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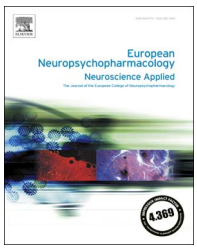

Noradrenergic modulation of neural erotic stimulus perception

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Abstract
We recently investigated neuromodulatory effects of the noradrenergic agent reboxetine and the dopamine receptor affine amisulpride in healthy subjects on dynamic erotic stimulus processing. Whereas amisulpride left sexual functions and neural activations unimpaired, we observed detrimental activations under reboxetine within the caudate nucleus corresponding to motivational components of sexual behavior. However, broadly impaired subjective sexual functioning under reboxetine suggested effects on further neural components. We now investigated the same sample under these two agents with static erotic picture stimulation as alternative stimulus presentation mode to potentially observe further neural treatment effects of reboxetine.
19 healthy males were investigated under reboxetine, amisulpride and placebo for 7 days each within a double-blind cross-over design. During fMRI static erotic picture were presented with preceding anticipation periods. Subjective sexual functions were assessed by a self-reported questionnaire.
Neural activations were attenuated within the caudate nucleus, putamen, ventral striatum, the pregenual and anterior midcingulate cortex and in the orbitofrontal cortex under reboxetine. Subjective diminished sexual arousal under reboxetine was correlated with attenuated neural reactivity within the posterior insula. Again, amisulpride left neural activations along with subjective sexual functioning unimpaired. Neither reboxetine nor amisulpride altered differential neural activations during anticipation of erotic stimuli.
Our results verified detrimental effects of noradrenergic agents on neural motivational but also emotional and autonomic components of sexual behavior. Considering the overlap of neural

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network alterations with those evoked by serotonergic agents, our results suggest similar neuromodulatory effects of serotonergic and noradrenergic agents on common neural pathways relevant for sexual behavior.

1. Introduction

The investigation of human sexual activity and its modulation by central neurotransmission has been emphasized in recent years due to the increasing evidence of sexual dysfunction under psychopharmacological treatment, e.g. with selective serotonin reuptake inhibitors (SSRIs). Early insights into neuromodulatory effects of various neurotransmitters on different phases and components of the human sexual response cycle arose from clinical observations in patients with psychiatric disorders (La Torre et al., 2013a, 2013b) that may, however, be confounded by the disorder itself (Angst, 1998; Kennedy and Rizvi, 2009; Soldati, 2016).

We previously investigated the effects of various monoaminergic agents on neural correlates of visual erotic stimulus processing in healthy male subjects by functional magnetic resonance tomography (fMRI). Administration of serotonergic antidepressants was accompanied by a decrease of subjective sexual functions along with attenuated neural activations within brain regions corresponding to emotional and motivational aspects of the sexual response cycle (Abler et al., 2011). As revealed by psychophysiological interaction analyses, downregulation of the human reward system, particularly the nucleus accumbens, under serotonergic agents was mediated by serotonergic enhancement of prefrontal cortex activation (Abler et al., 2012). By contrast, neural activations and subjective sexual functions were unimpaired or even enhanced under bupropion, an antidepressant with a dopaminergic component (Abler et al., 2011). Beside these diverging effects on emotional and motivational aspects of the sexual response cycle, both, serotonergic and dopaminergic antidepressants decreased neural activations corresponding to cognitive components of the sexual response cycle along with diminished behavioral attentional functions (Graf et al., 2013, 2014). To further disentangle monoaminergic modes of action on sexual functioning we recently investigated the effects of the selective noradrenalin reuptake inhibitor (SNRI) reboxetine and the dopamine receptor affine drug amisulpride on neural correlates of visual erotic video stimulus processing in healthy subjects compared to placebo (Graf et al., 2015). In contrast to clinical observations, we found no significant alterations of subjective sexual functions or neural activations under amisulpride compared to placebo presumably due to its pharmacodynamic properties with dopamine agonistic effects under lower dosages as observed in animal studies (Schoemaker et al., 1997) as compared to antidopaminergic effects under higher doses. However, reboxetine was accompanied by a decrease in subjective sexual functioning along with attenuated neural activations upon visual erotic stimulation within the right caudate nucleus indicating disadvantageous effects on motivational components of sexual behavior.

We now examined the effects of the noradrenergic antidepressant reboxetine and the dopamine receptor affine amisulpride compared to placebo on visual static erotic picture stimulation in contrast to former dynamic video stimulation. As this study was conducted within the same study sample as described in Graf et al. (2015), we expected that this investigation would corroborate our previous results and further expand information on the networks involved. We hypothesized that differences in stimulus induced brain activities arising due to presentation mode (Bühler et al., 2008) would allow to complement current results and allow for linking diminished subjective sexual functions in the various domains with distinct neural network components (Graf et al., 2015). Through the application of an established erotic picture paradigm with preceding expectancy periods (Graf et al., 2013), the design also allowed the investigation of neuromodulatory effects of these two agents on attentional components of the sexual response cycle that have not been investigated so far.

2. Experimental procedures

2.1. Subjects

20 healthy heterosexual male subjects were investigated under subchronic administration of amisulpride (AMS), reboxetine (REB) and placebo (PLA) for seven days each in counterbalanced order. One subject was excluded due to newly observed cerebral gliotic lesions resulting in a final sample size of 19 participants (mean age 24.0 years, SD 3.1; range 20–32) in further analyses. Each participant received a full medical evaluation including a medical history, a physical examination and a Structured Clinical Interview for DSM-IV Axis I Psychiatric Disorders prior to the study. Laboratory blood-tests and an electrocardiogram were performed to exclude renal, hepatic or cardiac preconditions. Subjects with any current or past psychiatric or neurological disorder, any serious general medical condition, use of illegal drugs and excessive consumption of caffeine or alcohol ($>$ 14 units/week) were excluded. 3 subjects were occasional or moderate smokers. Upon recruitment, baseline depressive symptoms were assessed by the German version (Hautzinger and Bailer, 1993) of the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). The Massachusetts General Hospital Sexual Functioning Questionnaire (MGH-SFQ; Labbate and Lare, 2001) was administered to evaluate baseline sexual interest, sexual arousal, ability to achieve orgasm, ability to achieve and maintain an erection, and overall sexual satisfaction prior to the study. According to the study protocol, the questionnaire was modified to assess changes in subjective sexual functioning only over the past week of medication (Abler et al., 2011; Graf et al., 2015). The study was approved by the local ethical

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