the conditioning trial in compound with a second taste that had previously been paired with the US. Moreover, both safe and aversive taste memories are sensitive to the context where they are established. For instance, a context change either between preexposure and conditioning or between conditioning and testing can disrupt learning. In the former case, the context change disrupts LI, and conditioning proceeds as if a novel taste was used. In the latter case, the context change impairs retrieval of the taste aversion. For a summary of the behavioral procedures used see Table 1. Demonstrating each of the above-mentioned learning phenomena requires at least 2 groups of animals as the experimental group should show a different strength aversion than a control group without previous experience or not subjected to the context change. In order to detect differences in consumption between groups and to avoid ceiling effects, one-bottle tests are required. Lower US dosage and several trials are also applied for some of the effects to appear.

Although basic CTA does not involve the hippocampus, more complex learning phenomena may either be hippocampal or nonhippocampal dependent. Thus, taste memory may be a valuable tool for exploring the aging impact on hippocampal-dependent cognition.

Ageing and taste memories

Although ageing does not affect some taste memory abilities, it may induce either an enhancement or impairment of other taste memory tasks.

First, ageing does not impair unconditioned reactions to tastes. No effect of ageing has been reported in neophobia to a grape juice solution (Gallagher and Burwell 1989) or to sodium saccharin (0.1%) (Moron and Gallo 2006), sodium chloride (0.5%), and cider vinegar (3%) solutions (Morón, Ballesteros, et al. 2002). The acquisition of safe taste memories seems also to be largely spared in aged rats. Habituation of the neophobic response, implying an increased intake of the now familiar taste solution, is also evident in aged rats. Although a diminished habituation of grape juice neophobia in aged rats has been reported (Gallagher and Burwell 1989), we have found similar habituation of neophobia in adult and aged rats using a low concentration (0.5%) sodium chloride solution (Morón, Ballesteros, et al. 2002). Moreover, the LI phenomenon is not impaired by ageing. Both in young adult and ageing Wistar rats, the acquired safe taste memory after 6 preexposures to a saline solution interferes with the acquisition of an LiCl-induced aversion to this familiar taste. The experimental preexposed group showed weaker saline aversions than the control nonpreexposed group, as demonstrated by a higher saline intake in a one-bottle test (Morón, Ballesteros, et al. 2002).

Second, far from being impaired, the acquisition of aversive taste memories is even potentiated in aged rats (Misanin,

Table 1 Schematic representation of the behavioral procedures required to demonstrate some complex taste learning phenomena described in the text

	Preexposure	CTA	Testing	Outcome
LI				
Experimental group	Taste A	Taste A–LiCl	Taste A	Higher intake
Control group	—	Taste A–LiCl	Taste A	Lower intake
US preexposure effect				
Experimental group	LiCl	Taste A–LiCl	Taste A	Higher intake
Control group	—	Taste A–LiCl	Taste A	Lower intake
Blocking				
Experimental group	Taste A–LiCl	Tastes A + B–LiCl	Taste B	Higher intake
Control group	—	Tastes A + B–LiCl	Taste B	Lower intake
Context-dependent LI				
Experimental group	Taste A (Ctx A)	Taste A + LiCl (Ctx B)	Taste A (Ctx B)	Lower intake
Control group	Taste A (Ctx B)	Taste A + LiCl (Ctx B)	Taste A (Ctx B)	Higher intake
Context-dependent aversion				
Experimental group		Taste A + LiCl (Ctx A)	Taste A (Ctx B)	Higher intake
Control group		Taste A + LiCl (Ctx A)	Taste A (Ctx A)	Lower intake

A and B = taste solutions and Ctx = context.

Collins, et al. 2002; Misanin, Goodhart, et al. 2002; Morón, Ballesteros, et al. 2002). Saccharin (0.1%) taste aversions assessed in a 24-h saccharin–water choice test can be induced in 24- to 30-month-old Wistar rats using longer delays between the taste and the LiCl injections than in younger rats. Wistar rats of 2 and 2.5 years of age, but not those of 0.25, 1, and 1.5 years of age, developed taste aversions using a 360-min delay between saccharin and lithium (Misanin, Collins, et al. 2002). It has been consistently shown that when using a conventional 15-min delay between the taste solution and the lithium injection, a stronger taste aversion is found in ageing Wistar rats compared with young adult rats provided that ceiling effects are avoided by presenting a palatable 0.5% saline solution previously exposed (Morón, Ballesteros, et al. 2002), a 3% cider vinegar solution in compound with a 0.1% sodium saccharin solution (Morón, Ballesteros, et al. 2002), or by using a low LiCl dosage (1% body weight [b.w.], 0.15 M) after a saccharin solution intake (Moron and Gallo 2006). Although the latter aversions were assessed in one-bottle tests, an interpretation based on an age-related unspecific reduction of fluid intake seems to be excluded by the absence of differences between aged and young adult rats in taste consumption during the conditioning session.

Several explanations that could account for this enhancement of taste aversion learning in aged rats can be excluded. An enhanced sensitivity to the CS, leading to greater taste intensity, is not supported by the fact that the preference for the 0.1% saccharin solution over water does not change in 30 month-old rats compared with 3- and 12-month-old rats (Misanin, Collins, et al. 2002). Moreover, the amount of the taste solution ingested during conditioning follows a pattern of differences that does not correspond to the age differences during testing (Misanin, Collins, et al. 2002). In fact, it seems unlikely that ageing would increase taste sensitivity because the opposite, that is, decreased taste sensitivity, would be expected. A second explanation based on an increased effect of the US in aged rats is not supported by the results. For instance, an account based on there being a more intense US in aged rats because the higher amount of LiCl injected in heavier animals can be discarded because a fixed LiCl amount (2.3 ml) induced greater aversions in aged than in young adult rats (Misanin and Hinderliter 1994). Also, an increased sensitivity to LiCl in aged rats due to physical deterioration, such as renal dysfunction, this leading to a more intense US, cannot explain why the interval over which long-trace conditioning is evident can be extended by increasing the unconditioned stimulus intensity in old-age rats but not in young adult rats. (Misanin, Goodhart, et al. 2002). Finally, an effect of an increased familiarity with the cage context due to extended life experiences which could have reduced interference by the context in aged rats may not account for the aversions acquired with CS–US delays longer than in young adult rats. Aged rats but not young adult rats show aversions irrespective of the context in which they were kept during the interstimulus interval (Misanin and Hinderlitter 1995). Slowing down of a pacemaker that shortens the time between events has also been proposed as the explanation for the longer CS–US interval

at advanced age (Misanin, Goodhart, et al. 2002). However, this would not explain the reported enhanced taste aversion at conventional CS–US delays.

In all, the age-related potentiation of CTA can be considered as a learning superiority, which may represent an advantage for survival because aged rats may be less able to deal with poisoning. Moreover, it cannot be discarded that the effect of previous learning experiences during an extended life may play a role in the development of this adaptive age difference, but more research is needed to unveil the underlying mechanisms. This is consistent with the effect of previously learned taste aversions on later neophobia in 27- to 28-month-old Wistar rats. An enhanced effect of a previous saccharin aversion induced by a 1% b.w. injection of LiCl (0.15 M) on the later neophobic response to a 1% saline solution has been recently reported in aged rats (Moron and Gallo 2006). The increased neophobic response does not seem to be related to the enhanced saccharin aversion in aged rats because a similar strength aversion induced by a 2% b.w. LiCl injection in young adult rats did not induce a similar saline neophobia. Thus, this seems to be another example of age-related potentiation of taste memory functions.

Third, although ageing does not affect some complex taste learning phenomena such as LI, old rats do show impairments in other tasks such as blocking (Gallo et al. 1997; Morón et al. 2001; Morón, Ballesteros, et al. 2002) and the effect of unconditioned stimulus preexposure on later learning (Misanin et al. 1997).

Previous research in our laboratory has shown that blocking may be a sensitive assay for detecting age-induced cognitive deficits. We have found that blocking is absent in ageing rats (Morón et al. 2001; Morón, Ballesteros, et al. 2002). In 15- to 17-month-old rats, a previously learned saccharin (0.1%) aversion did not reduce the magnitude of a cider vinegar (3%) aversion presented in compound with saccharin during the conditioning trial, the vinegar aversion being as strong as if no previous experience had taken place. This deficit may appear as early as 8 months in Wistar rats (Gallo et al. 1997).

Similarly, the US preexposure effect seems to be also disrupted by ageing. Misanin et al. (1997) have reported that 6 daily 1% b.w. injections of 0.15 M LiCl interfered with the acquisition of a saccharin (0.1%) aversion induced by a similar LiCl injection in weanling (20–25 days) and young adult (90–105 days) but not in aged (635–725 days) rats.

Thus, taste learning and memory tasks reveal a complex but complete picture of ageing as inducing a different organization of the learning abilities instead of mere decay. Both enhanced and preserved functions besides those deteriorated represent useful tools to study the ageing brain.

Hippocampus and taste memories

The basic brain circuit required for CTA involves several brain areas, such as the nucleus of the solitary tract, the parabrachial nucleus, the insular gustatory cortex, and the amygdala (for reviews see Bernstein 1999; Gallo et al. 1999; Bermúdez-Rattoni 2004; Reilly and Bornovalova 2005). The hippocampal integrity is not required for basic CTA. In fact, permanent lesions of the dorsal hippocampus do not interfere with taste aversion learning (Gallo and Cándido 1995a). Moreover, enhanced taste aversion learning after temporary dorsal hippocampal inactivation by muscimol infusions has been reported (Stone et al. 2005). However, the hippocampus may have a critical role in mediating some of the effects of previous experience on subsequent taste learning.

On the one hand, the role played by the hippocampus in LI has been controversial, especially using taste learning tasks, and this remains to be clarified. Disruption, no effect (Gallo and Cándido 1995a), or enhanced (Reilly et al. 1993; Purves et al. 1995; Stone et al. 2005) LI of taste aversion learning by hippocampal lesions or by inactivation have all been reported (for a critical review of early studies reporting disruption, see Gallo et al. 1999). These discrepancies have been attributed to differences in the behavioral procedures used and total time of CS exposure which may interact with the hippocampal lesion, thus affecting CS novelty (Buhusi et al. 1998). However, a hippocampal role in LI of CTA different to that observed in LI when using other learning tasks cannot be discarded because the facilitatory effect of hippocampal lesions on LI has been reported only using a taste aversion procedure (Buhusi et al. 1998). In general, the present evidence does not support a critical hippocampal role on LI of taste aversion learning, but some modulatory function cannot be excluded.

On the other hand, previous results obtained in our laboratory have shown that the hippocampus becomes critically involved in other complex taste learning phenomena such as blocking and the contextual modulation of learning. Consistent with findings from other learning procedures, permanent electrolytic lesions (Gallo and Cándido 1995a) or reversible inactivation by TTX injections (Gallo and Cándido 1995b) of the dorsal hippocampus, while not affecting LI of either saccharin (0.1%) or saline (0.5%) aversions, impair blocking of cider vinegar (3%) aversions when presented in compound with a previously conditioned saccharin solution in adult rats. This impairment can be reversed by hippocampal fetal transplants in lesioned rats (Gallo et al. 1997).

In addition to the above, some effects of the contextual information on various memory tasks have also been demonstrated to be hippocampal dependent in adult rats (Honey and Good 1993; Holland and Bouton 1999; Maren and Holt 2000), but this remains to be investigated using taste learning tasks. In fact, both aversive (Puente et al. 1988; Bonardi et al. 1990; Loy et al. 1993; Boakes et al. 1997) and safe (Hall and Channell 1986; Rosas and Bouton 1997) taste memories are bound to the external environment in which learning occurred.

The context dependency of taste aversive memories was probably not revealed in the early studies due to ceiling effects induced by the conventional one-trial taste aversion learning protocol. Consistently, Bonardi et al. (1990) used NaCl (1%) and HCl (1%) for testing the contextual specificity of taste aversions induced by a low (1% b.w.) dose of LiCl (0.3 M) after a previous habituation session with each of 2 contexts which included visual, tactile, auditory, spatial, and temporal differences. They reported no differences between the groups tested in the same or different context throughout 6 one-bottle extinction tests in a single trial protocol. However, after 5 conditioning pairings, a weaker aversion was evident in the group tested in a different context by the third extinction test as the aversion began to diminish. Similarly, other studies showing a context specificity of learned taste aversions have used several conditioning trials (Puente et al. 1988; Loy et al. 1993; Boakes et al. 1997). However, a study reporting negative results applied a single saccharin–LiCl pairing (Rosas and Bouton 1997). Although it has been proposed that a single pairing might not be sufficient for establishing the context as a conditional cue controlling the CS–US association (Bonardi et al. 1990), we have demonstrated the context dependency of a saline (1%) aversion after a single conditioning trial by using a behavioral procedure that included 2 habituation days to the contexts and 2 saline preexposures. The reduced saline aversion when tested in a different context was clear if a place context was used and reached significance in the second extinction test when the time of day was used as a context (Morón, Manrique, et al. 2002). The hippocampus does not seem to play a role in the contextual specificity of taste aversions because N-methyl-D-aspartate (NMDA) induced lesions of the dorsal hippocampus do not disrupt the effect when changes of the temporal context are used (Gallo 2005).

On the contrary, the hippocampus may be involved in the contextual specificity of safe taste memories. Both the development of a safe taste memory during extinction and the LI effect depending on the safe taste memory developed during preexposure have been demonstrated to be context specific. Returning to the conditioning context after extinction in a different context may lead to a renewal of the previously learned taste aversion (Rosas and Bouton 1997; Morón, Manrique, et al. 2002). Also, a context change between preexposure and conditioning disrupts LI, leading to increased aversions in the group subjected to the context change compared with that preexposed and conditioned in the same context. The context dependency of LI is evident using either 6 (Hall and Channell 1986) or 5 (Manrique et al. 2004) habituation days to the contexts used. Moreover, the effect appears not only using a mixture of spatial, visual, texture, and time cues to conform the context (Hall and Channell 1986) but also using the time of day itself (Manrique et al. 2004). This latter effect has been reported to be hippocampal dependent because NMDA lesions of the dorsal hippocampus disrupt it in young adult rats.

Hippocampal decline and ageing impact on taste memories

The hippocampus of the rat shows changes in its functional organization during ageing without significant neuron loss (Erickson and Barnes 2003; Kelly et al. 2006). Anatomical studies have shown no cell loss that could be related to memory impairment in any of the aged hippocampus fields (Rapp and Gallagher 1996; Rasmussen et al. 1996). However, ageing is associated with changes in connectivity and functional responsiveness of the hippocampal neurons (Erickson and Barnes 2003; Rosenzweig and Barnes 2003; Kelly et al. 2006; Wilson et al. 2005). Alterations in connectivity have been reported, including a decline in functional cholinergic transmission, fewer but compensatory increases in the strengths of remaining synapses in the dentate granule cells, loss of functional synapses in CA1 pyramidal cells, and increased gap junctional connectivity. Moreover, the aged hippocampus shows alterations in different forms of plasticity. In addition to a reduced persistence of long-term potentiation (LTP) and LTP induction deficits using perithreshold parameters, long-term depression is more easily induced in aged rats.

The variety of neurophysiological and biochemical alterations in the hippocampal functions during ageing may account for the failure to support some complex learning tasks. Thus, impaired performance of aged rats has been reported in a variety of learning and memory tasks requiring an intact hippocampus (Gallagher and Rapp 1997; Erickson and Barnes 2003).

We have compared the performance of adult hippocampal and old rats in a variety of taste memory tasks (Morón, Ballesteros, et al. 2002). In accordance with an explanation of the age-related cognitive impairment based on the decline of the hippocampal function, LI, but not blocking, was preserved both in aged and hippocampal rats. Moreover, blocking was reestablished by fetal hippocampal transplants both in hippocampal lesioned and in intact aged rats (Morón et al. 2001). However, aged, but not adult hippocampal lesioned, rats showed an enhancement of taste aversion learning (Morón, Ballesteros, et al. 2002). Moreover, hippocampal grafts, which reinstated blocking, did not reverse this age-induced enhancement (Morón et al. 2001). This suggests that, in addition to hippocampal-related impairments, ageing induces independent changes in the brain circuit required for basic taste aversion learning, which may be responsible for enhanced taste memory functions.

Conclusion

Taste recognition memory may be proposed as a choice model for the study of the ageing impact on memory. Taste learning tasks represent useful behavioral tools for studying ageing-related changes in cognition because they allow us to investigate the participation of different types of memory by introducing variations in the same basic procedure. Thus,

sensory, motor, motivational, and emotional requirements are shared, and this facilitates comparisons. The results show impaired, preserved, and enhanced functions in aged rats, indicating alterations in the organization of the memory systems during ageing. Some of the effects of dorsal hippocampal lesions in adult rats are also seen in aged rats. Both aged and hippocampal adult rats show an intact LI effect. Similarly, conditioned blocking is absent in both aged and hippocampal adult rats. Thus, it is conceivable that the aged hippocampus is unable to support certain types of taste memory modulation. However, with the behavioral procedure used, aged rats exhibited an enhancement of basic taste aversion that is not induced by hippocampal lesions in young adult rats.

In all, the results confirm that the impact of age on memory is complex and cannot be explained by a general cognitive decline or exclusively by hippocampal function decay. Rather, the present results suggest that there is reorganization within the brain memory systems during the ageing process.

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