Psychoneuroendocrinology (2009) **34**, 1263—1271

available at www.sciencedirect.com

ScienceDirect

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

Endogenous noradrenergic activation and memory for emotional material in men and women

Sabrina K. Segal *, **Larry Cahill**

200 Bonney Research Labs, Center for the Neurobiology of Learning and Memory, Department of Neurobiology and Behavior, University of California, 2205 McGaugh Hall, Irvine, CA 92697, USA

Received 29 July 2008; received in revised form 15 April 2009; accepted 30 April 2009

KEYWORDS
Salivary alpha-amylase;
Norepinephrine;
Memory;
Adrenergic;
Emotion;
Sex

Summary A plethora of evidence from the animal and human literature suggests that emotionally arousing material is often remembered better than is neutral material, and that this effect critically involves noradrenergic activation during and soon after exposure to the emotional material. A crucial prediction of this hypothesis is that endogenous adrenergic activation should relate positively and selectively to memory for emotional events in humans. Salivary alpha-amylase (sAA), a biomarker for adrenergic activity was measured in response to viewing a series of mixed emotional and neutral images to test this prediction in healthy men and women. One week after viewing these images subjects returned for a surprise free recall test. Endogenous noradrenergic activation, defined as an increase in sAA immediately after versus before slide viewing, occurred in 24 of 67 subjects. Regression analysis of the data revealed a significant positive correlation between the increase in sAA and the percentage of emotional pictures recalled. No correlation existed in the same subjects between sAA and the percentage of neutral pictures recalled. Additionally, the difference between these two correlations closely approached significance. The findings therefore demonstrate a relationship between a measure of endogenous noradrenergic activation and long-term memory performance in humans. The results support the view that adrenergic activation underlies enhanced memory for emotional material in humans, namely, that endogenous adrenergic activation in response to an emotional event should predict long-term memory for the event. The selectivity of the relationship for emotional, and not neutral, material supports the view derived from earlier research that stress activation does not necessarily enhance memory for all aspects of an emotional event; rather, that it acts disproportionately to influence memory for the more emotional aspects of an event. These findings are the first involving human subjects to indicate that the degree of endogenous noradrenergic activation in response to emotionally arousing stimuli predicts the strength of long-term memory for those stimuli.

1. Introduction

Abundant evidence from animal studies suggests that noradrenergic activation is related to memory enhancement,

* Corresponding author.
E-mail address: ssegal@uci.edu (S.K. Segal).

0306-4530/$ — see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psyneuen.2009.04.020

particularly for emotionally arousing material. Post-training systemic, or intra-basolateral amygdala (BLA) infusions of adrenergic agonists, leads to retrograde memory enhancement (Ferry et al., 1999; Lalumiere et al., 2003; McGaugh et al., 1984, 1996; Soetens et al., 1995; Liang, 1985; Liang et al., 1986, 1990; Hatfield and McGaugh, 1999; Power et al., 2001). In contrast, post-training systemic or intra-BLA infusions of adrenergic antagonists produce retrograde memory impairment (Gallagher et al., 1977; Gallagher and Knapp, 1981; McGaugh et al., 1984, 1996; Cahill et al., 2000). A common interpretation of these findings is that stress hormones released during and after emotionally arousing events lead to noradrenergic activation in the BLA, resulting in enhanced memory for emotional events.

In addition to the pharmacological evidence that the adrenergic system is involved in memory modulation, there is evidence to suggest a strong relationship between training-induced endogenous noradrenergic activation, measured directly from the BLA using *in vivo* microdialysis, and retention of the training experience. Post-training BLA levels of norepinephrine (NE) increase directly with foot shock intensity (Galvez et al., 1996; Quirate et al., 1998) and the amount of increase in NE measured after acquisition of stressful learning tasks strongly correlates with memory performance for those tasks (Galvez et al., 1996; McIntyre et al., 2002). These findings converge with evidence from the pharmacological studies indicating that noradrenergic activation is critically involved in memory modulation for emotional events.

Pharmacological manipulation of the adrenergic system in humans also suggests its participation in modulating human memory for emotional material. In one such experiment, in which subjects viewed a series of images, post-training intravenous administration of epinephrine enhanced recall 1 week later for those images associated with a greater arousal reaction at initial encoding (Cahill and Alkire, 2003). In another experiment, subjects received either placebo, yohimbine (an alpha-2 adrenergic antagonist), or metoprolol (a selective beta 1A-adrenergic antagonist) prior to viewing an emotional slide show. The results indicated that yohimbine subjects recalled significantly more, and the metoprolol subjects significantly fewer, images than did the placebo subjects (O'Carroll et al., 1999). Several human subject studies have also examined the effects of beta-adrenergic blockade on memory for emotional material via administration of propranolol, an adrenergic receptor blocker (Cahill et al., 1994; O'Carroll et al., 1999; Cahill and vanStegeren, 2003; van Stegeren et al., 1998, 2005). In an experiment in which men and women viewed a range of emotionally arousing images (van Stegeren et al., 2005), beta-blockade significantly decreased amygdala activation in response to emotional, but not neutral pictures. Memory for emotional slides was also significantly reduced in the beta-blocker condition compared to the placebo condition.

Evidence from experiments that indirectly measure autonomic activity also suggests associations between psychophysiological indices of adrenergic activation and memory. Cahill and Alkire (2003) demonstrated enhanced recall for images that elicited higher electrodermal activity at the time of encoding. (Bradley et al., 1992) reported that high levels of arousal, as measured by skin conductance at the time of encoding were associated with faster recognition time. Collectively, these studies are consistent with the findings from animal research in pointing towards the critical role of NE in memory modulation. However, no prior study has related endogenous noradrenergic activation to memory for emotional events in humans, in part because of difficulties associated with measuring endogenous adrenergic activity.

Recently, a kinetic enzyme assay has been developed that measures concentrations of a salivary enzyme, alpha-amylase, a known biomarker for NE (Chatterton et al., 1996). Strong evidence indicates that measurement of this salivary enzyme is a superior assessment of central endogenous noradrenergic activation, as compared with measurement of NE via blood plasma (Ehlert et al., 2006). Alpha-amylase is an isoenzyme that is involved in the transformation of starch into glucose and maltose, and is present in saliva. Evidence from animal experiments, involving infusions of alpha- and beta-adrenergic drugs, indicates that secretion of salivary alpha-amylase (sAA) is primarily mediated by stimulation of beta-adrenergic receptors (Gallacher and Peterson, 1983; Skov et al., 1998). In addition, evidence from several pharmacological experiments in humans and animals supports the notion that sAA is a valid biomarker for noradrenergic activity. Alpha- and beta-adrenergic drugs, such as isoprenaline (beta-adrenergic agonists) and yohimbine (alpha-2 receptor antagonist) significantly increase sAA (Speirs et al., 1974; Ehlert et al., 2006). Conversely, beta-adrenergic antagonists such as atenolol, and propranolol significantly decrease sAA (Speirs et al., 1974; Nederfors and Dahlof, 1992; Nederfors et al., 1994; van Stegeren et al., 2005). There has been some controversy as to whether changes in sAA levels reflect alterations in *plasma* NE levels (Chatterton et al., 1996; Nater et al., 2006; Rohleder et al., 2004; Ehlert et al., 2006). However, the discrepancy in the correlations between blood plasma NE and sAA appears to reflect the difference in the origin of the sample and suggests that sAA is more reflective of central noradrenergic release (Ehlert et al., 2006). Norepinephrine measured in blood reflects adrenomedullary NE, as well as peripheral spill-over. Salivary alpha-amylase appears to be more accurate a measurement with respect to the timing of alterations in central NE, since animal research indicates that secretions of sAA result primarily from NE released from sympathetic nerves that innervate acinar cells in the parotid gland (Ehlert et al., 2006; Castle and Castle, 1998; Whelton, 1996). Norepinephrine binding to g-protein coupled receptors on the acinar cells of the parotid gland activates cAMP, resulting in the synthesis and secretion of alpha-amylase within approximately twenty seconds of NE binding to the receptors (Yoshimura et al., 2002). Thus the discrepancy between NE levels in the blood, and alpha-amylase levels in saliva is likely attributable to the difference in origin between central and peripheral NE (Ehlert et al., 2006). Furthermore, since alterations in sAA levels are detected almost immediately after NE binds to the receptor in these acinar cells, it is a much more accurate measurement of central NE activity than NE in blood plasma. The pharmacological evidence, along with the almost immediate sAA synthesis in response to norepinephrine binding, strongly indicates that sAA is an appropriate biomarker for endogenous noradrenergic activation in humans.

Evidence from several studies suggests that the adrenergic system is critically involved in memory enhancement for emotional, but not neutral material (O'Carroll et al., 1999;