Hormones and Behavior 66 (2014) 449–456

Contents lists available at ScienceDirect

Hormones and Behavior

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

Regular article

Decision-making impairments in breast cancer patients treated with tamoxifen

Xingui Chen [a,b,1], Jingjing Li [c,d,1], Juluo Chen [b], Dandan Li [a], Rong Ye [a], Jingjie Zhang [e], Chunyan Zhu [a], Yanghua Tian [b], Kai Wang [a,b,*]

[a] Laboratory of Neuropsychology, The First Affiliated Hospital of Anhui Medical University, Hefei, China
[b] Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei, China
[c] Department of Oncology, The Second Affiliated Hospital of Anhui Medical University, Hefei, China
[d] Department of Oncology, The Second Hospital of Zhejiang University College of Medicine, Hangzhou, China
[e] Department of Breast and Thyroid Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, China

ARTICLE INFO

Article history:
Received 13 August 2013
Revised 2 July 2014
Accepted 9 July 2014
Available online 15 July 2014

Keywords:
Breast cancer
Endocrine therapy
Iowa Gambling Task
Game of Dice Task
Tamoxifen

ABSTRACT

The selective estrogen receptor modulator tamoxifen (TAM) is most commonly prescribed for patients with hormone-sensitive breast cancer. Although TAM can bind to estrogen receptors in the nervous system, it is unknown whether it acts as an estrogen agonist or antagonist in the human brain. Several studies have reported the negative effects of TAM on cognitive function; however, its effects on decision-making function have not been previously explored. The present study aimed to investigate the decision-making function under ambiguity and risk in breast cancer patients treated with TAM. Participants included breast cancer patients taking TAM (TAM, n = 47) and breast cancer patients not taking TAM (non-TAM, n = 45) as well as their matched healthy controls (HC, n = 50). All participants were given the Iowa Gambling Task (IGT) to assess their decision-making under conditions involving ambiguity, the Game of Dice Task (GDT) to assess their decision-making under conditions involving risk, and a battery of neuropsychological tests. Our results indicated that patients in the TAM group were significantly impaired as assessed by both the IGT and GDT and performed significantly worse on some aspects of various tasks involving memory and information processing. Furthermore, we found that decreased performance on verbal memory testing significantly correlated with IGT performance, and executive dysfunction was associated with poor GDT performance in breast cancer patients undergoing TAM treatment. This study demonstrates that breast cancer patients taking TAM have several decision-making impairments. These findings may support the idea that TAM resulting in cognitive changes plays an antagonistic role in the areas of the brain where estrogen receptors are present, including the prefrontal cortex, hippocampus and amygdala.

Introduction

The survival rate of breast cancer patients is increasing with the development of screening and systemic treatment, but complaints of cognitive changes have become common in breast cancer survivors. Initially, researchers studied cognitive changes and found that this phenomenon was associated with chemotherapy treatment (Ahles and Saykin, 2007). However, some studies have recently shown that adjuvant endocrine therapies which play a key role in hormone-sensitive breast cancer treatment are a potential cause of this cognitive dysfunction (Buwalda and Schagen, 2013; Phillips et al., 2011).

Endocrine therapies are most commonly prescribed for patients with hormone-sensitive breast cancer and include selective estrogen receptor modulators (SERMs) and aromatase inhibitors. Among SERMs, tamoxifen (TAM) is frequently prescribed for the treatment of breast cancer in both pre- and post-menopausal women. Aromatase inhibitors are primarily prescribed to post-menopausal women because of their good curative effects and have become increasingly popular in recent years (Burstein et al., 2010). Nevertheless, we felt that TAM was the most plausible choice for our study because it is currently recommended for pre-menopausal breast cancer patients.

TAM, a mixed agonist/antagonist, readily crosses the blood brain barrier and binds to estrogen receptors (ERα and ERβ) in the nervous system (McEwen and Alves, 1999). However, it is unknown whether TAM acts as an estrogen agonist or antagonist in the human brain. Estrogen receptors have been identified in several areas of the brain that are important for cognitive functions, including the prefrontal cortex, hippocampus and amygdala. These brain structures are associated

* Corresponding author at: Laboratory of Neuropsychology, Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei 230032, China. Fax: +86 551 62923704.
E-mail address: wangkai1964@126.com (K. Wang).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.yhbeh.2014.07.005
0018-506X/

with cognitive functions, such as executive function, memory, learning and decision-making. Some studies have reported that TAM users perform significantly worse than healthy controls on assessments of verbal memory (Schilder et al., 2009; Shilling et al., 2003), executive function (Schilder et al., 2010), visuospatial ability and processing speed (Palmer et al., 2008; Shilling et al., 2003). One animal study showed that repeated administration of TAM produced deficits in the acquisition or retention of learned responses; this finding suggests that TAM could evoke memory and learning deficits (Walker et al., 2011). In addition, one neuroimaging study combining positron emission tomography (PET) and magnetic resonance imaging (MRI) found that the brains of TAM users were more similar to women not taking estrogen replacement therapy (ERT) than to women who were taking ERT. Specifically, reduced activity in the inferior and dorsal lateral prefrontal cortex and reduced volume in the hippocampus were observed, suggesting a possible antagonist influence (Eberling et al., 2004). On the basis of the cognitive changes and brain alterations previously described, it is plausible to presume that TAM has estrogen antagonistic effects in some brain tissues.

Theoretically, it is likely that the effect of TAM treatment influences brain functions and cognition, leading to cognitive deficits related to information processing speed deficits, memory loss and executive functions and affects the daily function and quality of life of breast cancer survivors (Hogervorst et al., 2002). To our knowledge, there have been no studies to date that examine cognitive deficits pertaining to decision-making in breast cancer patients receiving endocrine therapies. It is essential to select the best alternative among the varied options in real-life situations, which is referred to as the cognitive process of executive function. From the neuroscientific viewpoint, at least two types of decision-making processes exist: decision-making under ambiguity and decision-making under risk (Bechara, 2004; Brand et al., 2006). These two types of decision-making are primarily based on processing available information about the consequences and probabilities of certain events.

In a decision-making under ambiguity task, the decision maker has to find effective information by processing feedback on previous choices using the Iowa Gambling Task (IGT) (Bechara et al., 1994, 1999). In the decision-making under risk task, decisions are made based on explicit information regarding the inferential probabilities and consequences of the different options presented; the Game of Dice Task (GDT) is chosen to measure this type decision-making (Brand et al., 2006, 2007). Neuroimaging and neuropsychological studies have suggested that executive decision-making tasks depend on supporting systems in different areas of the brain; those areas include the prefrontal cortex, amygdala and striatum. There is a general agreement that the prefrontal cortex, including the orbitofrontal and ventromedial prefrontal cortices, and cingulate cortex play a major role in decision-making under ambiguous situations (Bechara et al., 1997, 1999; Hsu et al., 2005). On the other hand, decision-making under situations involving risk seems to strongly activate the dorsolateral prefrontal cortex, amygdala and basal ganglia (Carter and van Veen, 2007; Dagher et al., 2001).

Estrogen has been shown to affect the cognitive performance of both pre- and post-menopausal women. Generally, higher estrogen levels can enhance performance on tasks involving verbal (Morgan et al., 1996; Wolf et al., 1999) and working memory (Epperson et al., 2012; Grigorova et al., 2006; Lacreuse et al., 2002) as well as executive function (Ghidoni et al., 2006; Wegesin and Stern, 2007). On the contrary, the reduction of estrogen that accompanies natural menopause has been associated with reductions in cognitive function (Ahles and Saykin, 2007). Reduced estrogen levels have been associated with decreased verbal fluency and memory performance (Hampson, 1990; Phillips and Sherwin, 1992). In addition, previous studies have shown that chemotherapy itself can induce cognitive change (Ahles and Saykin, 2007; Barton, 2013; Phillips et al., 2012). Therefore, for breast cancer patients that are treated concomitantly with endocrine therapies and chemotherapy, it is necessary to explore the relationship between cognitive function and endocrine therapies.

Based on the data mentioned above, it is possible that TAM plays an antagonistic role in the areas of the brain where estrogen receptors are present and are associated with the decision-making function. In addition, considering that menopausal symptoms and chemotherapy may yield confounding effects, the aim of the present study was to investigate potential alterations in both types of decision-making (under ambiguity and risk) in pre-menopausal breast cancer patients that were treated with TAM without chemotherapy. We hypothesized that these patients would have impaired performance on decision-making tasks compared to breast cancer patients without TAM treatment and healthy control participants. We also examined the relationship between deficits in decision-making and other cognitive changes, such as memory and executive function in breast cancer patients that were treated with TAM.

Materials and methods

Participants

All participants were recruited from the First Affiliated Hospital of Anhui Medical University, in Hefei, China. All participants were premenopausal and could understand and speak the Chinese language. Participants had to satisfy the following inclusion criteria: no evidence of metastatic disease, no history or current diagnosis of psychological disorders and no alcohol or drug abuse. All participants with a subtle or severe affective disorder that might have led to deviant test results (Hamilton Depression Rating Scale scores >7 and/or Hamilton Anxiety Rating Scale scores >7) were excluded. All participants provided written informed consent and did not receive any financial or material compensation. The present study was executed in agreement with the Declaration of Helsinki and was approved by the local Ethics Committee. One hundred and forty two participants were assigned to the three groups in this study. The TAM group included 47 breast cancer patients whose cancer was positive for the estrogen receptor (ER) and/or progesterone receptor (PR). Patients from this group were treated with TAM (20 mg daily) for mean 37.5 ± 11.1 months, and TAM was given for at least 12 months. The non-TAM group consisted of 45 female patients previously diagnosed with Stage I breast cancer who had not received any endocrine therapies. All patients in the TAM group and non-TAM group had undergone local surgery and/or locoregional radiation therapy but did not receive chemotherapy. The duration since surgery in the non-TAM group was 34.0 ± 9.8 months. Additionally, 50 matched healthy controls recruited from the patients' relatives and local university participated in this study. The detailed information gathered from each participant is described in Table 1.

Neuropsychological background tests

All patients and healthy controls were evaluated using neuropsychological tests that were composed of standardized tests to investigate their cognitive problems, fatigue, anxiety and depressive symptoms in daily life. Their overall cognitive function was measured using the Beijing Version of the Montreal Cognitive Assessment Test (MoCA Test) (Nasreddine, 2006); scores >24 points were required for inclusion in this study. Neuropsychological functional domains and their associated tests used in this study are as follows: attention (Digit Span of the Wechsler Adult Intelligence Scale) (Wechsler, 1981); memory (Chinese version of the Auditory Verbal Learning Test) (Schmidt, 1996); executive function (Stroop Color Word Test) (Stroop, 1935); verbal fluency (Chiu et al., 1997) and information processing speed (Trail Making Test) (Klove, 1963). The Chinese version (So et al., 2003) of the Cancer Related Fatigue (CRF) test (Piper et al., 1998) was used to rule out possible fatigue symptoms; scores <27 points were required for inclusion in the study. The Hamilton Depression Rating Scale (HAMD) and Hamilton