Pharmacology, Biochemistry and Behavior 121 (2014) 138–145

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

Antidepressant-related sexual dysfunction — Perspectives from neuroimaging

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ARTICLE INFO

Available online 11 December 2013

Keywords:
Neuroimaging
fMRI
Antidepressants
SSRI
Sexual dysfunction

ABSTRACT

Sexual dysfunction is not only a common symptom in major depression but also a frequent side-effect of antidepressant medication, mainly of the selective serotonin reuptake-inhibitors (SSRI) that are often prescribed as a first line treatment option. Despite of the increasing incidence and prescription rates, neuronal mechanisms underlying SSRI-related sexual dysfunction are poorly understood and investigations on this topic are scarce. Neuroimaging techniques, mainly functional magnetic resonance imaging (fMRI), provide a feasible approach to investigate these mechanisms since SSRI-related sexual dysfunction is most likely related to central nervous processes. This review summarizes the recent literature regarding the basic clinical findings and imaging correlates of antidepressant-related sexual dysfunction linking brain regions and networks potentially involved to phases and subcomponents of sexual processing and antidepressant action. In particular, fMRI studies on SSRI antidepressants including paroxetine and SNRIs including bupropion are highlighted.

1. Brain imaging of sexual processing

Neuroimaging studies investigating brain activations during sexual stimulation in humans confirmed and expanded the current knowledge on related neural mechanisms from animal experiments (see Pfaus, 1999; Pfaus et al., 2012 for reviews) and observations in patients with brain lesions (Baird et al., 2007). Studies mainly using functional magnetic resonance imaging (fMRI) and some using positron emission tomography (PET) revealed neuronal networks and their potential role for subcomponents and phases of sexual processing. These consecutive phases have been conceptualized as desire, arousal and orgasm (Kaplan, 1979; Masters, 1966). Neuronal networks previously linked to the processing of emotion, motivation and attention (Mouras et al. 2003; Walter et al. 2008a) were found involved as well as activations of subcortical brain areas previously investigated in animal studies like the hypothalamus, thalamus, basal ganglia and brain stem (Metzger et al., 2010; Ponseti et al., 2006; Redoute et al., 2000; Walter et al., 2008a).

Sexual responses were induced by using erotic stimulation via static pictures (Moulier et al., 2006; Mouras et al., 2003; Ponseti et al., 2006; Redoute et al., 2000; Walter et al., 2008a) and video clips (Abler et al., 2012; Abler et al., 2011; Gizewski et al., 2006; Karama et al., 2002; Miyagawa et al., 2007) as well as penile stimulation (Georgiadis et al., 2010; Georgiadis and Holstege, 2005; Holstege et al., 2003). While investigations using pictures or videos are rather apt for conclusions regarding the desire and arousal phase of the sexual cycle, direct genital stimulation studies allow for assumptions regarding brain networks involved in the orgasm phase. A recent review by Georgiadis and Kringelbach (2012) summarizes the findings from brain imaging of sexual responses with the conclusion that the functional neuroanatomy of sexual behavior closely resembles that of other pleasures or rewarding experiences. They link the desire phase to the "wanting" component of rewards (Berridge et al., 2009) with increased activations in cortical and subcortical brain areas involved, such as hypothalamus, ventral striatum, amygdala, anterior insula and orbitofrontal cortex. Arousal and orgasm phases are summarized as related to the "consummatory" component of rewards with decreased amygdala and ventromedial frontal cortex activations, particularly during orgasm. The refraction phase following orgasm is linked to increased activations within the hypothalamus, amygdala and the orbitofrontal cortex. The studies summarized in this review support the conclusion that increased anterior midcingulate cortex and posterior insula activations are only found during the arousal phase. Fig. 1 summarizes the schematic distribution of regional activation during the linear stages of sexual arousal as proposed by Georgiadis and Kringelbach (2012) and links them to the dimensional subcomponents of the 4-component model of sexual processing as suggested by Redoute et al. (2000).

As reviewed in Metzger et al. (2013) the autonomic and endocrinological component regulating physiological processes that lead to readiness for sexual behaviors has been linked with neural activations in the

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http://dx.doi.org/10.1016/j.pbb.2013.12.003

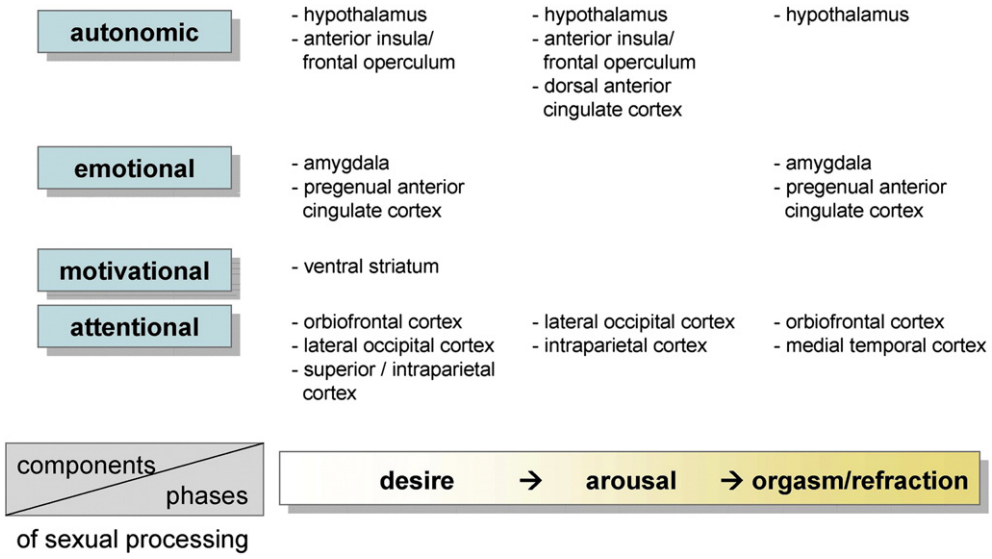

Fig. 1. Brain regions with increased activation related to phases of the sexual response cycle (modified from Georgiadis and Kringelbach, 2012) and subcomponents of sexual processing as suggested by Redoute et al. (2000). The orgasm phase itself was rather related to activation decreases different from the following refraction phase.

hypothalamus, anterior insula and dorsal parts of the cingulate cortex (Moulier et al., 2006; Redoute et al., 2000). The motivational component (Fisher et al., 2006; Redoute et al., 2000) involves increased activation in the ventral striatum and the emotional component within the amygdala, pregenual anterior cingulate cortex and the mediodorsal thalamus (Metzger et al., 2010; Walter et al., 2008a). Cognitive aspects of sexual processing as conceptualized in an attentional component of sexual processing were linked to a temporo-occipito-parietal network and orbitofrontal brain regions (Moulier et al., 2006; Mouras et al., 2003; Walter et al., 2008a, 2009). In line with the recent proposition by Georgiadis and Kringelbach (2012), an earlier study (Walter et al., 2008a) could directly discern circumscribed activations specific to sexual arousal in the hypothalamus and ventral striatum only, while less specific activations related to accompanying general emotional attachment were related to a wider affective network encompassing the amygdala and the medial thalamus. On a higher spatial resolution however, additional regions specifically involved in processing the sexual information were identified along the paraventricular thalamic nuclei (Metzger et al., 2010; Walter et al., 2008b). This is in line with a previously established network which connects these structures to the earlier identified hypothalamic and ventral striatal structures (Metzger et al., in press; Ongur et al., 1998). Overall, these studies revealed that brain networks involved in sexual processing can be reliably studied within the framework of functional imaging, thus allowing the investigation of modulators of the activations such as disorders of sexual functioning or pharmacological interventions as with antidepressants.

2. Antidepressant-related sexual dysfunction — a challenge in psychopharmacology

Depression is increasingly recognized and diagnosed as a major health problem in western countries. Concurrently, prescription rates of antidepressant medications are increasing (Bauer et al., 2008). Due to the otherwise favorable spectrum of side effects with good tolerance, for example even in patients with heart disease, selective serotonin reuptake inhibitors (SSRIs) are very commonly prescribed as a first line medication. However, although relatively safe in other health domains, pharmacologically induced sexual impairment is frequent under SSRIs. Due to the high prescription rates, it is hardly neglectable as a side effect (Serretti and Chiesa, 2009). A better understanding of SSRI-related alteration of sexual functioning is not only relevant because the side effect is frequent and unpleasant, but particularly because it causes patients to discontinue therapies, especially after remission of depressive symptoms (Finger, 2001). As early discontinuation compared to the recommended maintenance therapies over several months is related to increased rates of relapse (Gaebel and Falkai, 2001), this can compromise the overall success of antidepressant therapies.

Sexual dysfunction is a common symptom of depression itself and impairments are possible for all phases of the sexual cycle (Atlantis and Sullivan, 2012). 40% of male unmedicated patients have reported problems regarding sexual interest or arousal and up to 20% complain of problems with ejaculation or reaching orgasm (Kennedy et al., 1999). However, the additional relationship between intake of serotonergic drugs and sexual side effects has been demonstrated convincingly. Depressed patients taking serotonergic medication showed higher overall prevalences of sexual dysfunction (Clayton et al., 2007, 2002). Moreover, patients with comparable complaints upon study onset developed this side effect more frequently under SSRI's when compared to placebo intake (Coleman et al., 1999; Croft et al., 1999).

Investigating this side effect using neuroimaging techniques seems particularly interesting, because decreases of sexual arousal and libido under SSRIs are quite likely related to central nervous, and only to a lesser extent to peripheral mechanisms (Frohlich and Meston, 2000). While pharmacologically induced sexual dysfunction for example under blood pressure medication (Manolis and Doumas, 2012) largely seems to relate to peripheral influences on blood perfusion or vegetative innervation of the genitals, animal experiments support the notion that SSRIs cause sexual impairment via central mechanisms (Waldinger et al., 1998). Particularly decreased libido, linked to the desire phase of the sexual cycle, that occurs in males and females under SSRIs can be attributed to central mechanisms. Thus, imaging of neural correlates of erotic picture and video viewing seems a feasible approach. Impaired erection and ejaculation in males might be related to central as well as peripheral influences of the drugs. Overall, up to 60% of patients treated with SSRIs report sexual dysfunction of any kind (Gregorian et al., 2002). The highest rates (64.7%) are reported for paroxetine (Clayton et al., 2002). Understanding the neuronal mechanisms of SSRI induced ejaculatory dysfunction may further help to unmask target mechanisms of therapeutic approaches of serotonergic action in the treatment of premature ejaculation, with dapoxetine as the first substance with a specific approval for this indication (McMahon, 2012).

The sexual response cycle premises a complex interplay between the autonomic nervous system, hypophyseal–pituitary–adrenal axis, sex hormones and neurotransmitters that ensures its functioning