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REVIEW ARTICLE

SEXUAL DISORDERS CAUSED BY ANTIDEPRESSANTS: CONSIDERATIONS IN THE CONTEXT OF BRAIN HEMISPHERE FUNCTIONS

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Abstract

All phases of normal sexual activity are under the control of the right hemisphere coupled with limbic structures, and depression is characterized by the functional insufficiency of this system. At the same time, those modern antidepressants that cause sexual disorders are activating the left hemisphere and determine its domination on the expense of the right one and disturb free and spontaneous emotional interrelationships, sexual behavior and pleasure. Those antidepressants that do not cause sexual dysfunction are not activating predominantly the left hemisphere structures and activate the limbic brain zones responsible for reward, reinforcement and emotional excitement.

Key words: Antidepressants; Brain Hemispheres; Sexual Dysfunction

The aim of this theoretical review is to reconsider the mechanisms of sexual disorders caused by the most common antidepressants by taking into consideration the interrelationships between the left and the right hemisphere and their role in different phases of sexual activity. I will start with this topic and afterward turn to the antidepressants that cause and do not cause sexual disorders.

BRAIN MECHANISMS OF SEXUAL ACTIVITY

There are four consecutive phases of normal sexual activity: sexual excitation (arousal), plateau, orgasm and resolution. Each phase is characterized by the specific combination of activation and deactivation of brain structures. Some of these patterns are similar and some are different in men and women.

Orgasm is a peak of sexual experience. According to Georgiadis et al. (2009) in both genders orgasm is characterized by the functional activation of anterior lobe of the cerebellar vermis and deep cerebellar nuclei as well as pontine tegmentum, and deactivation of the left dorsolateral, ventromedial anterior orbitofrontal cortex and temporal lobe. In comparison to clitorial stimulation in women when orgasm has to be avoided, orgasm is characterized by the relative decrease of cortical blood flow (rCBF) in the left lateral orbitofrontal cortex, inferior temporal gyrus and anterior temporal pole (Georgiadis et al., 2006). In comparison to the rest state, orgasm is characterized by decreased rCBF in ventro – and posterolateral parts of the left temporal lobe, left amygdala and right anterior temporal pole, and by increased blood flow in central sulcus (a primary somatosensory cortex), in primary motor cortex, in deep cerebellar nuclei and in adjacent anterior lobe of vermis. In comparison to sexual stimulation of erotic zones, orgasm is characterized by an increase of rCBF in the left deep cerebellar nuclei and by decrease of blood flow in the left lateral orbito-frontal cortex, left ventrolateral temporal lobe, fusiform gyrus, left anterior temporal pole and left posterior insula (see Georgiadis et al., 2006).

Ejaculation (that in most cases is the sign of orgasm in men) is accompanied by increased functional activity (according to rCBF) of the right prefrontal cortex and decreased activity in all other cortical areas, combined with activation of brain structures in subcortical areas (Georgiadis et al., 2006). In men orgasm and ejaculation are accompanied by activation in the anterior part of cerebellum and decreased rCBF in the left temporal structures, ventromedial prefrontal cortex and right anterior temporal pole. It corresponds with data that temporal lobe resection and frontal lobe deficiency cause

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hypersexuality and are linked to increased sexual activity. Georgiadis et al. (2006) emphasize that frontal and temporal lobes have inhibitory control over sexual behavior and according to the abovementioned data it is possible to suggest that this inhibitory control is performed predominantly by the left frontal and temporal cortex. Hyperactivity of the orbito-frontal cortex is present in obsessive –compulsive disorders with excessive self-control and reduced sexual behavior.

Dorsomedial prefrontal cortex in healthy subjects is involved in moral reasoning and social judgment and it looks very relevant that it is deactivated during orgasm in order not to interfere with its emotional excitement, agitation and non-restricted spontaneous and relaxed behavior. Presumably this function of control and judgment is related predominantly to the left prefrontal cortex only, because it was shown that right prefrontal cortex was activated by masturbation leading to orgasm (Ozkara et al., 2006), and that ejaculation is accompanied by the functional activation of the right prefrontal cortex (Georgiadis et al., 2006).

The abovementioned data show that, in opposite to the left brain cortex, the subcortical brain areas are activated in different combinations in all phases of sexual activity.

Lesions of the prefrontal cortex led to the dyscontrolled sexual behavior (Spinella, 2007). Of course, inability to perform control over own motivations may cause maladaptive behavior. Actually, individuals with orbitofrontal cortex damage do not have normal anticipatory affective response to potential punishment (Bechara, 2004). Persons with this damage are oblivious to the future consequences of their actions and are sensitive only to immediate reinforcement and punishment and their actions are guided only by immediate consequences. In most conditions it has a negative outcome. However, the surplus control over the motivation and behavior prevents the normal sexual intercourse between partners who are in love and has to be avoided.

By investigating epileptic seizures that appear in some women after sexual intercourse and orgasm, Ozkara et al. (2006) found that epileptic focus in 4 cases was in the right temporal area and only in 1 case in the left frontal area. It confirms data of Janszky et al., 2002, that in epileptic seizures-related sexual phenomenon epileptogenic zones are predominantly in the right hemisphere that plays a dominant role in sexual functions: orgasmic sensation is a production of right temporal lobe and right amygdala. Data presented and cited by Bianchi-Demicheli and Ortigue 2007, are in agreement with the above-mentioned data and confirm that orgasmic aura is mostly originated from the right hemisphere. According to Meston et al. (2004) orgasm is a peak sensation of intense pleasure, creating an altered state of consciousness, and altered states of consciousness are based on the functional domination of the right hemisphere (Ornstein, 1972; Rotenberg, Arshavsky, 1991). Orgasmic sensation might be the result of the spread of focal activity within the right hemisphere, especially within temporal lobe in cortical and subcortical areas and if this mechanism is not disturbed even women with spinal cord injuries are able to experience orgasm (Bianchi-Demicheli, Ortigue, 2007). Right hemisphere and particularly right temporal lobe have close and strong relationships to the limbic system responsible for the emotional live (Rotenberg, Weinberg, 1999). Limbic system plays a key role in the experience of orgasm and other sexual sensations. Nucleus accumbens is activated during intense pleasure (the key feature of orgasm). Activation of the cingulated cortex and medial amygdala during orgasm corresponds to their activation during sexual arousal, in the process of regulation of the emotional state (Bianchi-Demicheli, Ortigue 2007). In the article of these authors is also emphasized that orgasm, in comparison to the state of rest and sexual arousal, is characterized by decreased activity of prefrontal cortex and left orbito-frontal cortex, inferior temporal gyrus and anterior temporal pole (in parallel with the behavioral disinhibition during orgasm). At the same time are activated cingulated cortex and insula, brain structures that are implicated in pleasure, empathy, craving, partner selection. Empathy during sexual relationships is especially important because it allows women during orgasm to imagine and estimate how partner perceives the situation, and feeling empathy is a function of human right prefrontal cortex (Shamai-Tsoori et al., 2003).

Domination of the right hemisphere during orgasm characterizes also men. According to Tiihonen et al. (1994) photon-emission tomography shows the ejaculation-related decrease of activation in almost all cortical areas, except the right prefrontal cortex that displayed the increased activity. It was confirmed in PET investigation performed by Holstege et al., 2003, who found an ejaculation related activation of the right anterior frontal gyrus, parietal and inferior temporal cortex, in parallel with some limbic structures, like mesodiencephalon region, putamen and insula. At the same time, cerebral blood flow is decreased in the left hemisphere except of a small portion of superior frontal gyrus and visual cortex (although subject's eyes during the sexual intercourse were closed). It can reflect the active visual imagination on the top of sexual sensation.

The differentiation between the excitation and plateau phases according to brain activity is not so clear as characteristic of orgasm. In men during the excitation phase (that corresponds to the initiation of penile erection by audiovisual sexual stimuli) was found a functional activation of the right cerebellar vermis, bilateral extrastriate cortex and right orbitofrontal cortex, right anterior cingulated cortex and left insula (see Miyagawa et al., 2007). There are some contradictions in literary data. According to some authors (Dominguez, Hull, 2005)

male sexual behavior is regulated by the medial preoptic area at the rostral end of the hypothalamus. This area receives direct and indirect input from medial amygdala. However, according to Redoute and al., 2000, during the presentation of sexual film clips the magnitude of penile tumescence was positively related to cerebral blood flow in bilateral claustrum, left anterior cingulated gyrus, left putamen, right caudate nucleus, but it was no activation of amygdala or hypothalamus. In another investigation, Redoute et al. (2005) have shown the increased activity of the right orbitofrontal cortex, insula and claustrum during sexual arousal. Arnow et al. (2002) found penile erection to be associated with activity in the right claustrum, left caudate putamen, right middle occipital/ middle temporal gyri, bilateral cingulated gyrus, right hypothalamus, right sensorimotor and premotor regions. Ferretti et al. (2005) confirmed that penile erection was associated with activity of the secondary somatosensory cortices and different parts of limbic system: anterior cingulated, insula, amygdala, and hypothalamus. The letter was activated during the onset of erection and deactivated during the maintenance of erection.

Karama et al. (2002) have shown that viewing erotic film excerpts in comparison to viewing emotionally neutral film excerpts was associated, for both genders, with bilateral blood oxygen level dependent signal increases in the anterior cingulated, medial prefrontal, orbitofrontal, insular, occipitotemporal cortices, and also in amygdala and in ventral striatum. In men only erotic film activated thalamus and hypothalamus that play an important role in sexual behavior, and activation of hypothalamus may explain greater sexual arousal generally experienced by men.

Gizewski et al. (2006) have also used sexual stimulation during viewing of erotic stimuli. Women in mid-luteal phase (compared to their menses state) displayed superior activation in the anterior cingulated, left insula and left orbitofrontal cortex. Men being compared with women in mid-luteal phase demonstrated superior activation in the bilateral amygdala and left thalamus. Both genders revealed activation of the left inferior parietal cortex. The activation of temporal and parietal cortex that represents visual association areas may be related not precisely to the erotic nature of the visual sexual stimuli per se but to the more general state of visual attention (Park et al., 2001). It is reasonable to take into consideration these more general aspects of sexual experience. It can also explain the engagement of the bilateral amygdala in sexual activity.

In the comprehensive review, Cyders and Smith (2008) have shown that amygdala plays a key role in the experience of affect and in the directing attention to emotionally salient stimuli, particularly to stressful stimuli (cit. Davidson, 2003). It was shown (Dominguez, Hull, 2005) that medial amygdala is important for the realization of the androgen-induced enhancement of male sexual behavior, and lesions of medial amygdala impair copulation. There are reciprocal interrelationships between the amygdala and the orbito-frontal cortex that modulates emotional reactivity and regulates subject's readiness for actions (Barbas, 2007; Lewis, Todd 2007). Projections from amygdala to the limbic structures (the striatum, the nucleus accumbens and the ventral tegmental area) in parallel with projections to the frontal cortex, contribute to the both meaningful emotional experiences and actions according to these experiences (Cardinal et al., 2002). The ability to concentrate attention on the emotionally meaningful information is very important for building intimate relationships.

Orbito-frontal cortex after getting information from amygdala regulates connections between affect and behavioral response on this affect by taking into consideration the possible outcomes of this response and by forming bias toward the long-term goals (Lewis, Todd, 2007).

Cyders and Smith emphasize that particularly the left ventro-medial prefrontal cortex is responsible for avoiding immediate reward, impulsive response on the emotional signal and for maintaining one's pursuit and one's longer term goals. It is very adaptive in most conditions however it may be maladaptive in sexual interrelationships, in the process of sexual intercourse that has to be more spontaneous and free from rational analytical control in order to be successful and to bring pleasure.

In order to prevent impulsive emotional response, the left ventro-medial prefrontal cortex inhibits amygdalar activity. It is very relevant when it blocks the experience of negative affect and decreases the attention to the unavoidable stressful stimuli that can produce learned helplessness and depression or the maladaptive affect triggered actions, but it is not relevant when it appears in the process of sexual relationships. Amygdala is related to appraisal process through which erotic stimuli are evaluated as sexual incentives. According to Hamann and Canli, 2004, amygdala mediates sex differences in responses to appetitive emotional stimuli and may be implicated in the greater role of visual stimuli in male sexual behavior.

In PET study of Bocher et al. (2001) sexual arousal in men was associated with bilateral but predominantly right activation of the interoposterior extrastriate cortices, of the right interolateral prefrontal cortex and of the mid brain.

According to Miyagawa et al., 2007, excitation phase was characterized by activation of bilateral extrastriate cortex, right orbitofrontal cortex, right cerebellar vermus, right anterior cingulated gyrus, left insula. It is worth to stress that authors are speaking about the right prefrontal and frontal cortex activation during sexual arousal and it corresponds with the abovementioned data of the positive role of the right hemisphere in sex-

ual activity. The plateau phase was accompanied by the activation of the right ventral putamen that represents a motivational component of the sexual response via the limbic reward circuit and was strongly related to the degree of penile tumescence. Ventral putamen is a part of limbic dopamine system responsible for the hedonic properties of expected reward.

Dopamine contributes to hedonia by mediating the sensory pleasure or reward. Dopamine removes tonic inhibition in brain regions that are important for male sexual behavior in the presence of a sexually exciting stimulus or during copulation. Dopamine in general enhances sensori-motor integration. Increased dopamine in the nigrostriatal system enhances the motoric readiness to respond to sexual stimuli. Increased dopamine in the mesolimbic system is important for motivation and reinforcement. Increased dopamine in medial preoptic area is important for motor patterns of copulation and sexual motivation, for genital reflexes. Dopamine agonists apomorphine and L-Dopa induces erection, while antipsychotic drugs being dopamine antagonists cause erectile impairment.

In most investigations it was shown that dopamine facilitates male sexual behavior (see Dominguez, Hull, 2005; Peeters, Giuliano, 2008). Romantic love is associated with elevated activity of central dopamine (Fisher et al., 2006). There are positive relationships between the level of central dopamine, sex steroids, sexual arousal and sexual performance (Fisher et al., 2006).

Dopaminergic hyperactivity might be involved in premature ejaculation (Paglietti et al., 1978). Dopaminergic antagonists (antipsychotics) delay ejaculation in humans. High levels of dopamine are associated with impulsivity (Friedel, 2004) and display a tendency to engage in approach behavior (Zald, Depue 2001) and reward-seeking behavior (Spear, 2000) that are very important in sexual activity.

Dopamine antagonists impair copulation, genital reflexes and sexual motivation. LDOPA, dopamine precursor, increases libido. Dopamine enhances sensorimotor integration in the presence of sexually exciting stimulus or during copulation, and enhances the motoric readiness to respond to sexual stimuli. Dopamine agonists facilitate penile erection and may enhance sexual drive and orgasmic quality (Kruger et al., 2005). Probably the role of dopamine in general arousal, in stimulation of motor functions and in general motivational circuity can partly explain its effect on sexual behavior

Brain norepinephrine is also positively linked with sexual motivation and arousal (Clayton et al., 2002). Amphetamine enhances sexual desire (Buffum et al., 1988). It was shown by Kruger et al., 2006, that sexual arousal elicited by erotic film correlates with norepinephrine. Moderately increased noradrenergic activity stimulates sexual function. Norepinephrine increase in cerebrospinal fluid during audiovisual masturbation induced sexual arousal and orgasm (Kruger et al., 2006).

At the same time, 5-HT activity (serotonin) modulates dopaminergic activity (Spoont, 1992) performing rational inhibitory control over appetitive drives or approach behavior. As a result, low level of 5-HT is associated with greater rates of risky, irritable and impulsive behavior (Cyders, Smith, 2008) SSRIs produce a reduction in sexual drive as a result of hyperprolactinemia (Hummer, Huber, 2004, Labbate et al., 2003) in addition to its activation of the left hemisphere structures.

Extrastriate cortex was activated symmetrically during the excitation phase and showed right-side dominance during the plateau phase. It is a correlation between visual signal intensity in the right middle occipital gyrus and the magnitude of penile tumescence in response to visual sexual stimuli during the excitation phase.

Males showed more activity in visual processing area, females showed more activity in the caudate, posterior parietal cortex and septum. Anterior cingulated gyrus plays a key role in evaluation of motivational/emotional information, initiating a goal-directed behavior. Supplementary motor area and visual cortex in the left hemisphere are deactivated during the plateau phase. Plateau phase is characterized by right- dominant activation of the extrastriate cortex, ventral putamen, right posterior auditory cortex, left hypothalamus. Excitation phase is characterized by the activation of the bilateral extrastriate cortex, right orbitofrontal cortex, right cerebellar verms, right anterior cingulated gyrus and left insula (see Miyagawa et al., 2007).

Tactile genital stimulation produces sexual excitation (Georgiadis et al., 2009) and is accompanied in both genders by activation of the left somatosensory area and deactivation of right amygdala and left fusiform gyrus. In women it corresponds also to activation of left fronto-parietal areas (including motor cortex). While considering these data it is necessary to take into consideration that investigated subjects have been regularly instructed to stay as long as possible in the phase of sexual activity that was at that moment precisely investigated and not to drop from this phase into orgasm. This instruction can explain the activation of the left cortex that is responsible for the control of emotional behavior. During clitorial stimulation in such conditions is activated left somatosensory cortex, and deactivated is left amygdala. In men sexual stimulation is related to activation of right claustrum, ventro-occipital cortex and cerebellar vermis. Stimulation of erect penis causes activation of the right claustrum, insula, secondary somatosensory cortex, occipitotemporal cortex, and deactivation of right amygdala and of the left inferior temporal gyrus. Thus, during genital stimulation are activated brain areas that are responsible for the regulation of perception and motor activity.

Probably it means that stimulation, in opposite to orgasm, causes not a pure pleasure, it is a pleasure combined with attitudes towards behavioral control of the state (see above) or toward further activity. Visually evoked sexual arousal elicitates in men more activation in amygdala and hypothalamus.

Tactile sexual genital stimulation elicits differences in fronto-parietal activity between genders (in women is activated fronto-parietal area, in men occipitotemporal cortex, while left inferior temporal gyrus is deactivated). Probably the fronto-parietal activity in women during tactile sexual stimulation is related to the more prominent activation of mirror neurons during sexual interrelations (Georgiadis et al., 2009). According to mirror neuron theory, some neurons became activated both during the execution of action and the perception of the same action (or probably even during the intention of action) performed by another person. It is a neural basis for understanding of each other's actions. Main elements of this system (premotor cortex, inferior parietal lobule, posterior parietal cortex) showed female biased activation. Women (as individuals with a high capacity to sense the perspective of others) display stronger activation in mirror areas. Females have stronger motor embodiment of their partner actions (genital stimulation) and became more excited by feelings of the partner. Dorsal premotor activity was seen in response to unseen hand actions (Georgiadis et al., 2009).

Claustrum involvement reflects cross modal transfer of visual input to imagined tactile penile stimulation. With eyes closed it could point to cross-modal transfer of genital sensory information to a visually imagined situation (claustrum is connected to visual cortical area). Higher sensitivity and attention to visual stimuli in emotional paradigm is typical for men, men are more interested than women in visual sexual stimuli. This visual sexual stimulation (imagination) may intend subject toward further sexual activity.

By investigating regional blood flow in women, Georgiadis et al. (2006) have found increased rCBF in the left secondary and right dorsal primary somatosensory cortex during sexual stimulation.

In healthy men, decreased rCBF in the left lateral OFC (orbito-frontal cotex) was found in response to visual sexual stimuli.

Activity in orbito-frontal cortex increased when men who watched erotica voluntary suppressed feelings of sexual arousal (women in this investigation were suggested not to come up to orgasm). Thus, conscious control over basic sexual drive may be reflected by the activation of the left lateral OFC.

It is worth to conclude that while limbic structures during sexual arousal are activated in both (left and right) sides of the brain, the cortical structures are activated predominantly in the right hemisphere, and it is confirmed by the investigation of Beauregard et al., 2001, who showed that erotic film elicited activation in the right anterior temporal pole, in addition to right amygdala and hypothalamus. At the same time, the activation of the left cortical areas, especially orbito-frontal and temporo-parietal, are related, directly or indirectly, to the inhibitory control over the sexual excitement and behavior.

ANTIDEPRESSANTS THAT CAUSE AND DO NOT CAUSE SEXUAL DYSFUNCTIONS

According to Werneke et al. (2006) 70% of patients with depression have sexual dysfunctions. At the same time, paradoxically, antidepressants by themselves, although improving mood and restoring optimism and activity of these patients, cause sexual dysfunctions, especially tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs). Tricyclic antidepressants usually combine serotonin (5-HT) and norepinephrine (NE) reuptake inhibition, and those tricyclics that preferentially block the reuptake of NE are less associated with orgasm disorders than SSRIs (Werneke et al., 2006). Those antidepressants that have a more prominent anticholinergic activity, like nortriptyline (in comparison to amitryptiline and clomipramine) may cause more often erectile dysfunctions (Stahl, 1998) but are less associated with orgasmic problems (Sanchez, Hyttel, 1991). For men and women, orgasm quality was lower and orgasm delay longer on SSRI treatment. Erection scores were also lower over time, but this result was nonsignificant (Labbate et al., 1998). According to these authors, libido, sex frequency and lubrication did not change over time following treatment with sertraline, fluoxetine and paroxetine, and they come to the conclusion that SSRIs may affect orgasm more than other sex functions. On the other hand those antidepressants that block dopamine (DA) reuptake, have a tendency to enhance sexual functions in all domains (libido, arousal, orgasm) and for this reason are often used together or instead of SSRIs in order to protect or improve sexual functions, like bupropion that is dopaminergic and noradrenergic agonist (Baldwin, 2004). Sertraline that is not only SSRI but also DA reuptake blocker at high doses (Damasa et al., 2004) is supposed to have less sexual side effect in comparison to pure SSRIs (Werneke et al., 2006). According to (Bymaster et al., 2001), the equilibrium between serotonin and NE reuptake suggests relative absence of sexual side effects.

Actually, Werneke et al. (2006) have shown that problems with sexual desire and experience of orgasm are especially prominent in clomipramine use that is at serotoninergic end of tricyclic antidepressants. Balon and Segraves (2008) confirm that serotonin reuptake inhibitors cause sexual dysfunctions. Amitryptiline and doxepine, being on more noradrenergic end, had a lower

incidence of sexual dysfunction (Montgomery et al., 2002). Venlafaxine as one of the most strong 5-HT reuptake inhibitors, is most likely to cause sexual dysfunction (Montejo et al., 2001).

According to Serretti and Chiesa (2009) drugs acting on the serotoninergic system cause global sexual dysfunctions including sexual desire, disruption of sexual arousal and orgasm. The highest rate of sexual dysfunctions was caused by citalopram, fluoxetine, paroxetine, sertraline, venlafaxine. Drugs associated with global sexual dysfunctions were related to dysfunction in every single phase of sexual response: desire, arousal, orgasm, although in different proportions. A possible mechanism of desire dysfunction is a reduction of DA activity in the mesolimbic system by serotonin reuptake blockers (Baldessarini, Marsh, 1990). Arousal dysfunction is also determined by the reduction of DA levels in the mesolimbic system related to the potent and selective 5-HT reuptake inhibition and to the inhibition of spinal reflexes (Segraves, 1989). Orgasm dysfunction is linked to the decreased DA and NE levels induced by 5-HT2 activation (Pollack et al., 1992; Crenshaw et al., 1996). These changes result in alteration of the sympathetic and parasympathetic systems, which tone has an important role in mediating orgasm and ejaculation (Pollack et al., 1992).

Non-serotoninergic antidepressants, such as bupropion, reboxetine, mirtazapine and trazodone usually do not cause sexual dysfunctions and have to be used instead of SSRIs in order to prevent these dysfunctions and restore sexual functions like erection.

Bupropion have a pro-dopaminergic effect positively related to sexual behavior (Melis, Argiolas, 1995). In depressed patients with sexual disorders before treatment such antidepressants enhanced sexual functions (Philipp et al., 1993; Baldwin et al., 2006)

Almost all the same drugs that were not related to global sexual disorders showed no significant difference with placebo in the specific analyses.

However, the difference between antidepressants according to their effect on monoamines do not explain by itself the mechanism of sexual disorders caused by some of them as well as the similarity between these disorders on the antidepressants and in the untreated depression. It is necessary to discuss the influence of different antidepressants on the brain mechanisms related to sexual functions.

ANTIDEPRESSANTS AND ACTIVITY OF DIFFERENT BRAIN STRUCTURES

Antidepressants that cause sexual dysfunctions

Many investigations have shown that antidepressants that cause sexual dysfunctions are activating predominantly the left hemisphere structures.

Depression is characterized by the relative hypofunction of both hemispheres and the functional deficiency of the right hemisphere (that plays so important role in normal sexual behavior) is a key factor in the pathogenesis of depression (see Rotenberg, 2004, 2008). At the same time, Lefaucher et al. (2008) have shown that glutamatergic and GABAergic pathways may be defective in the left hemisphere in depression and depression is related to the hypoexcitability of the left frontal region.

According to the investigations of Bruder et al. (2001; 2004; 2007), Buchsbaum et al. (1997), Davidson et al. (2003), Hoehn-Saric et al. (2001) those depressed patients who display a positive response on the antidepressive treatment, especially SSRI, differ from non-responders in favoring left over right hemisphere processing of dichotic stimuli, words and complex tones. This relatively higher left hemisphere activity of responders determines the success of those antidepressants that affects the serotoninergic system asymmetrically distributed between brain hemispheres (Tucker, Williamson, 1984). Nishikawa et al. (2003) found that in depressed patients serotonin synthesis is lower in the left hemisphere and has to be compensated by SSRIs administration. It was shown that in healthy adults serotonin-releasing drugs (SSRIs) increased glucose metabolism in different left hemisphere areas (Mann et al., 1996a; Soloff et al., 2000; Smith et al., 2002). Single dose of fluoxetine overactivates the sensory-motor cortex and improved motor performance (Pariente et al., 2001). In paroxetine treatment activation was observed in the left superior temporal and supramarginal gyri. Mental stimulation of action performed during this treatment caused activation in the left inferior parietal cortex, right inferior frontal cortex and left frontal cortex. Paroxetine (SSRI) induced modulation of cortical activity supporting language representation of action, and language representation is based on the left hemisphere activity. Paroxetine reduced cerebral physiological activation in tasks involving semantic processes related to action representations; this reduced physiological activity in the premotor and prefrontal cortex was associated with high (ceiling-level) tasks performance what means that less synaptic/dendritic activity is required to recruit the cortical network involved under paroxetine (see Del-Ben et al., 2005; Peran et al., 2008).

According to data of Bruder et al. (2001, 2004) it is possible to conclude that responders to antidepressants (SSRIs) display relatively more normal functions and a more normal physiological state of the parieto-temporal part of the left hemisphere in comparison to nonresponders. Consequently, treatment responders display a potential preservation or even a compensatory overactivation of the left hemisphere functions that corresponds with a positive response to antidepressant treatment (see Rotenberg, 2008).

Anderson et al. (2008) presented a very substantial investigation of the serotonin function in neural processes.

Serotonin is involved in cognition, in memory and response inhibition, in motor function, in emotional processing, and correlates with the alteration of the brain activity (inhibition of amygdala and task specific modulation of the ventro-lateral orbitofrontal cortex).

A chronic SSRIs treatment improves motor performance and all sensorimotor functions in parallel with the decrease of the physiological activation of the primary sensorimotor cortex to both motor and sensory tasks. Loubineux et al. (2005) proposed that it happens due to desensitization of 5-HT receptors or due to neurotropic changes in sensorimotor neurons. In any case it probably means that chronic treatment with SSRIs enhances the functional efficiency of the sensorimotor cortex that decreases the necessity of its additional physiological activation. According to Lefaucher et al. (2008), depression is characterized by hypoexcitability of the left frontal region, including inhibitory and excitatory pathways. Glutamatergic and GABAergic pathways may be defective in the left hemisphere in depression, and they are targets for the antidepressants treatment.

Escitalopram that increases 5-HT transmission (Rose et al., 2006) increased response in the left ventrolateral orbitofrontal cortex, and acute triptophan depletion (ATD) that decreases 5-HT transmission reduces blood-oxygen- level dependent fMRI response in the left supplementary motor area. This area is involved in planning and initiating of movements, and a chronic treatment with SSRIs enhances the functional efficiency of this area what displays itself in a decreased physiological activation. Planning and initiating of movements belong to the goal-directed activity that is disturbed in depression.

The role of 5-HT in response inhibition is more complicated (Anderson et al., 2008). Serotonin may not be directly involved in the behavioral output of response inhibition, but possibly in evaluating and integrating sensory information. ATD increases depression scores (at least in females with family history of depression) and increases right amygdala activation to emotional faces as well as activation of right ventromedial prefrontal cortex. Conversely, the enhance of 5-HT function with citalopram decreased amygdala responses to negative vs. neutral and happy faces, it means decreases subject's sensitivity to such negative experience. This sensitivity makes subject vulnerable and unhappy without providing him/her with a definite way how to cope with this experience and causes giving up (renunciation of search, Rotenberg, 1984). The decrease of subject's sensitivity goes in parallel with the increase of active goal directed behavior.

If SSRIs increase the functional activity of the left hemisphere, it may explain all the abovementioned outcomes: left hemisphere organizes any information in a well-structuralized system, in the monosemantic context (Rotenberg, 1979; 1994) that on the one hand provides subject with the opportunity for the constructive goal-oriented activity and on the other hand decreases the sensitivity to the emotional stimuli that are polysemantic according to their nature and are in the competence of the right hemisphere (Rotenberg, 2004). Mental stimulation on treatment causes activation in the left inferior parietal cortex and left frontal cortex (Peran et al., 2008). The more severe pessimism in major depression is accompanied by the lower level of serotonin, while acute shift toward optimism appears after raising extracellular serotonin with alpha-fenfluramine. 5 –HT2 receptor density in cortex increases when extracellular serotonin is chronically lowered in depressive episodes with severe pessimism (Meyer, 2007).

The abovementioned approach to the role of the left hemisphere in the treatment of depression by using SSRIs (see Rotenberg, 2008) is also confirmed by the similarity in brain glucose metabolism in responders to venlafaxine (that inhibits serotonin and norepinephrine reuptake transporters) and in responders to cognitive behavior therapy (that is definitely oriented on the activation of the left hemisphere (Kennedy et al., 2007).

Thus it is possible to suggest that the effect of the antidepressants that block predominantly the brain serotonin reuptake are responsible for the activation of the left hemisphere structures if they are initially predisposed for such activation and determine active goal –oriented behavior and search activity that are opposite to depression (see Rotenberg, 1984; 2009).

It may be also partly the effect of the tricyclic antidepressants. Chronic treatment with amitryptiline induced increase in rCBF in the left frontal region that was in major depression before the treatment lower than in healthy subjects (Passero et al., 1995).

However, the relationship between the effect of antidepressants and brain laterality is more complex. It was shown (Bruder et al., 2007) that those patients who do not respond to fluoxetine treatment but respond to bupropion treatment differed from non-responders to bupropion in the relatively higher left hemisphere advantage for dichotic words. Nevertheless of such advantage they do not respond to fluoxetine treatment. It seems reasonable to suggest that bupropion and some other antidepressants that do not cause sexual disorders are effective due to activation of other brain structures apart from or in addition to the left hemisphere (see the next part of review).

According to Kampf-Shert et al. (2004) favorable response to SSRIs in depressed patients was associated with relatively high ventrolateral versus dorsolateral prefrontal index before treatment and with better functioning in "simple" tasks that requires impulsive almost automatic reaction and worse functioning in "complex" tasks that require patients to wait and/or to process large amount of information. Impulsive behavior that sacri-

fices long-term considerations for short-term gain focuses on a narrow range of stimuli and fails to accumulate and consider enough information before acting. This behavior was associated with lower serotonin (Robert et al., 1999) and presumably with less activity of the left frontal lobe that is responsible for the analysis of information and probability forecast (see Rotenberg, 2007). Impulsive behavior in depressed patients may be manifested in suicidal tendency (Asberg et al., 1976; Mann et al., 1989), anger attacks, and all these disorders are effectively treated by SSRIs, as well as other forms of impulsive behavior like bulimia and cleptomania (Lopez-Ibor, 1988). However, in the context of the topic of the present review it is necessary to take into consideration that the normal realization of the erotic excitement during the sexual intercourse is exactly "impulsive", has to be not restricted by the long-term considerations, and SSRI treatment that stimulates left frontal lobe may suppress this normal sexual behavior together with all abovementioned negative outcomes of serotonin deficiency.

Recently Fales et al. (2009) have shown that after 8 weeks of SSRI treatment patients with depression showed increased dorsolateral prefrontal cortex activity to unattended fear-related stimuli and no longer differed from controls in either dorsolateral prefrontal or amygdala activity. Dorsolateral prefrontal cortex is responsible for the cognitive control of emotional responses (Ochsner & Gross, 2005). Reduced cognitive control is accompanied by simultaneous amygdala overactivation. Antidepressants improve recruitment of dorsolateral prefrontal cortex during performance of emotional interference tasks and reduce the activation of amygdala. Drevets and Raichle (1998) found the reciprocal relationships between the amygdala and lateral prefrontal cortex in healthy subjects during cognitive or emotion processing. Authors are not sure whether increased amygdala activity suppresses dorsolateral prefrontal cortex or increased activity of this structure serves to suppress amygdala activity. Probably the relations are bi-directional: increased amygdala activity means high emotional excitation that blocks normal mechanisms of information consideration, and increased DL PFC activity determines high rational control over the emotional excitement.

By using magnetic resonance investigation, Chen Chi-Hua et al. (2008) found that in depressed patients amygdala was positively coupled bilaterally with medial temporal and ventral occipital regions and negatively coupled with anterior cingulated cortex. Antidepressant treatment increased coupling between left amygdala and right frontal and cingulated cortex, striatum and thalamus. Treatment-related increases in functional coupling to frontal and other regions were greater for the left amygdala then for the right. This increase of functional coupling may be a mechanism that reduces the overactivation of amygdala in depression. Excessive amygdalar activity in depressed patients is related to the tendency to ruminate on emotional aversive memories (Drevets, 2001). According to Barbas, 2000, there are two key functions of amygdala: 1) processing of emotionally valent sensory input signals and emotional memories by interacting with sensory cortices, thalamus and hippocampus; 2) expressing emotions by connecting with central autonomic structures. Pezawas et al. (2005) found an excitatory influence from the amygdala to the subgenual anterior cingulated cortex during perception of threating stimuli, while Chen Chi- Hua et al. (2008) found negative connections between these structures during perception of sad faces. It might suggest that in the emotional state caused by the perception of sad faces (negative affect combined with helplessness, see above) amygdala have an inhibitory effect on activity in the anterior cingulated cortex. Fear that stimulates fight or flight may cause activation of connections between amygdala and anterior cingulated cortex, and for sexual excitement this connection probably has to be blocked. Interactions between amygdala and fronto-striato-thalamic systems may determine the appropriate emotional behavior, and increased coupling between the amygdala and right lateral prefrontal cortex might facilitate the prefrontal modulation of amygdala activity. Unmedicated depressed patients display decreased functional inter-relationships between the pregenual anterior cingulated cortex and limbic regions (amygdala, striatum, thalamus) in comparison to healthy controls, and it may reflect decreased cortical regulation of limbic regions in response to negative stimuli (Anand et al., 2005a).

Antidepressants may enhance the cortical regulation of abnormal limbic activation (Anand et al., 2005b), but it may have a negative outcome for the erotic excitement and sexual intercourse (that are in any case relatively low in the untreated depression partly due to the functional insufficiency of the right hemisphere with all its relationships to the limbic system).

As it was already mentioned the treatment-related increase in functional coupling to different brain structures is more prominent for the left amygdala than for the right (Chen Chi-Hua et al., 2008). It can be explained by data of Iidaka et al. (2001) that left amygdala is related more strongly to the bilateral prefrontal cortex, and the right amygdala to the right temporal lobe. Left amygdala might be more sensitive to emotional stimuli with negative valence and more associated with bilateral cortical activity which plays a role in regulation or suppression of emotional response (see Chen Chi-Hua et al.). Arce et al. (2008) have shown that in healthy subjects subchronic SSRI administration attenuates amygdala activation to negatively but not positively valenced emotional faces, and it would be interesting to check whether this subchronic administration

causes sexual disorders. Probably not, in depressed patients they appear after chronic administration.

Left stroke seems to be a risk factor for selective serotonin reuptake inhibitors treatment resistance (Spaletta et al., 2003): depression on fluoxetine or sertraline improved much more in right hemisphere stroke vs. left hemisphere stroke. It corresponds to our suggestion that SSRIs are effective because they activate the left hemisphere. However, Andersen et al., 1994 by using citalopram did not find any effect of side of lesion. This contradiction can be explained by taking into consideration the key role of the right hemisphere deficiency in the pathogenesis of depression (Rotenberg, 2004). The localization of the damage may be crucial for the outcome. The damage of the parietal and temporal right hemisphere zones as well as the damage of the limbic system may decrease subject's sensitivity to the negative messages and as a result increase the effect of the left hemisphere stimulation with antidepressants. But the damage of the right frontal pole may decrease the subject's ability to integrate the negative and frustrating information and as a result to increase subject's vulnerability that cannot be compensated by the left hemisphere activity. Probably a heavy damage of the right frontal lobe may be comparable to the left hemisphere damage according to the resistance of depression to the treatment. The same reason may explain why it is a lack of direct relationship between cognitive impairment and severity of symptoms of depression in brain-damaged patients (Robinson, 1998) – severity of depression is determined not only by the left hemisphere dysfunction but even more by the right hemisphere dysfunction.

According to Sheline et al. (2001) depressed patients have exaggerated left amygdala activation to all faces, especially to fearful faces. Following treatment patients displayed reduced amygdala activation to masked fearful faces and to all faces. Thus, depressed patients have left amygdala hyperarousal even when processing stimuli outside of consciousness. Increased amygdala activity normalizes with antidepressant treatment.

As it was already stressed above, amygdala processes emotionally valenced stimuli (Aggleton, 1992) particularly fear. Amygdala is activated during negative affective states (sadness, anxiety). Depressed patients demonstrate abnormal recognition of facial expression and impaired production of emotional facial expression (Gur et al., 1992) Amygdala play a key role in nonconscious processing of emotion. Drevets et al. (1992) have shown increased resting metabolism and blood flow in left but not right amygdala of depressed vs. control subjects. Abercrombie et al. (1998) found no differences in resting glucose metabolism between depressed and control subjects but in depressed subjects increased metabolic rate in the right amygdala correlated with negative affect. However, Wright et al. (2001) found that in normal subjects left amygdala was more activated to fearful vs. happy faces and the right amygdala displayed more habituation. Phillips et al. (2001) also found that left amygdala respond more active to the fearful faces. What is the reason of these differences between investigations is not clear but probably it is related to the asymmetric interrelationships between left and right amygdala and cortical structures.

The investigation of Sheline et al. (2001) is the first fMRI report of increased amygdala activation in major depression. In depression perhaps all faces represent potential threats. Why they have greater left amygdala activation in response to masked faces is not clear. Antidepressants decrease amygdala activation. Amygdala is the most important site for antidepressant action, and it is especially obvious when we are speaking about antidepressants that do not disturb sexual activity (see the next part).

Buchsbaum et al. (1997) studied the effect of sertraline on regional metabolic rate in patients with affective disorders. The middle frontal gyrus showed increased activity on both sides, in contrast with temporal and occipital areas. Sertraline increased metabolic rate in right parietal lobe and in left occipital area, decreased metabolic rate in right occipital area.

Devous et al. (1993) showed reduced metabolism in frontal lobe in depression especially in medial frontal and cingulated area and in dorsolateral prefrontal cortex. Normalization on the treatment was found in medial frontal lobe and cingulated gyrus, and the greater was the normalization of the activity of cigulated gyrus the greater the improvement. Spontaneous mood change was not associated with anterior cingulated change.

Parallel between patterns of 5-HT distribution and of metabolic rate changes with the administration of sertraline is most marked for frontal and limbic structures. Metabolic rate is lowered by antidepressant treatment.

Our general conclusion of this part is that the effect of those antidepressants that cause sexual dysfunctions is determined by its predominant activation of the left hemisphere activity on the expense of the right hemisphere functional activity.

BRAIN LATERALITY AND LIMBIC ACTIVITY ON ANTIDEPRESSANTS THAT DO NOT CAUSE SEXUAL DYSFUNCTIONS

Now let us turn to the investigations of brain activity on antidepressants that do not cause sexual dysfunctions and even are used to compensate such dysfunctions. Bruder et al. (2007) have estimated the therapeutic response to secondary treatment with bupropion – antidepressant that is widely used to improve sexual disorders caused by SSRI treatment. Bupropion increases the activity of NE and DA brain systems. By using dichotic listening test these authors have shown that bupropion responders vs. nonresponders had larger left hemisphere advantage for words but there was no group difference

in right hemisphere advantages for tones. At the same time men who responded to fluoxetine differed from nonresponders in reduced right hemisphere advantage for dichotic tones (Bruder et al., 2004) probably due to a very prominent and broad left hemisphere advantage for any kind of signals, words and tones. This difference was not found between bupropion responders and non-responders probably because for the effect of bupropion the initial predisposition of the left hemisphere overactivity is less important – bupropion is using also other brain mechanisms.

Little et al. (2005) have compared bupropion and venlafaxine responders in the group of patients with unipolar depression. They have found that pretreatment frontal and left temporal hypometabolism (in comparison to control subjects) is linked to positive antidepressant response to both antidepressants, while bupropion responders displayed also cerebellar hypermetabolism and hypermetabolism in posterior cingulated and cutaneous cotex, in comparison to nonresponders.

When Little et al. (2005) have found that bupropion responders are characterized by hypermetabolism in the cerebellum, posterior cingulated and cutaneous cortex, and non-responders – by hypometabolism in right anterior cingulated, cerebellum and left inferior parietal cortex, they became surprised because bupropion increases DA in dorsal and ventral striatum (Asher et al., 1995). Little et al. expected, in contrast to their real finding, that bupropion responders would have baseline hypometabolism in basal ganglia that will increase on the treatment. However, it is possible to suggest that the relatively high initial metabolism of responders being not high enough to protect subject from depression is nevertheless high enough to predispose subject to the response on antidepressant treatment, in the same way how it is going on with the activity and metabolism of the fronto-temporo-parietal part of the left hemisphere that predisposes patients to the positive response on SSRIs (see Rotenberg, 2008).

Bupropion and SSRIs are activating different brain zones and it may be the explanation of their different influence on sexual functions. Little et al. stressed that frontal and left temporal hypometabolism in bupropion responders contrasts with data of previous investigations (Mayberg et al., 1997; Buchsbaum et al. 1997) Probably for the effect of bupropion is less important the activity of those brain zones that are important for SSRIs treatment and are related to sexual disorders, and are more important the alterations of activity in other brain zones.

Treatment with bupropion reduced fMRI activation during emotional distractors (administration of Emotional Oddball Task) in right amygdala/parahippocampal area, in right caudate, right fusiform gyrus, and in many different parts of right and left cortices. However, only changes in fMRI activation in the amygdala correlated with the decrease of Hamilton Rating Scale for depression (Robertson et al., 2007).

Treatment with reboxetine, a selective noradrenaline reuptake inhibitor, that also do not cause sexual disorders, was associated in healthy volunteers with a reduced amygdala response to fearful faces and increased activation to happy vs. neutral faces expressions in the right fusiform gyrus (Norbury et al., 2007). Depression is associated with an increased amygdala response to subliminal presentation of fearful facial expressions and this response became attenuated in parallel with remissions of symptoms after chronic treatment with antidepressants (Scheline et al., 2001; Fu et al., 2004). Thus, the noradrenaline and dopamine reuptake inhibitors have a positive outcome on depression without crucial activation of the left hemisphere but by modulating of activity of amygdala and other limbic structures.

It is necessary to take into consideration that this effect (the inhibition of the amygdala response) was achieved after prolonged treatment with the noradrenaline reuptake inhibitors, while the acute enhance of the NE (like it happens during stress) by the single dose of reboxetine induced a decrease of amygdala activation to positive stimuli but increased amygdala activation to negative stimuli (Kukolja et al., 2008).

According to Segraves (1995) only bupropion and nefazodone do not cause orgasm disorders and anorgasmia may be mediated by 5-HT2 antagonism of adrenergic mechanisms that underlie normal orgasm.

The all abovementioned data show that there are two main targets of the antidepressants. The activation of the left hemisphere, especially left frontal, temporal and parietal areas, increases subjects availability for the goal-oriented activity based on the analysis and selection of information, on the discrimination between relevant and irrelevant information elicited by the environment, on its organization into a monosemantic context. It helps to overcome depression but at the same time it inhibits the emotional reactions and suppresses the spontaneous free reactions that are essential for the sexual relationships and are based on the activity of the right hemisphere coupled with limbic structures like amygdala. If the right hemisphere cortical structures in cooperation with subcortical limbic structures are responsible for normal sexual excitation, sexual behavior and orgasm, than the relative increase of the left hemisphere domination and the consequential decrease of the right hemisphere participation in behavior is going to suppress sexual activity and sexual pleasure.

Those antidepressants that do not cause sexual dysfunction are not activating predominantly the left hemisphere structures, do not cause the domination of the left hemisphere over the right one, and at the same time are activating the subcortical (limbic) brain zones that are responsible for reward, reinforcement, emotional excitement that are so important for the free sexual beha-

vior as a part of the interpersonal emotional interrelationships.

It means also that all psychotherapeutic methods that can enhance right hemisphere activity must be used in the process of the treatment of depression in addition to any antidepressants.

CONCLUSION

According to the all abovementioned data, it is possible to conclude, that sexual excitement and orgasm are related to the high functional activity of the right hemisphere combined with the limbic system and being free from the inhibitory control of the left frontal cortex. At the same time, those antidepressants that cause sexual disorders are known to activate the potential resource of the left hemisphere in order to structuralize the stream of the outward information and the inner world of emotions and images. This goal is achieved on the expense of the free right hemisphere activity. Those antidepressants that do not cause sexual disorders are modulating the activity of amygdala and other limbic structures.

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