The role of the noradrenergic system in emotional memory

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Received 14 December 2006; received in revised form 6 October 2007; accepted 24 October 2007

Available online 19 December 2007

Abstract

This contribution is an overview on the role of noradrenaline as neurotransmitter and stress hormone in emotional memory processing. The role of stress hormones in memory formation of healthy subjects can bear significance for the derailment of memory processes, for example, in post traumatic stress disorder (PTSD).

Increased noradrenaline levels lead to better memory performance, whereas blocking the noradrenergic receptors with a betablocker attenuates this enhanced memory for emotional information. Noradrenaline appears to interact with cortisol in emotional memory processes, varying from encoding to consolidation and retrieval.

Imaging studies show that confronting human subjects with emotional stimuli results in increased amygdala activation and that this activation is noradrenergic dependent. The role of noradrenaline in other brain areas, such as hippocampus and prefrontal cortex, is shortly summarized.

Finally, the pros and cons of a therapeutic application of betablockers in the (secondary) prevention of PTSD will be discussed.

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PsyclNFO classification: 2343; 2360; 2580; 3340

Keywords: Noradrenaline; Amygdala; Memory; Betablocker; PTSD; Human

1. Introduction

Almost 15 years ago, The Netherlands were shocked by an event that was unique to our history: the “Bijlmer Disaster”. In this airplane disaster, on October 4th, 1992 a Boeing 747 air freighter crashed on two apartment buildings in the southeastern part of Amsterdam, and took the lives of 43 people. This event had an enormous emotional impact and triggered all aspects that have been studied and analyzed in the psychological and medical literature about the traumatic memory processes (Brewin, 2003; McNally, 2003). Testimonies on the event varied enormously in content and were highly debated. It is illustrative for the complexity of traumatic memories and emotional information processing. It highlights the fact that a disaster can cause a wide range of emotions that are accompanied by both physical arousal and a noticeable impact on memory.

From an evolutionary point of view it seems logical that a confrontation with a stressful situation is better remembered than a neutral situation, resulting in a more adequate reaction in a similar situation. This reasoning led to a widely accepted view that the memory for emotional information is generally better than for neutral information (Cahill & McGaugh, 1998; McGaugh, 2000).

The research reviewed here, focuses specifically on the neurobiological basis of stress, emotion, arousal and their effect on memory. This contribution, studies in particular the role of noradrenaline as neurotransmitter and stress hormone in emotional memory\(^1\) processing.

\(^1\) Throughout this paper, to refer to ‘memory for emotional stimuli, events or situations’ the term “emotional memory” will be used for readability purposes.
2. Sources of adrenaline and noradrenaline (NA)

Adrenaline and noradrenaline, also known as epinephrine (EPI) and norepinephrine (NE), are two separate but related hormones secreted by the medulla of the adrenal glands. These compounds are also produced at the ends of sympathetic nerve fibres, where they serve as chemical mediators for conveying the nerve impulses to the effector organs. Noradrenaline is formed in the body from the amino acid tyrosine, and adrenaline is in turn formed from noradrenaline (Kalat, 1992). Chemically the two compounds differ only slightly; they exert similar pharmacological actions, which resemble the effects of stimulation of the sympathetic nervous system. They are, therefore, classified as sympathomimetic agents. The active secretion of the adrenal medulla contains approximately 80% adrenaline and 20% noradrenaline; but this proportion is reversed in the sympathetic nerves, which contain predominantly noradrenaline.

Noradrenaline containing neurons can be found throughout the nervous system, and points therefore to a prominent role for this neurotransmitter in the central nervous system. The majority of these neurons in the brain are located in the locus coeruleus, a nucleus in the brain stem. This nucleus is a primary source for an extensive NA network in the forebrain and takes almost exclusively care of the NA supply of amygdala, hippocampus and neocortex (Vermetten & Bremner, 2002). The network function is twofold: it contains a neuronal basal activity in the forebrain, needed to acquire sensory information (being alert), and secondly, it increases and/or modulates the gathering and processing of emotional relevant and salient information via its action on sensory, attentional, motor- and memory processes (Berridge & Waterhouse, 2003).

3. Animal studies on noradrenergic modulation of memory in stress tasks

A wide array of animal studies has focused on the effect of stress hormones on memory performance in rats. In these studies a great variety of hormones and neurotransmitters have been tested that were either systemically injected or injected in relevant brain areas, such as the amygdalar complex (LeDoux, 2000; McGaugh & Introni-Collison, 1987; McGaugh et al., 1993). Adrenaline and its agonists applied at encoding or immediately post-training increase memory performance in all types of stress tasks. β-adrenergic antagonists, on the contrary, given at these same points in time (as in the studies with agonists) lead to decreased memory performance, e.g. longer retention times (McGaugh, 2004). Betablockade also decreased the performance that was raised artificially by agonistic working agents that were injected concurrently (Liang, Juler, & McGaugh, 1986). Summarizing these results in animals: increased (nor)adrenaline levels in body and brain lead to improved memory performance at the time of encoding, and – time- and dose-dependently – also immediately post-training, hence during the stage of consolidation (Ferry & McGaugh, 1999; Liang, Bennett, & McGaugh, 1985; Liang et al., 1986). β-adrenergic blockers, however, applied in comparable time-frames lead to reduced memory performance on stress tasks (Cahill & McGaugh, 1996; Liang et al., 1986; McGaugh, 2000, 2004). Although different types of β-adrenergic blockers have been used they were all successful in decreasing memory performance (Liang et al., 1985, 1986; Liang, McGaugh, & Yao, 1990; Rozendaal, Carmi, & McGaugh, 1996). Even solely peripheral stimulation of the NA system – for example peripheral NE or EPI injections (Liang et al., 1985, 1990), or stimulation of the vagal nerve (Hassert, Miyashita, & Williams, 2004; Williams & McGaugh, 1993), or systemic injection of a hydrophilic betablocker (BB) that would not easily pass the blood brain barrier, shows the same negative effect on memory performance.

4. Human studies on noradrenergic modulation of emotional memory

The effects of NA manipulations on long-term emotional memory has been explored in several (although a limited number of) human studies. Propranolol, a β1–β2 noradrenergic receptor blocker that easily crosses the blood brain barrier was predominantly used to explore the effect of NA on memory. One of the first human studies that changed the focus from a cognitive perspective to a more neurobiological viewpoint was of Cahill, Prins, Weber, and McGaugh (1994). They adjusted a slide show, used as stimulus material in an earlier study (Heuer & Reisberg, 1990) and showed all subjects the same set of slides, with only the accompanying narratives being different (emotional versus neutral). The participants were shown an arousal or neutral version of a picture story after receiving the betablocker (BB) propranolol (40 mg) or placebo. They found that the increase in memory for the emotional part of the story in the placebo group was blocked in the BB group. So, participants who received propranolol remembered the emotional story completely comparable to the neutral story. This result of the Cahill study first demonstrated the role of noradrenergic receptors in emotional arousal and emotional memory.

Intrigued by the effects of peripherally acting betablockers on memory in animals, our group designed a study in which we could possibly replicate the findings of Cahill et al. (1994). This time subjects received either the betablocker propranolol or a placebo – and we added a third new condition to the design. This third group of subjects received the peripherally acting hydrophilic betablocker nadolol that crosses the blood brain barrier to a much lesser extent than the lipophilic propranolol. If the peripheral BB nadolol would lead to a comparable decrease in emotional memory performance as propranolol (as was found in animals), this would seriously affect our view on the neurobiological underpinnings of emotional memory in humans.
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