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# Acute Stress in Patients with Panic Disorder Produces Effects on Salivary Amylase and Cortisol

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## 1. Introduction

Salivary alpha-amylase (sAA) has been suggested to reflect stress-related body changes. Psychosocial stress increases the release of salivary alpha-amylase, which reflects the activity of the sympathetic-adrenal-medullary (SAM) system. Therefore, it is presumed that sAA measurement is a useful tool for evaluating the SAM system. In addition, previous studies examining the response of sAA levels to SAM system activity showed that increased sAA levels were correlated with increased plasma catecholamine, indicating sympathetic nervous system activation. So far, numerous studies have shown that changes in sAA levels are dependent on stress stimuli. It is difficult to objectively evaluate the emotional and physical state. sAA measurement can be performed easily and quickly, and therefore, could be used to aid the evaluation of the psychosocial and/or physical stress levels. It is very important to be able to evaluate and understand the level of psychosocial and/or physical stress (distress) experienced by patients. The measurement of sAA is expected to be useful tool as a patient distress.

In panic disorder, stressful events are frequently comprised of both neutral and emotionally arousing information, yet the impact of stress on emotional and neutral events is still not fully understood. The hippocampus contains dense concentrations of receptors for stress hormones (such as cortisol), and elevated stress hormone levels can impair performance on hippocampal-dependent memory tasks. Yet, cortisol can also facilitate memory for emotional information, and this involves interactions between the hippocampus and amygdala. Physiological and psychological stresses have the short-term effects on salivary amylase (sAA) and salivary cortisol levels during both emotional and neutral episodes. The stress manipulation results sAA and salivary cortisol responsiveness. The stress manipulation also increases salivary cortisol levels, catecholamine function as indicated by

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the presence of alpha-amylase, heart rate, and subjectively reported stress levels. Stressed patients with panic disorder reported more anxiety compared to non-stressed control subjects, and these anxiety levels are positively correlated with salivary amylase and cortisol levels, providing evidence for a relationship between stress and hormonal responses. Stress produces physiological responsiveness under neutral versus emotional episodes in panic disorder.

## **2. Relationship between the hippocampus, amygdala, cortisol and amylase**

The hippocampus is a bilateral, subcortical brain structure with an elongated shape and complex microcircuitry. This structure functions in both declarative memory (episodic memory and semantic memory) and spatial memory (Squire, 1992). Along with the amygdala, the hippocampus is one of the most frequently studied brain regions in terms of neuronal plasticity. Neuronal plasticity is thought to represent the cellular mechanism associated with both learning and the storage of memories (Cooke and Bliss, 2006). The hippocampus is also a region susceptible to damage via both hypoxic encephalopathy and Alzheimer's disease. The amygdala is an almond-shaped, bilateral structure located inside the temporal lobes. Previously, the amygdala was considered a functionally vague area of the brain, and did not generate much scientific interest. However, today it is one of the most frequently studied brain regions as an essential location of fear and anxiety mechanisms. In addition to animal experiments using fear conditioning methods, fMRI studies in humans have become increasingly important for these investigations. The lateral nucleus of the amygdala is considered an important region for the formation and storage of emotional memory. During the formation of emotional memories, associations between stimuli and emotional responses are thought to be encoded by neural plasticity in the lateral amygdala. The lateral amygdala also communicates this information with other brain regions involved in fear memory storage and functional output. For example, the central nucleus of amygdala is a critical region of emotional output (Phelps EA, LeDoux JE 2005). Cortisol is a steroid hormone secreted from the adrenal cortex. Cortisol levels are increased by stress (Simon and Gorman, 2004) and, as a result, blood pressure and blood sugar levels are also increased, while immune function and fertility are compromised. The digestive enzyme amylase is contained in pancreatic fluids and saliva and breaks down starch and glycogen. Salivary amylase is also secreted by stress via activation of the sympathetic nervous system and the action of  $\beta$ -adrenergic receptors (van Stegeren et al. 2006). Chronic stress over long periods leads to cortisol secretion in large quantities, and such excessive cortisol levels can result in hippocampal atrophy. Patients with depression (Campbell and Macqueen 2004) or post-traumatic stress disorder (PTSD) (Woon et al. 2010) are likely to be susceptible to this mechanism. Excessive cortisol administration in rats also causes increased corticotropin-releasing factor (CRF) levels in the amygdala, along with increased amygdala excitability. In turn, activation of the amygdala further potentiates cortisol release. Thus, in contrast to the traditional negative feedback systems limiting cortisol activity via the hypothalamus, cortisol produces a positive feedback signal regulating its levels via the amygdala (Makino et al 1994).

Recently Inagaki et al., (2011) reported that saliva samples were taken at three points, and sAA activity was measured using a hand-held monitor before the test, immediately after

the test, and 10 min after the test. In the study, a marked increase in sAA activity due to physiological stress and a rapid return to the baseline level were observed. This physiological stress method might be useful for evaluating stress. Engert et al., (2011) reported that there was the cross-correlation of salivary cortisol and sAA responses to psychological stress. The participants were exposed to a psychological laboratory stressor with high frequency saliva sampling in two independent studies. Synchronized time series of sAA and cortisol measures before, during and after stress induction were obtained. Cross-correlation analysis was applied to test for the association of sAA and cortisol levels at various stages relative to the onset of the stressor. Positive and negative cross-correlations between lagged pairs of sAA and cortisol measures were found in both studies. The strongest correlation was found for sAA preceding cortisol release. With a smaller effect size cortisol also significantly preceded sAA. sAA and cortisol stress responses are reliably associated at various time lags throughout a stressful situation. As a possible connection site between HPA axis and SNS that may underlie sAA-cortisol associations.

### 3. Panic disorder and salivary amylase

Panic disorder (PD), one of the most severe anxiety syndromes, is characterized by recurrent and unprovoked panic attacks. During these attacks, a variety of physical symptoms may occur accompanied by a sense of doom and a strong desire to escape present situations (Weissman et al., 1990). Extensive research has attempted to associate panic disorder with an abnormal functioning of the hypothalamic-pituitary-adrenal (HPA) system. Various reports have suggested increased basal cortisol production, yet blunted ACTH and cortisol responsiveness to CRF infusion, along with other subtle differences in feedback sensitivity of the HPA axis (Roy-Byrne et al., 1986; Holsboer et al., 1987; Gurguis et al., 1991; Schreiber et al., 1996; Abelson et al., 2007). Such seemingly inconsistent findings have persisted throughout the literature for decades. Interestingly, reports of naturally occurring panic attacks found that these attacks occur without an obvious secretion of cortisol in most instances (Cameron et al., 1987; Bandelow et al., 2000). The prominent lack of cortisol response to a situation often subjectively perceived by patients as life threatening is confusing, since HPA activity is well known to rapidly increase in times of threat or when encountering a harmful situation (Mason, 1968). However, most patients studied for acute endocrine responses to panic attacks (either naturally or in the lab) have most likely experienced many previous instances of panic attacks. Thus, it is tempting to speculate that the blunted cortisol response to acute panic attack simply reflects successful habituation to repeated stimulation by complex emotional events. In healthy volunteers, a rapid habituation of cortisol responsiveness can be observed when subjects are repeatedly exposed to stressful stimuli in the same environmental context (Kirschbaum et al., 1995; Schommer et al., 2003). As an extension of these studies, we have focused on salivary cortisol levels in patients with panic disorder following electrical stimulation stress. The SAM system is associated with both arousal and anxiety (Aston-Jones et al. 1994; Aston-Jones et al. 1998; Southwick et al. 1999; Berridge and Waterhouse 2003). As a part of this system, stress can trigger locus coeruleus (LC) firing and subsequent widespread norepinephrine neurotransmission in the

brainstem, amygdala and prefrontal cortex (Liddell et al. 2005). Activity in these regions leads to behavioral responses such as orienting to threat, fear, arousal and inhibition of general activity (Gray 1982; Redmond 1987; Coull et al. 2001; Liddell et al. 2005). sAA is secreted by the parotid gland in response to adrenergic activity and is suppressed by  $\beta$ -adrenoreceptor blockade. Alpha-amylase has emerged as a new biomarker for responses to psychosocial stress within the sympathetic nervous system (Ehlert et al., 2006; Granger et al., 2007), and it has been suggested that alpha-amylase levels could be used as an index of SAM activity. Acute investigational stressors induce alpha-amylase secretion, although chronic stress may be associated with reduced alpha-amylase output. Amylase secretion is independent of salivary flow rate and has an endogenous diurnal rhythm (Nater et al., 2007). However, some reports suggest that parasympathetic activation can also induce alpha-amylase release (Nater et al., 2006). Alpha-amylase is not a reliable marker of catecholamine levels. Therefore, alpha-amylase activity may best be described as an autonomic biomarker, complementing but not replacing the measurement of catecholamines and cardiac activity.

There is a strong relationship between anxiety and the degree of attention allocated towards threat-related cues. In a meta-analysis of 172 studies, Bar-Haim et al. (2007) found that anxious, but not healthy, subjects exhibit a selective attentional bias towards threatening cues. The direction of threat prejudice can be modulated by state and contextual factors. For example, situation anxiety increases attentional bias to threats (e.g., MacLeod and Mathews, 1988), but this bias diminishes if attention is directed towards an internal focus, e.g., self-awareness of physiological symptoms (Mansell et al. 2003) or external threats other than the threat stimuli presented during the attention task (Mathews and Sebastian 1993; Williams et al. 1996). In a previous study, patients with panic disorder who displayed panic attacks (46%) had markedly greater anticipatory anxiety before the delivery of 5% carbon dioxide, and this alteration was accompanied by increased  $\beta$ -adrenergic cardiac tone (Roth et al., 1992).

Some reports indicated a possible change in cortisol responsiveness to stress/novel situations in panic disorder subjects (Stones et al., 1999). This was considered to be consistent with previous suggestions of HPA axis dysregulation in panic disorder patients, although some research indicated under-responsiveness rather than a hyper-responsiveness to stress/novel situations in this group. Recently, Petrowski et al. (2010) reported a blunted cortisol response to moderate or intense psychosocial stress in a group of patients with panic disorder. Other studies also reported a hypo- or non-responsiveness to stress in patients with panic disorder (Leyton et al., 1996; Hoehn et al., 1997; Garcia-Leal et al., 2005).

sAA and salivary cortisol levels might differ according to the length of time a study participant had been in the hospital (Balodis et al., 2010). Further studies are needed to try to incorporate drug-free patients and make comparisons between treated and non-treated populations. sAA levels might be a predictive biological marker for antidepressant-responsiveness in patients with panic disorder. Additional studies incorporating more frequent measurements and additional combinations of stress markers will be needed in order to establish a predictive model for successful treatment of patients with panic disorder.

#### 4. Conclusion

Hippocampus and amygdala are important brain regions for learning and storage of memory. Hippocampus involves declarative memory and spatial memory, amygdala involves emotional memory. Excessive cortisol level can result in hippocampal atrophy. Cortisol decreases CRF secretion in hypothalamus, but increase CRF level in amygdala. sAA is parallel movement to stress and cortisol in blood vessel; it is a convenient method for stress.

sAA could be used as an index of SAM activity. The SAM system is associated with both arousal and anxiety. Acute investigational stressors induce alpha-amylase secretion, although chronic stress may be associated with reduced alpha-amylase output. SAA levels might be a predictive biological marker for antidepressant-responsiveness in patients with panic disorder.

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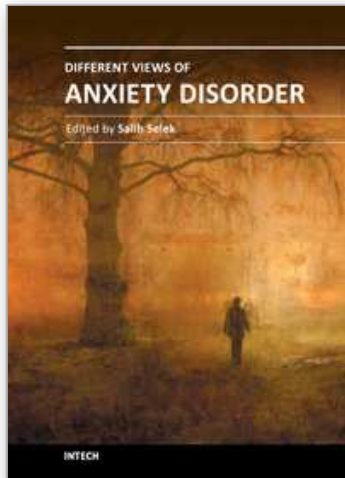
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