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The effect of selective estrogen receptor modulators on type 2 diabetes onset in women: Basic and clinical insights

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ABSTRACT

Selective estrogen receptor modulators (SERMs) are a class of compounds that interact with estrogen receptors (ERs) and exert agonist or antagonist effects on ERs in a tissue-specific manner. Tamoxifen, a first generation SERM, is used for treatment of ER positive breast cancer. Raloxifene, a second generation SERM, was used to prevent postmenopausal osteoporosis. The third-generation SERM bazedoxifene (BZA) effectively prevents osteoporosis while preventing estrogenic stimulation of breast and uterus. Notably, BZA combined with conjugated estrogens (CE) is a new menopausal treatment. The menopausal state predisposes to metabolic syndrome and type 2 diabetes, and therefore the effects of SERMs on metabolic homeostasis are gaining attention. Here, we summarize knowledge of SERMs' impacts on metabolic, homeostasis, obesity and diabetes in rodent models and postmenopausal women.

1. Introduction

Increased life expectancy in developed countries indicates that most women will spend the second half of their lives in an estrogen deficient state. In addition to increasing the risks of cardiovascular diseases, estrogen deficiency also predisposes to visceral obesity, metabolic syndrome and type 2 diabetes (T2D). Therefore, the broad impact of estrogen deficiency on the pathobiology of metabolic diseases in women represents a new therapeutic challenge. From that perspective, we need to dissect and harness the beneficial effects of estrogen on metabolic homeostasis while at the same time avoiding its adverse effects.

Selective estrogen receptor modulators (SERMs) are a class of compounds that interact with estrogen receptors (ERs) and induce a unique receptor conformation that correlates with specific behaviors in estrogen-responsive tissues. SERMs exert agonist or antagonist activity on ERs in a tissue-specific manner that depends on the complexity of ER signaling, including different tissue distribution of ERs (Pfaffl, Lange, Daxenberger, & Meyer, 2001), ligand binding specificity (Kuiper et al., 1997; Tee et al., 2004) and diverse interactions with coactivators or corepressors (Bramlett & Burris, 2002; Webb, Nguyen, & Kushner, 2003).

Tamoxifen, one of the first generation of SERMs, behaves as an ER antagonist in breast tissue and is used to prevent and treat ER-positive breast cancer (Early Breast Cancer Trialists' Collaborative Group, 1998). However, tamoxifen acts as an ER agonist in the endometrium and therefore increases endometrial carcinoma risk (Fornander et al., 1989; van Leeuwen et al., 1994). The second-generation SERMs were developed to overcome the adverse effect of tamoxifen on endometrial proliferation. Raloxifene, for example, retains anti-estrogenic activity in breast tissue (Vogel, 2007; Vogel et al., 2006) and also exhibits estrogenic activity in bone, thus preventing osteoporosis (Ettinger et al., 1999). Bazedoxifene, a third-generation SERM, is used to prevent osteoporosis in postmenopausal women without raising the safety concerns related to endometrium and breast (Archer et al., 2009; Komm & Chines, 2012; Komm & Mirkin, 2013). The pairing of bazedoxifene with conjugated estrogen (CE) in a tissue-selective estrogen complex is a novel menopausal therapy (Pinkerton, Utian, Constantine, Olivier, & Pickar, 2009) which provides the benefits of CE treatment, and with the addition of BZA, protects breast and uterus from estrogen stimulation without using a progestin (Komm & Mirkin, 2013; Santen et al., 2014).

In addition to the established impacts of SERMs on breast, bone and endometrium, the impact of SERMs on postmenopausal metabolic dysfunction is gaining attention. Here, we summarize the accumulated knowledge of SERMs' impacts on diabetes, obesity and metabolic homeostasis in rodent models and postmenopausal women.

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2. The effects of SERMs on glucose homeostasis and diabetes

Tamoxifen has been used for over 40 years to treat ER-positive breast cancer due to its anti-estrogenic effect on breast tissue (Tee et al., 2004). It has been gradually recognized that tamoxifen causes metabolic side effects such as diabetes, lipid abnormities and hepatic steatosis. Independent population-based studies conducted in women with breast cancer have revealed a correlation between tamoxifen treatment and an increased incidence of diabetes (Hejazi & Rastmanesh, 2012; Lipscombe et al., 2012; Sun, Chen, Liang, Li, & Kao, 2014) (Fig. 1). For example, in a Canadian case–control study of 14,360 breast cancer survivors, tamoxifen use was associated with a 24% increased risk of developing diabetes (Lipscombe et al., 2012). In another Asian population-based cohort study of 22,257 breast cancer patients, tamoxifen use was associated with a 31% higher diabetes risk (Sun et al., 2014). The mechanisms of the diabetogenic effects of tamoxifen are unclear. One possibility is that tamoxifen exhibits adverse effects on pancreatic β cells. For example, in wild-type female mice, tamoxifen reversed the protective effect of estradiol on preventing insulin-deficient diabetes induced by streptozotocin (STZ), suggesting that tamoxifen acts as an ER antagonist in pancreatic β cells and impairs pancreatic islet survival (Le May et al., 2006). In addition, tamoxifen impairs embryonic and adult mouse β-cell proliferation by antagonism of ERα (Yuchi et al., 2015). Treatment with tamoxifen or genetic elimination of ERα in male mice similarly decreased the expression of the endocrine specification factor Neurogenin3 (NGN3) and β-cell proliferation in the partial duct ligation (PDL) rodent model of β-cell expansion due to pancreatic injury. Further, ERα inhibition with tamoxifen in the embryonic mouse pancreas, or its deletion as in the ERα-deficient mouse, also decreased NGN3 expression and NGN3+ progenitors at the end of gestation (Yuchi et al., 2015). Thus, the generation of NGN3+ cells and the subsequent β-cell mass expansion in developing or injured mouse pancreas are both blocked by tamoxifen antagonizing ERα. Tamoxifen may also promote insulin resistance. In premenopausal women at high risk of breast cancer but with normal body weight, tamoxifen treatment did not alter insulin sensitivity (quantified with HOMA index) (Johansson et al., 2008). In contrast, in a subgroup of overweight women, tamoxifen treatment dramatically decreased insulin sensitivity (Johansson et al., 2008). The underlying mechanism by which tamoxifen increases insulin resistance remains poorly understood but could involve the development of hepatic steatosis, as we will discuss later.

Raloxifene can affect glucose homeostasis to varying degrees depending on treatment duration (Fig. 2). In postmenopausal women with and without type 2 diabetes mellitus, short-term raloxifene treatment (3 or 6 months) did not alter fasting blood glucose (Andersson et al., 2002; Cagnacci et al., 2002; Cucinelli et al., 2002; Nagamani, Szymajda, Sepilian, Urban, & Gilkison, 2008) or insulin level (Andersson et al., 2002; Cagnacci et al., 2002; Cucinelli et al., 2002). However, in a subgroup of women with hyperinsulinemia, raloxifene reduced insulin levels by enhancing both fractional hepatic insulin extraction and peripheral insulin sensitivity (Cucinelli et al., 2002). Similarly to short-term treatment, long-term raloxifene treatment (12 months) did not modify fasting glucose or glucose tolerance (Lasco et al., 2004). However, in contrast to short-term treatment, long-term raloxifene treatment decreased insulin sensitivity (Lasco et al., 2004). Since the number of study subjects in this latter study was small (only 24 patients), this duration-based effect warrants further investigation. In summary, tamoxifen and raloxifene exhibit either deleterious or neutral effects on glucose homeostasis.

The combination of bazedoxifene with CE improved glucose homeostasis in OVX mice fed a Western diet (Fig. 3). Blood glucose and insulin levels were significantly decreased after bazedoxifene/CE treatment under both fasting (Barrera et al., 2014; Kim, J.H., et al., 2014) and fed conditions (Barrera et al., 2014; Kim, J.H., et al., 2014), and mice showed improved insulin sensitivity and glucose tolerance. These effects are similar to those observed with CE alone. When systemic insulin action was studied in euglycemic, hyperinsulinemic clamp conditions, the combination bazedoxifene/CE provided the same improvement in systemic insulin action in muscle and liver than BZA alone (Kim, J.H., et al., 2014). Yet, surprisingly, fasting blood glucose and insulin levels were not significantly changed in postmenopausal women taking the combination bazedoxifene/CE (Lobo et al., 2009). The bazedoxifene/CE combination and bazedoxifene alone reduced the severity of β-cells destruction and insulin-deficient diabetes induced by STZ in OVX female mice to an extent similar to that of CE alone (Kim & Mauvais-Jarvis, 2016). The prevention of STZ-induced insulin-deficient diabetes in mice is a marker of ERα agonist activity in β cells (Le May et al., 2006). Thus, the prevention of STZ-induced diabetes by bazedoxifene suggests that in female mice, bazedoxifene acts as an ERα agonist in β-cells. In a preliminary report, the effect of bazedoxifene/CE was assessed in the Akita mouse model of β cell endoplasmic reticulum (ER) stress (Xu, Allard, & Mauvais-Jarvis, 2015). Bazedoxifene/CE decreased β cell destruction and helped prevent the development of diabetes in Akita mice to an extent similar to that of CE alone. In cultured islets from female mice exposed to ER-stress induced by thapsigargin, CE, BZA or bazedoxifene/CE decreased the expression of markers of ER stress (Xu et al., 2015). Thus, the combination of bazedoxifene with CE used for menopausal hormone therapy could act as a pharmacological ER stress mitigator and protect women from estrogen deficiency-induced β-cell dysfunction and damage.

3. The effects of SERMs on obesity

Tamoxifen significantly reduced food intake, body weight, and fat mass in OVX rats (Wade & Heller, 1993) (Fig. 1). In neutered female Wistar–Kyoto (WKY) rats, tamoxifen also suppressed weight gain partially by suppressing food intake (Wallen, Belanger, & Wittnich, 2001). This effect could reflect the activation of ERα in hypothalamic neurons which is known to suppress food intake in rodents (Mauvais-Jarvis, Clegg, & Hevener, 2013).

Serum leptin positively correlates with body fat mass and plays a key role in regulating energy balance (Considine et al., 1996). Therefore, serum leptin level serves as an indicator of obesity. Serum leptin levels were higher in breast cancer patients receiving tamoxifen than in those not taking tamoxifen (Ozet et al., 2001). Another study conducted in breast cancer patients who received short term tamoxifen treatment showed that those who developed fatty liver during the 3-month tamoxifen treatment had elevated serum leptin levels compared to those without fatty liver (Gunel et al., 2003). However, in non-cancer patients, tamoxifen decreased body weight (Lopez et al., 2006). Weight gain (expressed as BMI increase) was smaller in obese women taking tamoxifen compared to those taking placebo, indicating that tamoxifen had a predominant anorectic effect, which was also observed in rats. In these animals, tamoxifen-induced anorexia was associated with decreased FAS mRNA expression, which caused malonyl-CoA accumulation in the hypothalamic ventromedial nucleus (Lopez et al., 2006). Therefore, how tamoxifen regulates energy balance as an ER agonist in the hypothalamus deserves further investigation.

Raloxifene prevented estrogen deficiency-induced weight gain in OVX rats (Meli et al., 2004; Sato, Rippy, & Bryant, 1996) (Fig. 2). In healthy postmenopausal women, a 12-month raloxifene treatment inhibited body weight gain and abdominal adiposity by changing fat distribution from an android distribution to a gynoid distribution (Francucci et al., 2005). Another study conducted in postmenopausal women reported that a 12-month raloxifene treatment failed to affect body weight, but remarkably altered body composition by increasing fat-free mass and total body water (Jacobsen, Samson, Emmelot-Vonk, & Verhaar, 2010). However, a 6-month raloxifene treatment was unable to increase either exercise-induced weight loss or fat-mass loss in

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