

Rigidity in social and emotional memory in the R6/2 mouse model of Huntington's disease

Alessandro Ciamei, A. Jennifer Morton *

Department of Pharmacology, University of Cambridge, Tennis Court Road, CB2 1PD Cambridge, UK

Received 3 August 2007; revised 22 October 2007; accepted 26 October 2007

Available online 20 February 2008

Abstract

Four experiments were conducted to examine social and emotional memory in the R6/2 transgenic mouse model of Huntington's disease. First, R6/2 mice were tested in a social transmission of food preference task where they had to acquire a preference for a flavoured food (acquisition) and subsequently to learn a preference for a different flavour (shifted reinforcement). R6/2 mice performed well in the acquisition trial. However, they were impaired in the shifted reinforcement trial and perseverated on the first preference learned. Second, mice were trained in an inhibitory avoidance paradigm, with either one or two footshocks delivered during the training. WT mice given one footshock showed retention levels lower than those of mice trained with two footshocks. By contrast, there was no difference in retention levels of R6/2 mice given either one or two footshocks. Third, mice were tested in an active avoidance task that paired a mild footshock with a warning light. R6/2 mice had a strong age-dependent deficit in this task. Finally, mice were tested in a conditioned taste aversion task that paired a saccharine solution with a nausea-inducing agent (LiCl). R6/2 mice displayed normal aversion, however this was not extinguished following repeated exposure to saccharine solution alone. Our data show that while R6/2 mice have functional hippocampus-based memory, they have deficits in striatum-based memory skills. Further, social and emotional memories appear to be encoded in a rigid way that is not influenced by subsequent learning or by arousal levels.

© 2007 Elsevier Inc. All rights reserved.

Keywords: Huntington's disease; R6/2 mice; Social transmission of food preference; Inhibitory avoidance; Memory systems

1. Introduction

HD is a progressive neurodegenerative disorder caused by an expanded CAG repeat in the HD gene. Symptoms in HD are associated with profound neuronal loss in the striatum and cortex (The Huntington's Disease Collaborative Research Group, 1993). Clinical symptoms of HD include motor abnormalities, cognitive decline and emotional disturbance (Bates, Harper, & Jones, 2002). HD patients also frequently exhibit psychiatric symptoms. These include deficits related to the processing of emotion (that are mainly due to a failure in the recognition of facial expression; Sprengelmeyer, Schroeder, Young, & Epplen,

2006), and to the ability to draw correct inferences from social situations (Snowden et al., 2003).

The R6/2 transgenic mouse model of HD is widely used because these mice show a progressive deterioration of locomotor and cognitive abilities (Carter et al., 1999; Lione et al., 1999; Murphy et al., 2000). R6/2 mice express the N-terminal fraction of the human HD gene containing a highly expanded CAG repeat (Mangiarini et al., 1996). However, in contrast to what is found in human patients, neuronal loss is only observed in R6/2 mice at a very late stage of the disease (Stack et al., 2005), whereas some cognitive deficits are present as early as 4 weeks of age (Lione et al., 1999). Further, abnormalities in hippocampal synaptic plasticity are present from 3 weeks of age (Gibson, Reim, Brose, Morton, & Jones, 2005). Therefore, cognitive impairments are unlikely to be due to neuronal degeneration, but rather are due to a 'functional' failure in neuronal

* Corresponding author. Fax: +44 01223 334100.
E-mail address: ajm41@cam.ac.uk (A.J. Morton).

mechanisms. The degree of cognitive decline depends upon the task. ‘Hippocampal’ tasks, such as spatial learning (Lione et al., 1999; Murphy et al., 2000) and acquisition of two-choice discrimination learning (Lione et al., 1999; Morton, Skillings, Bussey, & Saksida, 2006; Pallier et al., 2007) are impaired in mice with mid-late stage disease (older than 12 weeks), whereas reversal learning deficits that depend upon intact striatum are seen much earlier (by 6–8 weeks of age), before the development of abnormal locomotor signs. From these studies it seems likely that cognitive abilities of these mice are affected by a malfunction in frontostriatal and hippocampal memory systems.

Different brain regions, such as the medial temporal lobe, the basal ganglia or the amygdaloid complex, are known to be important for the consolidation of different forms of memory (e.g. declarative, procedural and emotional memory; Gold, 2004; McGaugh, 2004; Packard & McGaugh, 1996). ‘Emotional’ memory in R6/2 mice has been investigated in a single study, with deficit observed in R6/2 mice tested in a fear-conditioning paradigm (Bolívar, Manley, & Messer, 2003). Interestingly, the deficit was seen only in the contextual version of the task, and not in the cued one, suggesting a deficit in contextual memory rather than in the formation of memories for emotionally-relevant stimuli. Social cognition has not been yet investigated in the R6/2 mouse. Therefore, in this study, we tested R6/2 mice in tasks of social and emotional memory. We first examined social memory in R6/2 mice using a social transmission of food preference (STFP) task (Eichenbaum, 2000). In this task, information about a safe food (cued food) eaten by a demonstrator is transmitted to other mice through an olfaction-based social interaction. This form of social learning is a highly-preserved biological mechanism through which a colony of mice can avoid potentially unsafe foods on the basis of the experience of a single mouse (Sánchez-Andrade, Bronwen, & Kendrick, 2005). It has been shown to be largely dependent on an intact functionality of structures within the medial temporal lobe, including the hippocampus, the subiculum and the parahippocampal cortex (Alvarez, Lipton, Melrose, & Eichenbaum, 2001; Alvarez, Wendelken, & Eichenbaum, 2002; Ross & Eichenbaum, 2006). As with other forms of learning relating to individual survival (e.g. conditioned taste aversion; see below), the information learned is quickly stored in long-term memory, so that a single exposure is often sufficient to achieve memory consolidation (Welzl, D’Adamo, & Lipp, 2001).

In a second set of experiments, we tested R6/2 mice in a one-trial inhibitory avoidance paradigm. In this task, mice learn to avoid a place where they had previously received a footshock. Consolidation in long-term memory of this aversive experience is known to engage both hippocampus and striatum (Camarota, Bevilacqua, Köhler, Medina, & Izquierdo, 2005; Packard, Vecchioli, Schroeder, & Gasbarri, 2001; Solana-Figueroa, Salado-Castillo, Galinda, Quirarte, & Prado-Alcalá, 2002). Moreover, consolidation of this form of memory is normally modulated by the activity

of the basolateral nucleus of the amygdala (McGaugh, 2004). Through its main efferent path, the stria terminalis, the basolateral nucleus of the amygdala can influence the consolidation process in the structures in which it is taking place, according to the level of emotional arousal induced by the aversive stimulus used (McGaugh, 2004; Wilensky, Schafe, & LeDoux, 2000).

In a third set of experiments, we tested R6/2 mice in a two-way active avoidance paradigm. This multi-trial paradigm is a stimulus–response (S–R) learning task in which a light is used as conditioned stimulus (CS) and a footshock as unconditioned stimulus (US). The association between CS and US is learned quickly by the mice, and, following extensive training, is turned into a conditioned habit through which mice avoid the footshock using the CS as a predictor of the US. Contrary to what happens for the other procedures previously described, this task is mainly a response learning task, and as such largely depends on an intact striatum (Packard & McGaugh, 1996; Vécsei & Beal, 1991). Moreover, it has been shown that this form of fear-based conditioning also involves the amygdala (Rooszendaal, Koolhaas, & Bohus, 1993) and requires the release of dopamine in the medial prefrontal cortex (Stark, Bischof, Wagner, & Scheich, 2001).

In a fourth set of experiments, mice were tested in a conditioned taste aversion (CTA) paradigm. In this task, mice learn to reject a tastant (a solution of saccharine that represents the CS) if this is associated with subsequent malaise (US) induced through the injection of a nausea-inducing agent (LiCl). Following the initial learning trial, mice were tested in an extinction paradigm in which only the CS was presented over multiple subsequent trials. Although many brain regions are involved in CTA learning, particularly those related to the processing of visceral inputs to the brain and of gustatory information, a key role in this task is played by the amygdala (Dudai, 2002; Josselyn, Kida, & Silva, 2004; Welzl et al., 2001). Moreover, the amygdala has been shown to be involved in the formation of extinction memory for this paradigm (Bahar, Dorfman, & Dudai, 2004; Bahar, Samuel, Havzi, & Dudai, 2003), together with regions within the ventro-medial prefrontal cortex (vmPFC; Akirav et al., 2006; Mickley, Kenmuir, Yocom, Justin, & Biada, 2005).

2. Methods

2.1. Animals

Mice were taken from a colony established at the University of Cambridge on a CBA × C57BL/6 F1 background as described previously (Morton et al., 2005). Mice were housed in single sex, mixed genotype groups of 10 mice. All testing was performed on male mice. WT littermates were used as controls for R6/2 mice. Means (±SEM) CAG repeat length for R6/2 mice was 280 ± 2 . Genotyping and repeat length measurements were performed by Laragen, Los Angeles, USA. All studies were carried out in accordance with the UK Animals (Scientific Procedures) Act 1986. Mice were housed within a 12-h light/dark cycle (lights on at 7:30 AM and off at 7:30 PM) in a temperature-controlled (19–21 °C) and

متن کامل مقاله

دریافت فوری ←

ISIArticles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات