SOME ASSESSMENTS OF THE AMYGDALA ROLE IN SUPRAHYPOthalamic NEUROENDOCRINE REGULATION: A MINIREVIEW

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The amygdala is a complex structure playing primary role in the processing and memorizing of emotional reactions. The amygdalae send impulses to the hypothalamus for activation of the sympathetic nervous system, to the reticular nucleus for increasing reflexes, to the nuclei of the trigeminal nerve and facial nerve for facial expressions of fear, and to the ventral tegmental area, locus coeruleus, and laterodorsal tegmental nucleus for activation of dopamine, norepinephrine and epinephrine release. The amygdala plays a key role in what has been called the “general-purpose defense response control network” and reacts in response to unpleasant sights, sensations, or smells. Anger, avoidance, and defensiveness are emotions activated largely by the amygdale. The amygdala is responsible for activating ancestral signs of distress such as “tense-mouth” and defensive postures such as crouching. Poor functioning of amygdala has also been associated with anxiety, autism, depression, narcolepsy, post-traumatic stress disorder, phobias, frontotemporal dementia, and schizophrenia. Impairment of emotional event memory in patients with Alzheimer’s disease also correlates with the intensity of amygdalar damage. All these events speak out for the importance to preserve the normal function of the amygdala which can only be achieved by constant deepening of our knowledge about this unique structure.

Key words: Amygdala – Neurohormones – Suprahypothalamic regulations – Autism – Alzheimer’s disease – Social disorder – Anxiety – Schizophrenia

Introduction

The amygdalae (Latin, corpus amygdaloideum, singular, amygdala, from Greek αµυγδαλή amygdale, ‘almond’) are almond-shaped groups of neurons located deep within the medial temporal lobes of the brain in complex vertebrates, including humans. The amygdalae are considered as a part of the limbic system with primary role in the processing and memorizing of emotional reactions.

Amygdala is composed of more than 20 discrete nuclei arranged into larger formations and functional units interconnected mutually with a number of pathways (SWANSON 1998) of different chemical nature. Recent data of the amygdalae stresses a number of functionally distinct nuclei. Amygdala encompasses several nuclei with distinct functional traits. Among these belong the basolateral complex, the centromedial nucleus, and the cortical nucleus. The basolateral complex can be further subdivided into the lateral, the basal, and the accessory basal nuclei. Neuronal cell groups of the central and the medial amygdaloid nuclei extend through the sublenticular extended amygdala and the interstitial nucleus of the posterior limb of the anterior commissure to the bed nucleus of stria terminalis (BST) and form so-called extended amygdala (ALHEID et al. 1998).
The corticomedial nucleus senses olfactory bulb inputs. It projects to the hypothalamic ventromedial nucleus via striae terminalis. It is interconnected with the hypothalamus and contains receptors for gonadal and adrenocortical hormones. The basolateral nucleus receives information from higher-order sensory areas and associated cortex. Main outputs of these nuclei are directed to the cortex, basal nucleus of Meynert, thalamus, and central amygdalar nucleus. It also projects to hippocampal formation important in the context of emotional experiences. Finally, the central amygdaloid nucleus receives information from the basolateral nuclear group and mediates emotional and behavioral responses to emotional stimuli. Projections of this nucleus are directed to the brainstem and spinal cord autonomic nuclei, regulating the autonomic nervous system. It receives viscerosensory informations from the brainstem and projects back to brainstem via the ansa lenticularis. It receives information from higher-order sensory areas and associated cortex. Main outputs of these nuclei are directed to the cortex, basal nucleus of Meynert, thalamus, and central amygdalar nucleus. It also projects to hippocampal formation important in the context of emotional experiences. Finally, the central amygdaloid nucleus receives information from the basolateral nuclear group and mediates emotional and behavioral responses to emotional stimuli. Projections of this nucleus are directed to the brainstem and spinal cord autonomic nuclei, regulating the autonomic nervous system. It receives viscerosensory informations from the brainstem and projects back to brainstem via the ventral amygdalofugal pathway (LeDoux 2000). In addition, centromedial complex of nuclei gives rise to many peptidergic pathways of different phenotypic origin.

The amygdalae send impulses to the hypothalamus to activate the sympathetic nervous system, to the reticular nucleus for increased reflexes, to the nuclei of the trigeminal nerve and facial nerve for facial expressions of fear, and to the ventral tegmental area, locus coeruleus, and laterodorsal tegmental nucleus for activation of dopamine, norepinephrine and epinephrine release.

**Amygdala and signal filtration.** Amygdala is one of those areas of the brain which has been proposed to be a fundamental in the physiological processes that filter sensoric inputs (Cromwell et al. 2005). Medial and lateral amygdaloid nuclei exhibit 100 % inhibition of the sensory inputs and sensoric gating could allow for a rapid influence on vigilance and attention processes. Inhibitory mechanisms are reflected by reducing the neural responsiveness to repeated and well-predicted stimuli. Distinct filtering function of amygdala has also been shown in amygdala and hippocampus lesioned animals (Daenen et al. 2002).

**Amygdala and neurohormones**

**Vasopressin** and oxytocin are considered to be important neurotransmitters modulating a variety of behaviors including aggression and fear. The amygdala is involved in controlling fear and anxiety via detecting threat stimuli and linking them to defensive behaviors. This is accomplished by projections connecting the central nucleus of the amygdala to the brain stem and to hypothalamic structures, which organize fear responses (Debiec 2005). However, vasopressin and oxytocin modulate the excitatory inputs into the central amygdala in opposite manners (Huber et al. 2005).

**Vasopressin (VP)** is a peptide neurotransmitter excessively present in the limbic system of rats. It is synthesized in the medial amygdaloid nucleus in the presence of sex steroids, transported to other limbic structures such as the hippocampus and septum and secreted there by a calcium-dependent process (Tannahill et al. 1991). Stimulation of the VP cells produces alterations in sexual behavior in a manner consistent with the hypothesis that the medial amygdala organizes the appetitive phase of recognition of an appropriate partner and sexual arousal.

**Oxytocin (OXY)** has a role in social behaviors in many species, and so it seems likely that it has similar roles in humans. It has been suggested that deficiencies in oxytocin pathways in the brain might be a feature of autism. Huber and co-workers (2005) have identified discrete, anatomically separate populations of oxytocin and vasopressin receptors within the central amygdala. Based on the results with agonists and antagonists applications a hypothetical neural network has been constructed in which oxytocin and vasopressin have been shown to exert opposite effects on anxiety and fear. The behavioral effects of oxytocin are thought to reflect release from centrally-projecting oxytocinergic neurons, different from those that project to the pituitary gland (Huber et al. 2005).

**Corticotropin-releasing factor (CRF).** The amygdala is part of an endogenous CRF circuitry within the brain that mediates neuroendocrine, autonomic, behavioral changes, and responses to stress. High densities of CRF, CRF-binding protein, and CRF receptors are located in the amygdala. The amygdala is itself a major extrahypothalamic source of CRF containing neurons (Gray and Bingham 1996). CRF-containing neurons of the amygdala can be directly modulated by alterations in circulating glucocorticoids through glucocorticoid receptors, which are expressed in amygdaloid CRF-containing neurons. During periods of stress, CRF is released into the amygdala and local CRF receptor activation has been postulated as a substrate for stress-induced alterations. Affective behavior and stress induced plasticity within the amygdala may be a critical step in the pathophysiology of the chronic anxiety states (Shekhar et al. 2005). CRH in the central amygdala...
AMYGDALA AND NEUROENDOCRINE REGULATIONS

The amygdala may contribute to the psychological stress-evoked fear-related behavior such as hyperarousal. The amygdala CRH system is much more sensitive to psychological stressors than is the CRH system emanating from the PVN (MAKINO et al. 1999).

The central amygdaloid nucleus is the origin of major CRF-containing pathways in the brain. Amygdaloid CRF neurons project to many regions including the bed nucleus of the stria terminalis, lateral hypothalamus, midbrain central gray, raphe nuclei, parabrachial region, and the nucleus of the solitary tract. In addition, amygdaloid CRF neurons may project directly to dopaminergic, noradrenergic, and serotonergic neurons, which have widespread projections throughout the neuroaxis (GRAY 1993).

**Neuropeptide Y (NPY)** The basolateral nucleus of the amygdala (BLA) is a distinct division of the amygdala and contains the highest concentration of NPY neurons. Interaction between NPY and CRF within the basolateral amygdala may be critical for maintaining a normal homeostatic emotional state (SAJDYK et al. 2006).

**Cholecystokinin (CCK)** Immunoreactive cell bodies were identified in the bed nucleus of the stria terminalis (BNST), medial amygdaloid, central lateral, basolateral, basolateral ventral, medial, intercalated, anterior cortical, and posterior cortical nuclei and the amygdalo-hippocampal zone. In the rat male, in comparison with rat females, more dense aggregation of CCK containing cell bodies has been visualized in the medial amygdala, especially in the dorsocaudal part and in the encapsulated part of the BNST (MICEVYCH et al. 1988).

**Substantia P.** Function of the medial amygdaloid nucleus is related to the fear reactions. During stress 150% increase of substantia P has been measured in the medial amygdaloid nucleus in the rat (EBNER et al. 2004).

**Gamma-aminobutyric acid (GABA).** GABAergic neurons are distributed throughout the amygdaloid complex, especially in the lateral nucleus (PITKANEN and AMARAL 1994). These innervations, together with interaction of NPY and CRF, play an important role in the regulation of behavioral responses to environmental stimuli. Many GABAergic neurons project also from the central nucleus into the nucleus of the tractus solitarii with contranmission of somatostatin (Batten et al. 2002). Higher density of GABAergic neurons in amygdala may result into lower exploratory activity (Nelokov et al. 2006).

**Serotonin.** Acute serotonin release in the basolateral amygdala may directly activate GABAergic neurons of this region and through this activation to increase the inhibitory effect of GABA projecting neurons. Chronic serotonin release has opposite effect and may act in a feedback mechanism to prevent excess inhibition within this nucleus (RAINNIE 1999).

**Behavioral assessments**

The amygdala plays an important role in the differentiation and expression of so-called "delicate" emotional undertones and gives to physiological processes an emotional touch. With hippocampus, the amygdala forms a principal part of the limbic system important for store of memories and emotive events. Conditions such as aggression, anger, autism, depression, narcolepsy, traumatic response, post-traumatic stress disorder, rage, and phobias are assumed to be linked to abnormal functioning of amygdala due to damage, developmental disorders, or neurotransmitter imbalance. These concern many different situations such as friendship, fear, love, sexual behaviour, passion, anger, aggressivity, happiness, sadness, et al. (Rhawn 2000). The amygdala is sensitive to social and emotional stimuli, such as differences in the pronunciation and articulation and face expression which is often associated with lateralized response. (Rhawn 2000). The amygdala possesses an ability to respond to emotional stimuli conveyed through sound, kinaesthetically or by facial expression. It is able to recognize faces and facial expressions and responds differently to an angry face as opposed to a happy face. Curiously, the left amygdala responds to the eye movements of another person and the right amygdala is activated when you make eye contact (Rhawn 2000).

In contrast, the central amygdaloid nucleus is associated with emotional learning activities (Gallagher and Hollander 1994). It has been suggested that in part, violent psychopathic behaviours result from a malfunction in the amygdala, particularly that of the right hemisphere. For example, people who were once aggressive have been rendered quite pleasant by destruction to their amygdala. Some studies indicate that the amygdala is not necessary for species-typical social behavior or for gaining social knowledge during development but it is rather critical component of a system that evaluates the environment for potential dangers. Hyperactivity of the amygdala would be associated with increased fear or anxiety and may contribute to social disorders (Rosen 2006).
Amygdala and some disorders

1. Autism is a disorder of brain function with an unknown origin that appears early in life, generally before the age of three, and persists throughout adulthood. It is considered for a neurodevelopmental disorder that manifests itself in problems with social relatedness, communication, interest, and behavior.

   Autism means a developmental disability significantly affecting verbal and non-verbal social communication and social interaction, plus a strong tendency towards repetitive behaviour, although it may be observed an unusual behaviour (KAMIO et al. 2006). There are many studies indicating the existence of a relationship between autism and alterations in amygdala (KAMIO et al. 2006; BARON-COHEN et al. 2000). BROTHERS (1990) has proposed a network of neural regions that comprise the “social brain”, which includes the amygdala. It has been assumed that autism may be caused by an amygdalar abnormality (BARON-COHEN et al. 2000). There is evidence for an amygdalar deficit in people with autism, who are known to have deficits in social behaviour. Amygdala is not activated in patients with autism when making mentalistic inferences from the eyes, whilst people without autism did show amygdalar activity (BARON-COHEN et al. 1999).

   Many recent studies have documented the difficulties in persons with an autism spectrum disorder who have accurately perceiving facial identity and facial expressions. It is argued that the development of face perception and social cognitive skills are supported by the amygdalar-fusiform system (SCHULTZ 2005). There is no general agreement in regard to the size of autistic amygdala. Enlarged (SCHUMANN and AMARAL 2006), normal (PALMEN et al. 2006), and even smaller (MUNSON et al. 2006) size of amygdala have been debated between specialists. For example according to MUNSON and co-workers (2006) left amygdala is smaller in autistic brain, while DZIOBEK and co-workers (2006) have indicated besides smaller amygdala also occurrence of morphological abnormalities.

   Two principal neurotransmitter systems, serotonergic and glutaminergic, have been linked to autism (BLATT et al. 2001). Therefore this disease is also called as „hypoglutaminergic illness“. However, many other biologically active substances may take part in this disease including GABA, oxytocin, and vasopressin which are known to be involved in the regulation of social behaviour (INSEL et al. 1999).

2. Alzheimer’s disease (AD) is a neurodegenerative brain disorder that gradually destroys a person’s memory and ability to learn, make judgments and communications, and carry out daily activities. Symptoms including irritability, agitation/aggression, depression, hallucinations/delusions, and apathy are extremely common in AD, and may be present very early in the course of the disease (COPELAND et al. 2003).

   Neurodegenerative changes in Alzheimer’s disease, including neuronal cell loss, are followed by brain atrophy, which is the main gross pathological feature of the disease (HYMAN et al. 1990). Studies of autopsied cases of advanced Alzheimer’s disease have also demonstrated that amygdalar atrophy is related to the pathology of the disease (SCOTT et al. 1992). They show that the amygdalar atrophy in Alzheimer’s disease is due to the loss of neuronal somata and processes and the accumulation of neuritic plaque and neurofibrillary tangles, as well as extensive gliosis in discrete amygdalar subnuclei, in particular, the loss of large nerve cells in the magnocellular basolateral amygdalar nuclei group. The morphological deformation relates to intrinsic damage to the amygdalar subnuclei and their reciprocal circuitry with other brain regions.

   Amygdalar atrophy and intensity of amygdalar damage is related to impaired emotional memory (MORI et al. 1999), noncognitive features of AD (SMITH et al. 1999).

   Amygdalar activity correlates well with the severity of irritability and agitation symptoms in AD. AD patients had significantly greater amygdala responses to both neutral and emotional faces relative (WRIGHT et al. 2007). These amygdalar functional alterations may represent a physiologic marker for certain neuropsychiatric manifestations of AD (WRIGHT et al. 2007).

3. Social and anxiety disorders. There are five major anxiety disorders: social anxiety and phobias, generalized anxiety disorders, post traumatic stress dis-
orders (PTSD) and obsessive compulsive disorder (OCD). The amygdala is the "nerve centre" for the anxious response which causes anxiety disorders (GARAKANI et al. 2006). The basal amygdala, the lateral amygdala, and the central nuclei, are involved in the pathways of fear response and abnormalities in amygdala can affect the acquisition and expression of fear conditioning (ROSEN 2006). Animal studies, primarily on rodents, have shown that the amygdala, in connection with a complex network including the prefrontal cortex, thalamus, and hippocampus, is integral to multiple aspects of emotional processing including mediating adaptive and pathological fear responses (PHILPS and LEDOUX 2005).

The amygdala has also been implicated in the organization of social behaviors. The first study to the role of the amygdala in social behavior (ROSVOLD et al. 1954) has revealed that high-ranking and previously aggressive animals (rhesus monkeys) fell in the dominance hierarchy and became extremely submissive following bilateral amygdalectomy. Animals with bilateral damage of the amygdala and anterior temporal lobe did not re-establish contact with other group members, did not engage in social interactions, and usually remain socially isolated (DICKS et al. 1968). Amygdala-lesioned macaque monkeys demonstrated less oral and manual exploration of the cage or objects in the cage during social interactions (PRAFTER et al. 2001).

Amygdalar dysfunction has also been implicated in human disorders ranging from social anxiety (BIRBAUMER et al. 1998). The amygdala is involved in determining whether an object or organism is potentially dangerous. If danger is detected, it coordinates a variety of other brain regions to produce a typical species-dependent response to avoid the danger. The amygdala appears to be a highly plastic brain region that contributes to learning what is dangerous in the environment (LEDoux 2000). Humans with bilateral amygdalar damages are impaired in judging of negative emotion in facial expressions and in making accurate judgments of trustworthiness (ADOLPHS et al. 1998).

PTSD is related with pathophysiologic changes of the amygdala (VIEWEG et al. 2006). Laterality differences in the activity of the amygdala have been reported in PTSD patients, with presumed adaptive plasticity in the hippocampus and the amygdala. The mean right amygdalar volume of these patients has been shown to be significantly smaller than the left one (PAVLISA et al. 2006). Animal research related to PTSD showed that a single stress episode can cause a delayed alteration in synapse formation in the basolateral amygdala without changing dendritic length and branching (MILLER and McEWEN 2006).

PTSD patients showing smaller hippocampal and anterior cingulate volumes, increased amygdalar function, and decreased medial prefrontal/anterior cingulate function (BREMNER 2006). These patients also showed increased amygdalar reactivity during processing of certain types of emotional stimuli (e.g., fear, anger) (STEIN et al. 2007). Anxiety-prone subjects had significantly greater bilateral amygdala and insula activation to emotional faces than did the anxiety-normative comparison subjects. Higher scores on several measures assessing anxiety proneness (e.g., neuroticism, trait anxiety, and anxiety sensitivity) were associated with greater activation of the amygdala (predominantly left-sided) and the anterior insula (bilateral) (STEIN et al. 2007).

Phobics patients compared to controls showed greater subcortical, limbic, and lateral paralimbic activity (pons, striatum, amygdala/uncus/anterior parahippocampus, insula, temporal pole), regions important in automatic emotional processing, and less cortical activity (dorsal anterior cingulate/prefrontal cortex), regions important in cognitive processing (LORBERBAUM et al. 2004).

3. Schizophrenia. Schizophrenia is a highly complex disorder characterized by multiple independent domains of disease. Persons with schizophrenia experience have deficits in social cognition which have been shown to compromise long-term social functioning. These deficits include an impaired perception of emotional cues in faces, speech prosody, and complex interactions which might guide adaptive behavior in social situations (ADDINGTON and ADDINGTON 2000).

Several studies have indicated that schizophrenic patients show impaired performance in various aspects of social cognition, including theory of mind, emotion processing, and agency judgments. These patients indicated during such mental activity abnormal hemodynamic response in the amygdala (BRUNET-GOUET and DECETY 2006).

Deficits in the processing of emotion in schizophrenia are related to amygdalar abnormalities (LAWRE et al. 2003). In rats, a neonatal basolateral amygdala lesion induced behavioural features in adults reminiscent of the symptomatology of schizophrenia (BOUWMEESTER et al. 2006).
Amygdalar abnormalities are an endophenotype in schizophrenia and may be related to dysfunction of the cytomatrix zone of synapses in the amygdala (WEIDENHOFER et al. 2006). NELSON et al. (1998) have concluded that lower amygdalar volume is probably associated with schizophrenia. In functional imaging studies, schizophrenia subjects showed altered amygdalar activation in response to affective stimuli (KOZAKA et al. 2002).

4. Frontotemporal dementia. Frontotemporal dementia (FTD) is a neurodegenerative disease characterized by progressive behavioural abnormalities of emotional processing (LABVENU and PASQUIER 2005) and frontotemporal atrophy (BRAMBATI et al. 2007). In contrast to neurodegenerative diseases in which the memory loss is usually the first deficit, FTD is associated with early behavioural abnormalities, including apathy, disinhibition, moral behaviour, obsessive and compulsive behaviours, emotional blunting, and loss of sympathy and empathy. These behavioural signs characteristically precede impairment in memory and are among the most reliable means of differentiating FTD from other disorders causing dementia (SNOWDEN et al. 2001). These behavioural deficits are associated with amygdalar alterations (LABVENU and PASQUIER 2005), i.e. in these patients significant longitudinal changes in the left amygdala have been shown (BRAMBATI et al. 2007).

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AMYGDALA AND NEUROENDOCRINE REGULATIONS


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AMYGDALA AND NEUROENDOCRINE REGULATIONS


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