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Raloxifene exposure enhances brain activation during memory performance in healthy elderly males; its possible relevance to behavior

R. Goekoop,[a,*,1] E.J.J. Duschek,[b,1] D.L. Knol,[c] F. Barkhof,[d] C. Netelenbos,[b] Ph. Scheltens,[a] and S.A.R.B. Rombouts[a,e]

[a]*Department of Neurology, VU University Medical Center, De Boelelaan 1117 1081 HV, Amsterdam, The Netherlands*
[b]*Department of Endocrinology, VU University Medical Center, Amsterdam, The Netherlands*
[c]*Department of Medical Statistics, VU University Medical Center, Amsterdam, The Netherlands*
[d]*Department of Radiology, VU University Medical Center, Amsterdam, The Netherlands*
[e]*Department of Physics and Medical Technology, VU University Medical Center, Amsterdam, The Netherlands*

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Raloxifene is a selective estrogen receptor modulator (SERM) that is prescribed in females only, but its use in male subjects is increasingly considered. With a growing number of patients having potential benefit from raloxifene, the need for an assessment of its effects on brain function is growing. Effects of estrogens on brain function are very subtle and difficult to detect by neuropsychological assessment. Functional imaging techniques, however, have been relatively successful in detecting such changes. This study used functional magnetic resonance imaging (fMRI) to examine effects of raloxifene treatment on memory function. Healthy elderly males (n = 28; mean age 63.6 years, SD 2.4) were scanned during performance on a face encoding paradigm. Scans were made at baseline and after 3 months of treatment with either raloxifene (n = 14) or placebo (n = 14). Treatment effects were analyzed using mixed-effects statistical analysis (FSL). Activation during task performance involved bilateral parietal and prefrontal areas, anterior cingulate gyrus, and inferior prefrontal, occipital, and mediotemporal areas bilaterally. When compared to placebo, raloxifene treatment significantly enhanced activation in these structures (Z > 3.1), except for mediotemporal areas. Task performance accuracy diminished in the placebo group (P = 0.02), but remained constant in the raloxifene group (P = 0.60). In conclusion, raloxifene treatment enhanced brain activation in areas spanning a number of different cognitive domains, suggesting an effect on cortical arousal. Such effects may translate into small effects on behavior, including effects on attention and working memory performance, executive functions, verbal skills, and episodic memory. Further neuropsychological assessment is necessary to test the validity of these predictions.

Keywords: Raloxifene; SERM; Estrogen; fMRI; Memory; Arousal

Introduction

Selective estrogen receptor modulators (SERMs) are compounds that display both agonist and antagonist effects on estrogen receptors in a tissue-selective manner (Riggs and Hartmann, 2003). Raloxifene is a SERM of which several beneficial effects have been reported in postmenopausal women, including a reduced risk of breast carcinoma (Cummings et al., 1999), a reduced risk of vertebral fractures (Delmas et al., 2002; Ettinger et al., 1999), and beneficial effects on markers of cardiovascular disease, such as serum lipids and coagulation factors (Delmas et al., 1997; de Valk-de Roo et al., 1999; Walsh et al., 1998). To date, raloxifene can be prescribed in postmenopausal women only, to counter effects of osteoporosis. A growing number of beneficial effects of raloxifene treatment are, however, reported that may also apply to male patients. Raloxifene treatment is therefore being considered in males, which have already shown good tolerance to the substance (Blum et al., 2000; Doran et al., 2001). So far, however, research into the tolerability profile of raloxifene in males has lacked a more detailed assessment of its effects on brain function. With an increasing number of patients experiencing a potential benefit from raloxifene, the need for such an assessment is growing.

A large body of evidence suggests that sex steroids may influence brain function. In both sexes, estradiol is thought to be primarily responsible for effects of sex steroids on neural excitability, with testosterone in male subjects first requiring conversion to estradiol in order to exert its effects (Longcope et al., 1969; MacDonald et al., 1979). Estrogen receptors occur throughout the brain in both male and female subjects. Gender differences may influence their pattern of expression, suggesting different functions in both sexes (Kruijver et al., 2003; Osterlund et al., 2000; Zhang et al., 2002). A consistent finding is that low

* Corresponding author. Fax: +31 20 444 0317.
E-mail address: R.Goekoop@VUMC.nl (R. Goekoop).
[1] Both authors contributed equally to this study.
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sex steroid levels are associated with impaired memory performance in both sexes (Barrett-Connor et al., 1999; Maki and Resnick, 2001; Morley et al., 1997; Senanarong et al., 2002; Wolf et al., 1999). In contrast, enhanced estrogen levels in both males and females correlate with increased memory function in these subjects (Sherwin, 2003a, 2003b). It has even been suggested that estrogen supplementation may prevent Alzheimer's disease in postmenopausal women (Paganini-Hill and Henderson, 1996; Simpkins et al., 1997). Randomized controlled clinical trials, however, found no significant effects of estrogen treatment in dementia (Polo-Kantola et al., 1998). Instead, three recently published controlled clinical trials from the Women's Health Initiative (WHI) examining effects of hormone therapy in postmenopausal women have found adverse effects of combined estrogen and progestin treatment on brain function, including effects on mental performance and an increased risk of dementia (Rapp et al., 2003; Shumaker et al., 2003; Wassertheil-Smoller et al., 2003). Thus, estrogens affect mental performance under physiological circumstances, and the effects of long-term pharmacological intervention into sex steroid systems are still unclear. Indeed, very little is known about the effects of estrogen agonists on male brain function (Sherwin, 2003b). Potential future prescription of raloxifene in male subjects therefore requires additional study.

So far, research into the effects of sex steroid or SERM treatment on brain function largely depended on neuropsychological studies of behavior. Such studies typically show only minimal changes in behavioral measures (Sherwin, 2003a,b). In contrast, functional imaging techniques have shown relatively clear results after sex steroid treatment. Both estrogen and testosterone may increase brain activation in areas relevant to memory, reasoning, judgment and emotions (Azad et al., 2003; Maki and Resnick, 2001). Although the clinical significance of neurofunctional changes in the absence of behavioral changes may be questioned, the possibility that they bear some extra insight into behavior should not be dismissed (Wilkinson and Halligan, 2004). Hence, it has been suggested that functional imaging techniques may have greater sensitivity to the effects of sex steroids on brain function (and possibly behavior) than most neuropsychological assessment scales (Maki and Resnick, 2001; Neele et al., 2001). For this reason, we examined the ability of functional magnetic resonance imaging (fMRI) to screen for effects of raloxifene treatment on male brain function in a small group of subjects. The presence of such effects might justify more large-scale investigations into the behavioral effects of raloxifene treatment by means of neuropsychological assessment. Based on results from previous imaging studies (Maki and Resnick, 2001) and the sparse amount of data on the effects of estrogens on male brain function (Sherwin, 2003b), we hypothesized that raloxifene would influence brain activation during visuospatial memory performance. A face encoding task was chosen to elicit brain activation, since sex differences have been reported for visuospatial memory scores in general (Kampen and Sherwin, 1996; Sherwin, 2003b) and face encoding and recognition scores in particular (Yonker et al., 2003). Such 'sexual dimorphism' with respect to visuospatial memory suggests an effect of sex steroids on neural function associated with this task, making it a potentially sensitive tool to detect effects of treatment. Performance scores were monitored and activation changes were mapped to specific anatomic locations.

Materials and methods

Study design

Subjects were screened for participation in a randomized, double-blind, placebo-controlled study design. fMRI was performed at baseline (BL; no medication; session 1) and after 3 months of a once-daily oral intake of raloxifene 120 mg or placebo (TR; session 2). Both BL and TR sessions were performed on exactly the same time of day in each subject. If data acquisition failed, the subject's consent was asked for an additional scanning visit, up until which time the relevant medication regime (raloxifene or placebo) was continued, to obtain a maximum number of complete data sets. Study period extension was not to exceed 10 days.

Subject recruitment

The medical ethical review board of the VU University Medical Center of Amsterdam approved the study. Thirty healthy, right-handed elderly male subjects, aged 60 to 70 years old (mean 63.6 years, SD 2.4; range 60–69 years) were recruited by advertisement in local newspapers. All subjects provided informed consent during a screening visit in which the procedure was explained and contraindications were checked. Subjects were excluded if they had any significant medical, neurological or psychiatric illness, or if they were taking any medication or other substances that are known to influence cerebral functioning. Exclusion criteria to MRI involved the presence of metallic implants in high-risk areas and a history of claustrophobia. Formal education was determined using a Dutch system (low, middle, high).

Functional MRI (fMRI)

Data acquisition

Imaging was carried out on a 1.5-T Sonata MR scanner (Siemens, Erlangen, Germany), using a standard circularly polarized head coil with foam padding to restrict head motion. For fMRI, an echo planar imaging sequence was used (echo time 60 ms, flip angle 90°, matrix 64 × 64, field of view 192 × 192 mm), to obtain 21 transverse slices (thickness 5 mm, interslice-gap 1 mm). Task stimuli were projected on a screen located at the head end of the scanner table via an LCD projector located outside the scanner room. Subjects viewed the screen through a mirror located on the head coil. In each hand, subjects held an fMRI compatible response-box through which they were able to react to task stimuli by pressing a single button using one of their index-fingers. A T1-weighted structural MRI scan was obtained of each subject (MPRAGE; inversion time: 300 ms, TR = 15 ms; TE = 7 ms; flip angle = 8°; 160 coronal slices, 1 × 1 × 1.5 mm voxels). Total scanning time including structural imaging on average was 21 min for each visit.

Encoding task

A face-encoding task was used to examine brain activation related to episodic memory for visuospatial information. This task produces activation in bilateral prefrontal, bilateral parietal, anterior cingulate and (posterior) mediotemporal structures with a preference for the right hemisphere (Small et al., 1999), which