Neurological effects of endocrine therapy in the treatment of breast cancer

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1 in 8 women will suffer from breast cancer in their lifetime. Roughly three quarters of breast cancers can be classified as estrogen receptor-positive(ER+). Patients with ER+ tumors receive adjuvant endocrine therapy, in the form of selective estrogen receptor modulators(SERMs) or aromatase inhibitors(AIs), which prevent the synthesis of estrogen. The use of endocrine therapy has been associated with neurological and cognitive side effects, particularly problems with memory. Experimental and clinical data are conflicting, however. Experimental data indicates that SERMs act like estrogen and have beneficial effects on the brain, while AIs stop estrogen production and therefore have adverse cognitive effects. Clinical data however indicates that SERMs have adverse side effects, while AIs don't affect memory and cognition as much as would be expected.

Introduction

The most common cancer among women worldwide is breast cancer, with 1.38 million new cases estimated to have been diagnosed in 2008. Breast cancer constitutes 23% of all cancers in women, and 10.9% of all cancers overall. The incidence rate of breast cancer is 89.7 per 100,000 women in Western Europe and high throughout the developed world. Developing regions have a much lower incidence rate of under 40 per 100,000. In the developed world there is a relatively favorable survival of breast cancer (mortality rates range is approximately 6-19 per 100,000), ranking it as the fifth cause of death from cancer overall. For women however, breast cancer remains the most frequent cause of cancer death in developed regions (GLOBOCAN). A more tangible statistic is that 1 in 8 women in the US(and thus in the developed world) will develop invasive breast cancer in their lifetime(Siegel et al., 2012).

Many different genes may be involved in causing cancer, for example the *BRCA1* and *-2* gene in familial cancer(Judkins *et al.,* 2012). A more clinically relevant classification is whether a tumor is estrogen receptor positive(ER+) or negative(ER-). ER+ tumors express the estrogen receptor α(ERα), and proliferate under the influence of estrogen(Perou *et al.,* 2000). Often ERα expression occurs with other co-regulated genes, that are ER target genes(van 't Veer *et al.,* 2002). Overexpression of the enzyme aromatase, which in peripheral tissues converts testosterone into estrogen in commonly found in ER+ tumors(Maggiolini *et al.,* 2001). The proportion of patients with ER+ tumors is close to 75% of total cases(Anderson *et al.,* 2013; Anderson *et al.,* 2002). By 2018, the number of cases of ER+ breast tumors are expected to have increased by 15%, while overall breast cancer is only thought to have increased by 7%; meaning that the majority of breast cancers is ER+, and this percentage will only increase in the near future (Anderson *et al.,* 2013).

The clinical relevance of the ER+/- classification is that patients with ER+ tumors can be treated with adjuvant endocrine therapy. There are two main classes of drugs used in endocrine therapy; selective estrogen receptor modulators(SERMs) and aromatase inhibitors(AIs). The first SERM to be

used was tamoxifen, first in post-menopausal women, and since 1989 five years of adjuvant tamoxifen was standard for all women with ER+ breast cancer. Another SERM is raloxifene, which is currently used to prevent cancer in women with increased breast cancer risk, as well as to treat inflictions like postmenopausal osteoporosis (D'Amelio & Isaia, 2013).Tamoxifen and raloxifene are estrogen-receptor ligands, blocking the ER receptor and therefore transcription of estrogen-regulated genes, needed for growth in ER+ breast tumors. (The actual mechanism of SERMs depends on the tissue; SERMs act as ER-antagonists in breast cancer but as agonists in other tissues such as bone and uterus(Dutertre & Smith, 2000))More recently, aromatase inhibitors (AIs) have been introduced for adjuvant therapy in postmenopausal women. These bind to the enzyme aromatase to prevent the conversion of androgens into estrogen in peripheral tissue; the main source of estrogen in post-menopausal women. Recently, the benefits of switching from Tamoxifen to AIs such as anastrozole, letrozole and exemestane are being investigated(Sainsbury, 2013), but all are currently indicated for the treatment of ER+ breast cancer in postmenopausal women(Cardosa *et al.,* 2013). AIs are not used in premenopausal women, in which ovarian estrogen production is active. Decrease of estrogen levels by AIs cause the HPA axis to increase gonadotropin production, leading to increased androgen production and upregulation of the promoter of aromatase resulting in an overall increase in estrogen(Dowsett *et al.,* 2005) Often patients receive different SERMs and AIs during their treatment; this can be done because a tumor developed resistance to a certain drug, or doctors decide on a switching of approach after recurrence of tumors because resistance is feared. More recently a combination of different endocrinological therapies is under investigation; examples can be to use Tamoxifen for 2 years, and then switching to an AI for 3 more years(or vice versa) as first-line treatment in primary tumors (Cardosa *et al.,* 2013; Zeng *et al.,* 2013; Philips *et al.,* 2010). In a recent study into endometrial- and breast cancer, GPER30, A G-protein coupled estrogen receptor was found present in ER- tumors. In fact, ER-status was negatively correlated to the amount of GPER30, indicating a role for endocrine therapy in both ER- tumors as well as ER+ tumors(Wei *et al.,* 2012) The percentage of patients with breast cancer that receive hormone therapy is already as high as 83.9%(Kartal *et al.,* 2013)

One issue affecting the quality of life of women receiving endocrine therapy that patients suffer side effects, particularly on cognition and memory(see Berndt *et al.,* 2009; Jenkins *et al.,* 2007 for review). Clinical findings are discussed below.

As breast cancer is the most frequent cancer in women, and the proportion of estrogen receptor positive tumors is increasing, coupled with indications of adverse cognitive effects of endocrine therapy, the quality of life of a very large group of patients may benefit from research into neurological effects of endocrine therapy. This will be a review of the current knowledge of the effects of endocrine therapy, on cognition and memory, at the clinical, molecular and behavioral levels.

Clinical studies

There is considerable variation in findings on cognitive effects of SERM and AI that are currently used to treat post-menopausal women.

One of the largest studies into the side effects of SERMs is the Multiple Outcomes of Raloxifene Evaluation(MORE) trail, in which 7478 women were divided over a 60mg/day, 120mg/day or placebo group. Testing was done after 6 months, 1, 2 and 3 years of use and revealed no effects of raloxifene

on cognitive performance(Yaffe *et al.,* 2001). Subsequent results of the same trail however indicate that 120mg/day reduced the risk of mild cognitive impairment by 33% in population of 5386 postmenopausal women(Yaffe *et al.,* 2005). Verbal memory(measured as immediate and delayed recall of both simple and abstract words, reflecting short term memory) improved after 60mg/day in 198 late postmenopausal women(Jacobsen *et al.,* 2010). A large study into the effects of tamoxifen and raloxifene is the Study of Tamoxifen and Raloxifene (STAR) trial, studying the efficacy of both drugs in women with increased risk of breast cancer. 1498 of the 19747 women enrolled in STAR participated in Co-STAR; an auxiliary study into the cognitive side-effects. No effects on cognition or memory raloxifene or tamoxifen were found(Legault *et al.,* 2009). In the P-1 study, assessing the potency of tamoxifen in the prevention of breast cancer in women with increased risk, 13.388 women participated. As part of the study self-report checklists, inquiring the women's ability to concentrate, their forgetfulness were filled in. This study too failed to find any significant effects of tamoxifen on cognition(Cella *et al.,* 2008), as was the case after adjuvant treatment with tamoxifen in 120 patients(Debess *et al.,* 2010).

When it comes to AIs, a comparison with tamoxifen is often made, as it has been the standard adjuvant endocrine therapy for years(Sainsbury, 2013). In a small study of 31 postmenopausal women, Bender et al. (2007) found that anastrozole had more effect on learning and memory than tamoxifen. The lack of negative controls or pretreatment measurements make it impossible to make claims on the effects of tamoxifen. A later study of 73 participants did include negative controls and pretreatment evaluation, and concluded that both anastrozole and tamoxifen users were more likely to show cognitive decline than controls; anastrozole users showed greater decline(64%) than tamoxifen users(39%), compared to 7% in control condition, with the areas of processing speed and verbal memory affected most(Collins *et al.,* 2009). Poorer results after both tamoxifen and anastrozole treatment, compared to controls, on the areas of processing speed and verbal memory, but not working memory and attention, have been reported previously in a study of 129 patients(Shilling *et al.,* 2003).

However, opposing results have also been found; in the IBIS II study, comparing anastrozole to placebo in the treatment of cancer, failed to find any effects on cognition, in 151 postmenopausal women (Jenkins *et al.,* 2008). To further complicate matters, the cognitive effects of exemestane and tamoxifen were compared in a study with 299 postmenopausal breast cancer patients,. Only tamoxifen was found to significantly decrease verbal memory and executive functioning, as compared to healthy controls. Although the tamoxifen group did not perform significantly worse than controls on information processing speed and verbal memory, the slight improvement observed in the exemestane condition resulted in a significant difference between both groups(Schilder *et al.,* 2010). Poorer memory function was also found after comparing adjuvant tamoxifen (5 years of tamoxifen or 2 years of letrozole + 3 years tamoxifen) use, to letrozole (5 years of letrozole and 2 years tamoxifen + 3 years letrozole) condition. Comparisons between both groups that received 5 years of monotherapy and between both combination therapies could not be made because of insufficient statistical power(Philips *et al.,* 2010). One year after the end of treatment, memory and cognition improved in all groups(Philips *et al.,* 2011).

From these studies a very diverse picture emerges; SERMs have been found to have beneficial effects(Yaffe *et al.,* 2005; Jacobsen et al., 2010), no effects(Legault *et al.,* 2009; Cella *et al.,* 2008; Debess *et al.,* 2010), or negative effects(Collins *et al.,* 2009; Shilling *et al.,* 2003; Schilder *et al.,* 2010;

Phillips *et al.,* 2010). Positive effects of SERMs are mostly found in raloxifene when used to treat osteoporosis in postmenopausal women(Yaffe *et al.,* 2005; Jacobsen *et al.,* 2010), while negative effects on cognition are mostly found to be caused by tamoxifen in breast cancer patients(Schilder *et al.,* 2010; Shilling *et al.,* 2003; Phillips *et al.,* 2011). Still, both tamoxifen and raloxifene showed no effects in two studies in healthy postmenopausal women(Legault *et al.,* 2009; Cella *et al.,* 2008).

Cognitive side effects of AI also differ between studies; negative cognitive effects were found in one study(Shilling *et al.,* 2003), but no effects in others(Jenkins *et al.,* 2008 Schilder *et al.,* 2010); less adverse effects than SERMs(Philips *et al.,* 2010), or more severe cognitive side effects than SERMs(Bender *et al.,* 2007; Collins *et al.,* 2009). Even so, the cognitive effects of SERMs range from beneficial to adverse, while AIs show no effect at best.

Estrogen, Selective Estrogen Receptor Modulators and Aromatase Inhibitors.

The term "estrogen" encompasses many natural and synthetic compounds with estrogenic properties ranging from interaction with a certain estrogen receptor to displaying certain biological effects such as influencing secondary sex characteristics(Blaustein, 2008). The three most important physiological estrogens are estrone(E1), 17β-estradiol(E2) and estriol(E3), of which E2 is the most important and biologically active(Blaustein, 2008; Kuiper *et al.,* 1997). In this review, whenever the term estrogen is used, it refers to 17β-estradiol; the plural "estrogens" is used for the group of estrogenic compounds.

In pre-menopausal women, estrogen is mainly produced in the gonads, where the main precursor is cholesterol. Estrogen produced this way is distributed throughout the body and is commonly referred to as systemic estrogen. After menopause, ovarian production of estrogen ceases, and production of estrogen takes place in peripheral tissues instead. This is usually known as local estrogen. Peripheral estrogen production takes place in bone, aortic smooth muscle cells, and relevant to this review; adipose tissue of the breast(Simpson, 2003) and in the brain, especially in the hippocampus(Prange-Kiel *et al.,* 2003; Ishii *et al.,* 2007; Hojo *et al.,* 2013). Peripheral tissue is unable to use cholesterol as a precursor and have to rely on, amongst others, adrenal androgens as substrate (Maggiolini *et al.,* 2002; Simpson, 2003). The terms local and systemic estrogen will be used in this review in the described meaning.

The classical role of estrogen is that of a growth hormone, acting through nuclear estrogen receptors(ERs). This process works through two principal ERs, ERα and ERβ, that bind estrogen with similar affinity(Kuiper *et al.,* 1997). This pathway is present in the various estrogenic tissues of the body(Couse *et al.,* 1997), as well as in the brain, particularly the hippocampus(Prange-Kiel *et al.,* 2003). Upon binding of estrogen, ERα and ERβ form complexes with additional transcription factors to initiate gene transcription, particularly of genes involved in growth and proliferation(Kuiper *et al.,* 1997; Hall *et al.,* 2001).

When attempting to study the cognitive effects of endocrine therapy in breast cancer patients, it is important to first understand the role of estrogen in a normal setting. A challenge here is that studies into the normal role of estrogen often involve the manipulation of estrogen production using AIs(Chamniansawat & Chongthammukun, 2012 for example). Furthermore, the effects of AIs are often similar to (surgical) menopause in healthy women(Bender *et al.,* 2007), AIs are used preferably used in postmenopausal women, and many clinical trials directly compare AIs and SERMs. Therefore,

in the next section, studies into normal estrogen functioning, effects of AIs, SERMs and (surgical) menopause are combined to try and understand the neurological effects of endocrine therapy and to compare the effects of SERMs and AIs where possible.

Chamniansawat & Chongthammakun (2012) used anastrozole to investigate the role of local estrogen in hippocampal cell cultures, and found that the expression of the ERβ-subtype was reduced, while ERα expression remained unchanged. They conclude that neuronal functions of the hippocampus are mainly controlled by local estrogen; autocrine and paracrine activation of ERβ expression serves to prime hippocampal neurons for further activation by systemic estrogen, and that neuronal function is regulated by both local and systemic estrogen through the classical genomic ERβ-dependant mechanism. Conversely, Qu et al. (2013) found that ovariectomization of 3 month old female rats, leads to decreased serum estrogen concentration and reduced ERα expression, specifically in the CA1 and CA3 regions of the hippocampus, resulting in deficiencies in learning, memory and spatial cognition. When PPT, an ERα-specific ligand, is provided directly following ovariectomy, the decrease in learning and memory and in number of neurons is prevented by inhibition of apoptosis.

Another mechanism by which estrogen can exert its effects is through G-protein coupled estrogen receptors (GPERs). GPERs have been found to be involved in hippocampal neurogenesis, although it remains unclear whether estrogen acts directly on the GPERs or if GPERs are permissive to ERα and ERβ signaling(Ruiz-Palmero *et al.,* 2013). A specific member of the GPERs, GPER30, has been found to mobilize intracellular calcium and synthesize IP3 in response to activation by estrogen(Revankar *et al*., 2005). Intracellular calcium mobilization is essential for LTP generation, a process by which memories are thought to form(Bliss & Collingridge, 1993).

In a study using hippocampal slice cultures, the use of letrozole was found to cause a dose-dependent reduction of estrogen and subsequent decrease in spine synapse density (Kretz *et al.,* 2004), a result that was also found in both intact and ovariectomized mice (Zhou *et al.,* 2010). A possible explanation comes from a later study; systemic use of letrozole has been shown to almost completely suppress LTP generation in female rats. Interestingly, LTP was only reduced by 20% in male rats. The observed impairment of LTP in female rats was followed by spine and spine synapse loss (which is in agreement with the current views on the role of LTP in synaptic plasticity and changes in spine morphology, as mechanism of memory formation (reviewed in Yuste & Bonhoeffer,. 2001)) . The modest decrease in males did not lead to a reduction in spine density. Furthermore, letrozole had the same effect on LTP in both intact and ovariectomized females, suggesting the importance of local (rather than systemic) estrogen production in letrozole-induced LTP impairment(Vierk *et al.,* 2012).

Women receiving treatment for breast cancer also frequently report depression, which greatly affects the quality of life and outlook of the treatment(Badger *et al.,* 2000). The dorsal raphe nucleus is a structure implicated in depression and anxiety as a result of menopause, and in this structure, reduced ERβ expression is found in ovariectomized mice (Suzuki *et al.,* 2013). This is in accordance with the observation of mild anxious behavior after 3 weeks of letrozole use in ovariectomized mice, in the form of less open arm entries in an elevated plus maze(Meng *et al.,* 2011). Raloxifene on the other hand, was found to decrease anxiety(Strickler *et al.,* 2000; Florio *et al.,* 2001) and depression (Grigoriadis *et al.,* 2005)in postmenopausal women.

Studies into the effects of AIs and estrogen are also performed in song birds. Estrogen is involved in the processing of sensory information in the caudomedial nidopallium(NCM), an auditory area of the songbird forebrain(Saldanha *et al.,* 2000). When a Zebra Finch hears a song from a member of the same species, local estrogen increases in the NCM, and repeated playback causes adaptation of neural responses to that song. Depletion of estrogen by the AI fadrozole inhibits this neuronal memory formation for vocalizations, while leaving auditory processing intact(Yoder et al., 2012). The effect of fadrozole on spatial memory is divergent; female zebra finches that had learned and reached optimal performance on a spatial test, started to dramatically increase their rate of errors after fadrozole treatment. Naïve animals however showed improved ability to learn a spatial task; the use of AIs therefore impairs the retrieval of spatial memory, but improves memory acquisition(Rensel *et al.,* 2013). This divergent role of AIs in spatial memory is in line with contradicting results found in research into the effects of estrogen(deprivation) on spatial memory in rodents; letrozole has beneficial effects on spatial learning memory consolidation(Aydin *et al.,* 2008), an effect that was more pronounced in OVX rats than in intact females. Mice treated with letrozole show increased spatial learning and memory in the Morris water maze(Meng *et al.,* 2011). Qu and coworkers(2013), on the other hand, found marked spatial learning and memory defects in the Morris water maze in ovariectomized rats.

Another hypothesis about age-related cognitive decline is that it is caused by changes in the balance between reactive oxygen species(ROS) and antioxidants, which leads to neuronal damage(Davies, 2000; Radak *et al.,* 2007). Although there is no consensus on the subject, hormone replacement therapy (with for instance equine-derived estrogens) can have beneficial effects on cognition in postmenopausal women (Maki, 2013; Möller *et al.,* 2010). The restored levels of estrogens are thought to lead to a reduction of oxidative stress levels and activity, and improves memory function, although it remains unclear whether estrogen achieves this by acting as an antioxidant itself, or if it increases the levels of other antioxidants such as CAT(Shafin *et al.,* 2013). In a study into Parkinson's disease, both estrogen and tamoxifen were found to have neuroprotective properties; through the PI3K/Akt and MAPK/ERK pathways, tamoxifen was able to reduce ROS formation and thereby protect cortical neurons from oxidative stress(Lee *et al.,* 2009a).

When looking at the effects of AIs and estrogen deprivation, another level to consider is that of protein expression and availability. Both in hippocampal slice cultures and rats that are treated with letrozole, a dose-dependent downregulation of spinophilin (a marker of dendritic spines)and synaptophysin (involved in presynaptic vesicles) occurs(Kretz *et al.,* 2004; Prange-Kiel *et al.,* 2006; Zhou *et al.,* 2008). The spinophilin reduction was higher in the CA1 region, while the synaptophysin downregulation was stronger in the CA3 region, indicating that estrogen concentrations are not homogenous throughout the entire hippocampus(Prange-kiel *et al.,* 2006; Zhou *et al.,* 2010). Strangely, after initial downregulation, spinophilin and synaptophysin were upregulated after long term(4 weeks) letrozole treatment in OVX animals as compared to naturally cycling animals(Zhou *et al.,* 2010). Synaptophysin is also downregulated in the hippocampus of ovariectomized rats, but can be restored by the administration of tamoxifen after ovariectomy(Sharma *et al.,* 2007)

Letrozole administered to adult Sprague-Dawley rats, both intact and OVX, was found to improve spatial learning and memory in a previously mentioned study(Aydin *et al.,* 2008). In that study, increased expression was found of two isoforms of the neural cell adhesion molecules(NCAM) family; NCAM 180 and NCAM 140. Expression of noradrenalin and dopamine was reduced in the

hippocampus of treated rats, but effects of letrozole differed between catecholamines in the cortex(Aydin *et al.,* 2008).

Qu and coworkers (2013) studied the role of ERα in OVX-induced neuronal loss. They found that treatment of OVX rats with the ERα-specific ligand PPT, neuronal loss was prevented. In PPT-treated OVX animals they found, compared to untreated OVX animals, upregulation of synapsin 1, and increased levels of Bcl-xl(member of Bcl-2 family of anti-apoptosis proteins). Reduced levels of Bcl-2 were found in the hippocampus of ovariectomized rats in another study. Tamoxifen administration maintained Bcl-2 at the same levels as in intact-, and estrogen-treated OVX controls and prevented an upregulation of the pro-apoptotic Bax; indicating a neuroprotective role of tamoxifen through modulation of apoptotic proteins (Sharma & Mehra, 2008).

Glutamate is the predominant excitatory neurotransmitter in the CNS, and glutamatergic signaling is considered vital for memory formation and learning(Morgado-Bernal, 2011). Both ionotropic an metabotropic glutamate receptors were found to be reduced in ovariectomized rats, while PPT administration prevented such reduction(Qu *et al.,* 2013). CaMKIIα, ERK and Akt activation was observed after ERα-induced upregulation of mGluR1. Tamoxifen and raloxifene have neuroprotective effects through the activation of the MAPK/ERK (involved in transcription activation) and PI3K/Akt(involved in apoptosis) pathways (Du *et al.,* 2004; Lee *et al.,* 2009b, Florio *et al.,* 2001) through ERα, and tamoxifen has indeed been proposed for use in neurodegenerative disorders with altered glutamate homeostasis (Lee et al., 2009a). The association in the hippocampus of ERα and ERβ with various metabotropic glutamate receptors (mGluR1a/2) in Caveolin-mediated microdomains allows for rapid effects of estrogen and SERMs, which are independent from the activation by glutamate itself (Meitzen & Mermelstein, 2011).

Ionotropic NMDA-type glutamate receptors are co-localized with aromatase in the hippocampus of songbirds(Saldanha *et al.,* 2004), and NMDA NR1-receptors are downregulated as a result of letrozole use(Zhou *et al.,* 2010), as are NMDA NR2A receptors in ovariectomized rats(Qu *et al.,* 2013). In a brain slice ischemia model, tamoxifen has neuroprotective properties through reduction of AMPA/NMDA receptor-mediated excitotoxicity(Zhang *et al.,* 2009). Tamoxifen was also found to be protective action against spinal cord injury(Tian *et al.,* 2009) and Alzheimer's disease(O'Neill *et al.,* 2004).

The neurological effects of any pharmaceutical are always influenced by the penetration into the CNS, which is largely dependent on its ability to cross the blood-brain barrier(BBB). In a study in mice, the brain-to-plasma ratio of anastrozole was only between 8% and 16% of that of letrozole and vorozole, which were found to be able to cross the BBB easily. CNS penetration of anastrozole is mainly limited by active efflux by P-glycoprotein(Miyajima *et al.,* 2013).

Discussion

When combining the results from endocrine therapy in clinical trial in postmenopausal women with or without breast cancer with experimental data, a very confusing picture emerges. Both tamoxifen and raloxifene mimic the activity of estrogen in preventing cognitive decline as a result of menopause. In experimental setting, both in vivo and in vitro, tamoxifen shows positive effects on many different levels, from modulating synaptic proteins, transcription factors, apoptotic mechanisms, glutamatergic transmission, and offers protection against damage in models of

ischemia, spinal cord injury and Alzheimer's. But several studies indicate, that when used in the treatment of breast cancer in postmenopausal women, tamoxifen has negative effects on memory and cognition(Schilder *et al.,* 2010; Shilling *et al.,* 2003; Phillips *et al.,* 2011)(although absence of neurological effects was also found in adjuvant use(Debess *et al.,* 2010)) while the use of tamoxifen to prevent rather than treat breast cancer revealed no effects(Legault *et al.,* 2009; Cella *et al.,* 2008).

AIs on the other hand, show negative results in experimental settings: reduction of spine synapses, depression of LTP, neuronal cell death, memory impairment (although not in the case of spatial memory) and anxious behavior in animal models. But even so, there were no adverse cognitive effects found in several clinical trials with adjuvant AI use (Jenkins *et al.,* 2008 Schilder *et al.,* 2010), even if adverse effects of tamoxifen were found(Schilder *et al.,* 2010). When compared to tamoxifen, clinical data becomes more confusing; Owing to the BBB, brain penetration of anastrozole is very low compared to letrozole(Miyajima *et al.,* 2013), and thus more pronounced neurological effects of letrozole could be expected. Clinical data indicates the opposite; anastrozole had greater effect on learning and memory than tamoxifen(Bender *et al.,* 2007; Collins *et al.,* 2009), while letrozole caused less adverse cognitive effects than tamoxifen(Philips *et al.,* 2010).

Upon closer inspection, some of these seemingly contradictory results make more sense. Exemestane caused no adverse cognitive effects(Schilder *et al.,* 2010), possibly because exemestane and its metabolites exert androgen-like action(Ariazi *et al.,* 2007), compensating for the estrogen reduction. Androgens can increase spine synapse density in the hippocampus through mechanisms that don't require conversion by aromatase(Leranth *et al.,* 2004).The study of Phillips et al. (2010) suffered from low power, and measured cognition after 5 years of use. Long term letrozole administration in ovariectomized rats leads to, after an initial decrease, an upregulation of synaptic markers, implicating some compensatory mechanism(behavioral testing was not done in this experiment, so it is unclear if memory was restored)(Zhou *et al.,* 2010). The studies by Bender et al. (2007) and Collins et al. (2009) comprised only 31 and 45 participants respectively, and neither was a randomized trial; treatment allocations were purely based on treating cancer. In Bender et al.(2007) for example, women in the tamoxifen-group were significantly younger and had been receiving treatment for longer than the anastrozole-group, indicating a difficulty in clinical studies with cancer patients; survival is (understandably) more important than studying the cognitive effects. Further difficulties in clinical research include the use of self-report checklists as used in some studies, that might yield different result than neuropsychological assessment tests (in which for example a number of words or combination of numbers has to be remembered) as used in others, and time of testing also varies from evaluation after 3 months of use to testing after 5 years, which means that short term versus long term effects could be measured instead of the effects of different treatments.

Tamoxifen would be expected to have beneficial effects, based on experimental results. However, when used as adjuvant therapy in breast cancer patients, it usually leads to adverse effects on cognition. Explanations here can come from research into ERT; the so-called "critical period hypothesis" has to be considered(reviewed in Daniel, 2012). Briefly, this hypothesis states that after menopause, decreased systemic estrogen levels over time lead to an irreversible reduction of ERα-expression in the CNS. ERα is critical to neuroprotective properties of estrogen in the CNS, and the predominant target for agonistic action of SERMs. If ERT starts shortly after menopause, ERα expression is maintained. If initiation of ERT takes place too late, ERα loss has already occurred, and additional estrogen or SERM administration has adverse effects. Of course in cancer patients, SERM

treatment starts in response to the diagnosis of cancer, and chances of this happening just within the "critical period" are minute. This would however not be in agreement with findings that raloxifene prescribed to late postmenopausal women with osteoporosis have improved cognitive performance (Jacobsen *et al.,* 2010). Furthermore, as SERMs can act as both agonists and antagonists, depending on receptors in the target tissue(Dutertre & Smith, 2000), interplay with more brain regions with different relative amounts of ERα and ERβ, such as the prefrontal cortex, have to be considered.

The combined use of several SERMs and AIs in the treatment of postmenopausal breast cancer patients is currently still being developed. A clinical example is the sequential use of tamoxifen and letrozole in breast cancer patients(Phillips *et al.,* 2010). An example of an in-vitro experiment comes from Zeng and coworkers(2013), who are working on finding optimal combinations of letrozole and tamoxifen use in combination with radiotherapy. In breast cancer cell lines, they found no difference in the order of drug administration; First letrozole followed by tamoxifen or vice versa were equally effective in increasing the radiosensitivity of tumor cells. Given that some SERMs improve cogntion(Yaffe *et al.,* 2005, Jacobsen *et al.,* 2010), and that the combined use of AIs and SERMs is effective in treating cancer, the effects of this combination, and other AI-SERM combinations and protocols, should be tested in in-vivo behavioral experiments. The simultaneous use of tamoxifen and anastrozole is also possible(ATAC group, 2001), behavioral studies into simultaneous use of both drugs might yield interesting results; standard dose AI combined with a smaller dose of raloxifene, as would be used in treating osteoporosis but is too low for adjuvant cancer therapy on its own, could lead to favorable cognitive outcomes.

The findings that experimental results and clinical data on AIs and SERMs often seem to disagree makes the field of endocrine therapy for breast cancer an interesting one, with many questions left to answer. Why for example do most (animal) models poorly predict the clinical results of tamoxifen and AIs, and consequently, what model would better have better predictive validity? How, in current models, can the clinical observations be recreated, for example by varying dosage or through finding interactions with other treatments that cancer patients may be subjected to, in the form of radio- or chemotherapy(or even stress). The possibility of using several SERMs and AIs simultaneously might potentially reduce cognitive effects, as a lower dose than in monotherapy could be used, while retaining anti-cancer efficacy.

Because of the treatment of breast cancer but also of other problems associated with decrease in estrogen, a large proportion of women will receive endocrine therapy in their lifetime. While experimental data indicate the benefits of estrogen receptor modulators, and the problems associated with estrogen depletion, results of clinical use of endocrine therapy sometimes indicates the opposite. Research into models with better predictive capabilities might therefore help to improve the clinical use of endocrine therapy.

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