RECENT FINDINGS ON THE PATHOPHYSIOLOGY OF SOCIAL ANXIETY DISORDER

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Abstract

Social Anxiety Disorder (SAD) shows an early onset, a mildly high prevalence in general population and a chronic course which critically impairs social, affective, academic and working life. In SAD patients an altered amygdala activation to social-emotional stimuli has been reported, and brain areas such as amygdala, medial prefrontal cortex, dorsal raphe, locus coeruleus, prefrontal cortex, anterior cingulate cortex are often considered target regions for research on SAD pathophysiology. A wide range of neurotransmitters (serotonin, norepinephrine, dopamine) and neuropeptides (oxytocin) seems to be involved in SAD-related circuitry. Specifically, the role of oxytocin is becoming a major topic in this field, recent findings supporting the notion that OT is a prosocial hormone and, as such, it may play a direct role in specific anxiety disorders including SAD and have a great range of therapeutic applications. The aim of this paper is to review the recent findings on possible neurotransmitters and brain areas involved in SAD pathophysiology, and their therapeutic implications, providing suggestions for future research directions that could lead to more specific therapeutic interventions.

Key words: Social Anxiety Disorder (SAD), amygdala, medial prefrontal cortex, dorsal raphe, locus coeruleus, prefrontal cortex, anterior cingulate cortex, serotonin, norepinephrine, dopamine, oxytocin

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Introduction

Social Anxiety Disorder (SAD) general population prevalence is estimated among 1.9 and 12.1% (Pietrini et al. 2009). Nevertheless, it has been long neglected by both clinicians and researchers, probably due to both diagnosis related issues and health care seeking delay from SAD patients (Liebowitz et al. 1985, Stein and Gorman 2001). SAD onset generally happens in youth, even in childhood, and it shows a chronic course which critically impairs social, affective, academic and working life (Stein and Gorman 2001, Van Roy et al. 2009). Clinical samples yield no recognizable gender difference in SAD prevalence, while broader studies focusing on demographic samples outline a certain prevalence among women (Pietrini et al. 2009). This is probably due to social and cultural factors, since in some societies shyness and submissive behaviours are more accepted in women than in men, so that the first do not seek for treatment and the latter do this more often (Dell’Osso et al. 2002, 2003; Stein 2009; Pietrini et al. 2009). SAD is characterized by specific cognitive symptoms and behavioral patterns. SAD core clinical feature is marked and intense fear of social situations in which the patient may be scrutinized by others (American Psychiatric Association 2013). SAD fear is related to negative evaluation, and the danger of negative evaluation is often overestimated. SAD patients are generally concerned with being judged stupid, weak, boring, dirty or in any other subjectively negative way (American Psychiatric Association 2013, Stein and Gorman 2001). Specific features of fear depend upon many cultural, social, clinical and practical factors: a patient could fear of offending others with his/her gaze, or are concerned by shaking hands while his own are sweaty (American Psychiatric Association 2013). Exposure to feared social situations almost always provoke fear of anxiety; but type and degree of anxiety manifestation may vary from anticipatory anxiety to panic attack, including its somatic manifestations. Moreover most SAD patients do not fear all social situations, but only specific subtypes (American Psychiatric Association 2013). Due to the distressing nature of fear and anxiety manifestations, SAD patients tend to avoid social situations, both subtly (e.g., limiting eye contact) or intensively (e.g., not going to school/work). This avoidance of social situations can make SAD patients preoccupied by their social skills which are sometimes actually impaired (American Psychiatric Association 2013, Stein and Gorman 2001).

SAD was previously known as social phobia (SP), according to Pierre Janet’s definition at the dawn of the 20th century (Janet 1903). It was proposed as a distinct nosological category in 1966 (Mark and Gelder 1966), and officially included in the DSM-III in 1980 (American Psychiatric Association 1980). In the DSM-IV (American Psychiatric Association 1994) the term SAD was first introduced. This latest label highlights the pervasiveness and impairment produced by SAD and permits to differentiate more clearly this disorder from specific phobias (Furmark 2000, Liebowitz et al. 2000).

DSM-IV describes a generalized subtype of SAD (GSAD) (American Psychiatric Association 1994). It
was described as a more marked, severe form of SAD leading to a worse prognosis (Stein and Gorman 2001, American Psychiatric Association 2000). DSM-V does not include GSAD subtype anymore, since most researchers considered it a more severe occurrence of SAD (Bogels et al. 2010, El-Galbalwy et al. 2010). DSM-V now features a “performance only” specifier, which should be taken into account when SAD core fear is restricted to public speaking or performing settings (American Psychiatric Association 2013).

Comorbidity with other psychiatric disorders is common in SAD, particularly with other anxiety disorders, like obsessive-compulsive disorder (OCD) (Assunção et al. 2012), generalized anxiety disorder (GAD) (Rodriguez et al. 2005) and panic disorder (PD) (Talati et al. 2008). Even body dysmorphic disorder (BDD) is highly comorbid with SAD (Fang and Hofmann 2010).

Patients with SAD may also fulfill the criteria for a diagnosis of major depression, dysthymia or bipolar depression (Pini et al. 1997, 2006). Alcohol abuse and dependence are similarly very common (Behrendt 2011).

The aim of this paper is to review the recent findings on possible neurotransmitters and brain areas involved in the pathophysiology of SAD, and their therapeutic implications.

Brain circuits in SAD

Amygdala

For some decades, several findings have supported the pivotal role of the amygdala in conditioning and processing of fear (Adolphs 2002). Sensory fibers from visual, auditory, olfactory, nociceptive, and visceral pathways through the anterior thalamus arrive to the lateral nucleus of the amygdala (LNA), which is connected to the central nucleus of the amygdala (CNA). The CNA serves as a central processing hub for both information and execution of autonomic and behavioral fear responses. CNA efferents extend to the parabrachial nucleus and to the lateral hypothalamic nucleus (Cannistraro et al. 2003). Exaggerated amygdala responses in SAD have been observed during public speaking or the anticipation of public speaking (Tillfors et al. 2002, Lorberbaum et al. 2004) and negative comments (Cervenka et al. 2012), and also in response to neutral, angry, contemptuous, happy, and schematic angry facial expressions (Yoon and Fitzgerald 2007). The anterior cingulate cortex and neighboring prefrontal areas control the attention to threat-related stimuli and inhibit amygdala activity by top-down regulation. While the amygdala may be a trigger region predominantly responsible for eliciting certain emotions, the prefrontal cortex appears to be a modulatory region that is important for emotional control. Neuroimaging data may imply that the prefrontal cortex, including the ventromedial and dorsolateral regions, exerts inhibitory top-down control of amygdala activation, and a similar regulatory role has been proposed for the anterior cingulate cortex (Stein et al. 2007). Patients with GSAD and a control group were exposed to hostile vs happy facial emotion (Stein et al. 2002) or to neutral faces during functional magnetic resonance imaging (fMRI) (Cooney et al. 2006). Interestingly, the SAD patients showed an exaggerated right amygdala activation compared with control subjects. These findings emphasized modifications particularly in the amygdala/medial temporal lobe region, insula, and striatum of patients with SAD, and they stressed the alterations of serotonergic and dopaminergic neurotransmission. Therefore, activation studies in SAD patients, with a few exceptions, have demonstrated amygdala hyper-responsivity to different social-emotional stimuli, including anticipatory and situationally elicited speech anxiety (Stein et al. 2002, Cooney et al. 2006). However, it is unclear whether the amygdala is generally hyper-responsive or reacts exclusively to disorder-specific stimuli. An increased activity of the amygdala is associated with a decreased activation of the mesiofrontal cortex in patients with anxiety disorders (Schüle et al. 2013).

Dorsal raphe

Another area of interest in SAD-related circuitry is the dorsal raphe nuclei, where serotonin (5-HT) is produced. While projections from the prefrontal cortex and locus coeruleus inhibit the activity of the raphe nucleus (Frazer et al. 1994, Hajós et al. 1998), the raphe nucleus projections seem to inhibit the locus coeruleus and, interestingly, the hypothalamus and the amygdala (Aston-Jones 1991, Gorman et al. 2000). Dorsal raphe nuclei exhibit corticotropin releasing hormone (CRF) receptor-binding sites (Chalmers et al. 1995). CRF administration into dorsal raphe nuclei reduces the release of 5-HT levels in the lateral septum, which can be attenuated by pretreatment with a CRF receptor antagonist (Price and Lucki 2001). The dorsal raphe nucleus neurons innervates basal ganglia, while median neurons innervates the limbic structures (Marcin and Nemeroff 2003). It should be pointed out that projections from the prefrontal cortex and locus coeruleus inhibit the activity of the raphe nucleus (Frazer et al. 1994, Hajós et al. 1998). At the same time, the raphe nucleus projections inhibit locus coeruleus and, interestingly, the hypothalamus and the amygdala, the latter in an indirect way (Schüle et al. 2013, Carta et al. 2011). Two main pathways project from the dorsal raphe nuclei to the periaqueductal gray and also to the amygdala and frontal cortex, which mediate avoidance behavior to potential threats. Interestingly, a 5-HT releasing agent, seemed to decrease the rise of anxiety levels experienced in nonclinical subjects who were speaking in front of a video camera (Graeff et al. 1996).

Locus coeruleus

The activity of the locus coeruleus is implicated in the increased attention in response to threat, while the paragigantocellularis and prepositus hypoglossi nuclei are the primary modulators of norepinephrine (NE) release by the locus coeruleus. In particular, the prepositus hypoglossi nucleus shows CRF receptors that improve the release of NE in response to stress (Robbins et al. 1995, Valentino et al. 1993).

Prefrontal cortex

As reported above, alterations of the serotonergic system have been widely described in mesiofrontal areas during an exaggerated amygdala responsiveness in SAD patients (Adolphs 2002, Tillfors et al. 2002, Lorberbaum et al. 2004). Several functional studies have reported altered amygdala activation to facial stimuli in SAD patients, with a specific association of augmented...
responsiveness to anxious or angry faces (Stein et al. 2007, Stein et al. 2002).

Recently, hypoactive dorsolateral prefrontal cortex (dLPFC) response was described in pediatric patients with anxiety disorders, including SAD. These findings suggest that insufficient error-related engagement of the dLPFC are associated with anxiety across traditional diagnostic boundaries and appears during the early stages of illness (Fitzgerald et al. 2013). In a clinical trial, regional electroencephalography (EEG) activity was recorded in 23 SAD patients undergoing stress-related cognitive-behavioral therapy (CBT). The results showed that patients shifted significantly from greater relative right to greater relative left resting frontal brain activity from pre- to post-treatment. Authors suggested that resting frontal EEG asymmetry may be a predictor of symptom change and end-state functioning in SAD patients who undergo effective psychological treatment (Moscovitch et al. 2011).

To summarize, these are scattered, albeit interesting, data that require further support in larger and different clinical samples.

Anterior cingulate cortex

Facial expressions of fear and disgust led to an exaggerated activation response of rostral cingulate cortex (rACC) in SAD patients (Schneier 2009, Amir et al. 2005). One study reported increased orbito-frontal cortex activation to angry prosody (Quadflieg et al. 2008). In contrast, other studies described decreased activation (Van Ameringen et al. 2004) and glucose metabolic rates in the ventromedial prefrontal cortex, which both increased following treatment with tiagabine (Evans et al. 2009). Glutamate/creatine and N-Acetylaspartate (NAA)/creatine ratios appeared to be elevated in the rACC and related to symptom severity (Phan et al. 2005). Studies of dorsal anterior cingulate cortex (dACC) function in SAD have been somewhat controversial. Greater dACC activation has been reported in response to negative comments (Schneider et al. 2009) and harsh or disgusted facial expressions (Amir et al. 2005), while treatment with nefazodone decreased activation in the dACC (Kilts et al. 2006). In contrast, other studies have reported decreased dACC activation in anticipation of public speaking (Tillfors et al. 2002, Lorberbaum et al. 2004) as well as decreased glucose metabolism at rest (Dell’Osso et al. 2003). One possible explanation of these controversies is that medial prefrontal cortex/ dACC responses to faces in SP are temporally delayed (Campbell et al. 2007). Finally, one study reported reduced serotonin-1A (5-HT1A) receptor binding in the anterior cingulate cortex in patients with SAD, although it was not specified whether this finding occurred in the dACC or rACC (Lanzenberger et al. 2007).

Neurotransmitters/Peptides

Several neurotransmitters, in particular serotonin, norepinephrine, dopamine (DA), and neuropeptides, such as oxytocin (OT), have been hypothesized to be involved in the neurobiology of SAD. Although the data are still meager, they will reviewed in the next paragraphs.

Serotonin

Evidence toward a pivotal role of 5-HT in SAD is represented by the evidence that depletion of tryptophan (TRP), the 5-HT precursor, which temporally decreases serotonergic neurotransmission, can increase public speaking stress in patients with GSAD treated with selective serotonin reuptake inhibitors (SSRIs) (Van Veen et al. 2009).

Many studies in biological psychiatry have focused on the 5-HT transporter (SERT), a protein that represents the limiting factor of the intrasynaptic concentration of 5-HT (Holmes et al. 2003, Ansorge et al. 2004, Lohmueller et al. 2003, Caspi et al. 2003). The promoter gene that influences SERT is characterized by the presence of 2 alleles, which are labeled as short or long alleles (Heils et al. 1996). The presence of 2 long alleles is associated with increased 5-HT reuptake (Lesch et al. 1996). Development of 2 SERT knock-out (KO) mice provided a unique mean to study the effect of SERT loss on anxiety-related behaviors under genetic and environmental conditions. Interestingly, SERT KO mice show increased anxiety-like behaviors on different tests validated for their sensitivity to drugs that affect anxiety in humans, such as the elevated plus-maze and light/dark exploration test (Holmes et al. 2003, Ansorge et al. 2004, Borsini et al. 2002).

In addition, recent data have shown that a third line of mutants that lack the C-terminus of the SERT exhibited also heightened anxiety-like behaviors. Loss of SERT gene function is involved not only in increased anxiety, but also in the ability to cope with stress. Along this line, a positron emission tomography (PET) study of 18 patients with a DSM-IV diagnosis of SAD, which asked participants to perform a stressful speaking task in front of an audience or alone, led to intriguing findings. Individuals with 1 or 2 copies of the short allele exhibited significantly increased levels of anxiety-related traits and enhanced right amygdala response to anxiety provocation, as compared with subjects who were homozygous for the long allele. In addition, patients with short alleles showed significantly higher Beck Depression Inventory depression and anxiety trait scores than those with long alleles. The amygdala’s activity differed as a function of the SERT polymorphism only when passing from baseline to the provoked condition, while supporting the notion that the short allelic groups differed in neural responsiveness in parallel with the increased levels of anxiety related to the situational changes (Furmark et al. 2004). Further, individuals with the short allele were also more prone to develop major depression, but only if they had experienced multiple traumatic life events, such as childhood abuse or neglect, job loss, or divorce (Caspi et al. 2003). Other studies highlighted how the relation-ship between the short allele of the SERT promoter and stress reactivity was mediated by the level of functioning of the neural pathways that regulate emotion. The neural activation was assessed by fMRI in a relatively small (N = 14) number of short-allele individuals during perceptual processing of fearful and angry human facial expression (Hariri et al. 2002, Davis and Whalen 2001). During the task, short-allele individuals exhibited nearly 5-fold greater amygdala activity than long allele homozygotes. Genetically mediated changes in SERT function influence both structures and functions of the corticolimbic pathways that regulate the brain’s ability for effectively dealing with stress. Some authors suggested that these neural changes contribute to the emergence of individual differences in affect and temperament that are associated with SERT gene variation (Caspi et al. 2003). Such findings,
Therefore, would suggest a genetically determined link between serotonergic functions and brain processing of emotions. In such a framework, it is possible to hypothesize a neuroanatomical system where anxiety proneness and brain regions that are fundamental for emotional processing are strictly intertwined in such a way that certain genetic assets could be relevant for the vulnerability of developing SAD after emotionally relevant events.

**Norepinephrine**

NE is a neurotransmitter involved in the regulation of attention, concentration, memory, arousal, emotions, sleeping, dreaming and learning (Harley 1987, Ressler and Nemeroff 1999, Tanaka et al. 2000). The actions of NE are mediated by different adrenergic receptors, the so-called α (α1 and α2) and β. The current data on the possible role of NE in SAD are scant, obtained in small samples of patients and quite old and have never been replicated, and, as such, of limited value. Autonomic hyperarousal symptoms (blushing, tachycardia, tremors), are common in SAD, and suggest NE involvement. Higher NE plasma levels in patients with SAD or PD than in healthy control subjects or even in patients with PD after an orthostatic challenge test were reported more than two decades ago (Stein et al. 1990). These findings are consistent with findings of two separate studies reporting that SAD patients share a greater increase in heart rate than control subjects (Rosen et al. 1996, Heimberg et al. 1990). These data are also supported by the heightened cortisol response to fenfluramine, which is also a 5-HT releasing agent, in SAD patients (Potts et al. 1991). Limited data are also available on yohimbine, an α2 adrenergic antagonist, the administration of which increases anxiety levels in SAD patients, together with increased plasma concentrations of 3-methoxy-4-hydroxyphenylglycol, the main NE catabolite (Potts et al. 1996). It is probable, although NE does not seem to play a pivotal role in the pathophysiology of SAD, it is involved in the typical hyperarousal and vegetative symptoms of this disorder.

**Dopamine**

DA is a neurotransmitter that modulates motivation, pleasure, cognition, memory, learning, and fine motor control, as well as some neuroendocrine responses (Girault and Greengard 2004). There are at least five major dopamine receptor subtypes, D1, D2, D3, D4, D5, while other two, the so-called D6 and D7, have yet to be clearly identified. The intrasynaptic concentration of DA is regulated by an active transporter (DAT), which is mainly found in nigrostriatal, mesolimbic, and mesocortical pathways. Since DA is the key neurotransmitter in the striatum, neuroimaging studies using experimental tasks that activate striatal structures may be informative regarding its functioning. During a striatal-dependent learning task in a fMRI study, significantly lower BOLD response in the left caudate nucleus of GSAD patients was reported, as compared with control subjects (Sareen et al. 2007). Two independent single photon emission computed tomography (SPECT) studies confirmed this finding, and also showed reduced levels of striatal dopaminergic markers (Tiihonen et al. 1997, Schneier et al. 2000).

The distribution and density of DAT were explored in 11 patients with SAD and in a control group by the radioligand ([123 I]β-CIT) with SPECT. The results underlined that SAD patients had lower DAT striatal density than control subjects, and they suggested the presence of a lower number of dopaminergic synapses and neurons in the basal ganglia (Tiihonen et al. 1997).

In another study, D2-receptor binding was measured by SPECT in SAD patients and a group of healthy controls subjects during a constant infusion of the [123I]IBZM, a D2 tracer. The results demonstrated that the mean D2-receptor binding potential in the striatum was significantly lower in SAD patients than in the control group. These findings seem to be in agreement with preclinical studies, showing that animals with subordinate social status share behavioral features with human SAD, and may thus represent a useful model for understanding the brain function underlying human SAD (Olman et al. 1986). The same findings were obtained in a PET study of female cynomolgus monkeys, which revealed lower striatal D2 binding in subordinate animals (Grant et al. 1998). In humans, low D2 receptor binding seems to be strictly correlated with SAD, rather than representing a non specific correlate of stress and mental disorders (Schneier et al. 2000). It is, however, noteworthy that later the same authors did not replicate this finding in a larger group of GSAD patients (Schneier et al. 2009). Recently, lower levels of dopaminergic markers in frontal and limbic brain regions were noted in SAD patients than in control subjects (Cervenka et al. 2012). In this study, nine patients with SAD were recruited and examined by high-resolution PET and the high-affinity D2-receptor antagonist radioligand [11C]FLB457, before and after 15 weeks of CBT. The results showed a statistically significant reduction of social anxiety symptoms, as assessed by the anxiety subscale of Liebowitz Social Anxiety Scale (LSASanx), and negative correlations between the scale changes and those of the D2-receptor binding potential in dorsolateral prefrontal cortex, hippocampus and median prefrontal cortex. This last area seems to be involved also in monitoring the social evaluation and in fear extinction (Blair et al. 2008, Sotres-Bayon et al. 2006, Miland and Quirk 2002).

To summarize, these results would indicate that SAD may be associated with decreased central nervous system (CNS) dopaminergic transmission, although the available data are limited and need to be replicated in larger samples of patients (Schneier et al. 2009).

**Oxytocin**

Oxytocin (OT) is a neuropeptide produced in the paraventricular and supraoptic nuclei of the hypothalamus. After synthesis, OT is stored in the neurohypophysis (posterior pituitary) before being released into the bloodstream to exert its peripheral effect. This peptide is also released from the hypothalamus into the CNS in response to specific stimuli (Marazziti and Catena Dell’Osso 2008). In humans, OT generally facilitates social interactions and feelings of attachment, and is becoming increasingly established as a “prosocial neuropeptide”, with therapeutic potential in treatment of social, cognitive, and mood disorders (Guastella et al. 2010, Hollander et al. 2007, Bakermans-Kranenburg and van Ijzendoorn 2013, Domes et al. 2013, Hall et al. 2012, Eisenstein 2012, Stevens et al. 2012) this growing body of evidence implicates OT in mediation of complex social behaviors.

In fact, in highly social species, OT has been shown to be involved in monitoring the social evaluation and in fear extinction (Blair et al. 2008, Sotres-Bayon et al. 2006, Miland and Quirk 2002). To summarize, these results would indicate that SAD may be associated with decreased central nervous system (CNS) dopaminergic transmission, although the available data are limited and need to be replicated in larger samples of patients (Schneier et al. 2009).
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the rewarding aspects of attachment (Bartz et al. 2010, Meyer-Lindenberg 2011).

In particular, the mother–infant interaction and other aspects of the early postnatal period may alter response of adult neurogenesis to stress, and persistent changes in the CRF systems due to early life stress have been demonstrated (Heim et al. 1997, Mirescu et al. 2004). OT may be a candidate substrate for the transduction of early experiences into both short-term and long-term behavioral changes and other consequences, ranging from brain growth to later stress reactivity to social stimuli is in agreement with emerging primate lesion studies (Prather et al. 2001) and human data that indicate that social relevance of the stimuli is in agreement with emerging primate lesion (Prather et al. 2001) and human data that indicate that the role of OT would seem generally to be that of keeping anxiety levels under control to a point where they are no longer harmful, but may nevertheless lead to such strategies and behaviors as are best suited to ensuring a partner’s continued proximity both during the first and subsequent stages of the romance. OT might thus be considered an essential element in securing the rewarding effects of a romantic relationship, as a result of its increasing a prospective sexual partner’s willingness to accept the risk deriving from social contacts (Kosfeld et al. 2005) through the modulation of anxiety mechanisms.

Just a few data suggest a direct role of OT in specific anxiety disorders including SAD. OT is positively related with sociality, calm, and tolerance and seems to decrease stress response and anxiety levels. Pregnancy, a period characterized by increased OT levels, is protective for some anxiety disorders, including panic disorder. In fact, OT is released during the stress response and seems to be an important modulator of anxiety and fear response, mainly with anxiolytic effect (Jezova et al. 1995, McCarthy et al. 1996, Marazziti et al. 2006). From a neurobiological point of view, dysfunctions of the amygdala, which is implicated in the biological response to danger signals in social interaction, have been detected in depression and anxiety disorders. As already mentioned, its function is strongly modulated by OT, as its intranasal administration may reduce amygdala activation and its output to the brain regions involved in the autonomic and behavioral response to fear (Kirsch et al. 2005). Moreover, a down-regulation of OT receptors recently has been related to the pathophysiology of SAD, which might explain the cognitive misappraisals typical of the patients affected by this condition (Kirsch et al. 2005).

However, no significant differences in OT level were found in patients with SAD as compared with healthy control subjects; in the SAD patients, however, higher OT levels were associated with higher social anxiety symptom severity and dissatisfaction with social relationships (Hoge et al. 2008). Taken together, these findings support the notion that OT is a prosocial hormone and, as such, it may influence the development of SAD and other disorders. However, research in this field in humans is just at its dawn, and there is a great need for data in clinical samples.

Conclusion

SAD is a condition that is still poorly diagnosed and investigated. For this reason, available data on its possible neurobiology are scant, are often derived from findings obtained in other anxiety disorders, and are mainly hypothetical. In any case, while keeping in mind all these limitations, there exist preliminary data of involvement of some neurotransmitters and brain areas, so that a general and preliminary framework can
be drawn (figures 1 and 2). Serotonin seems to play a major role in SAD, and not surprisingly represents the major target of currently approved medications, that is to say, SSRIs (Blanco et al. 2013, Schneier 2011).

However, undoubtedly, NE and DA are also important in SAD and may well become some of the targets of future specific drugs, as they are neurosteroids. This is particularly relevant for OT, which seems to be a core element in the neural processes that promote human sociality. SAD may be the result of excessive negative attribution given to social stimuli, and/or deficit of prosocial mechanisms. Interestingly, there are some intriguing data showing that intranasal OT has anxiolytic and prosocial properties, so the modulation of this peptide and the development of agonist/antagonists acting at the level of its receptors seem to constitute a real step towards the discovery of novel therapeutic options for this disabling condition.
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