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Review

Positive and negative effects of glitazones in carcinogenesis: Experimental models *vs.* clinical practice

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ABSTRACT

Diabetes increases cancer risk, which may be modulated by careful choice of treatment. Experimental reports showed efficacy of glitazones in various *in vitro* and *in vivo* models of carcinogenesis, but procarcinogenic effects in some models were reported too, and, similarly, data on cancer incidence in glitazone users are inconsistent. This review summarizes oncostatic effects of glitazones in preclinical and clinical studies and brings a brief summary of their impact on cancer risk in diabetic patients, with a focus on the association between pioglitazone use and bladder cancer.

Contents

Introduction

Diabetic patients have an increased risk of developing various types of cancer. The connection between type 1 diabetes and cancer is uncertain although higher risk for pancreatic and endometrial cancer was observed [55,122], but increased risk of liver, pancreatic, breast, endometrial, colorectal, non-Hodgkin lymphoma, bladder, and kidney cancer has been reported in patients with type 2 diabetes [73,103,146]. On the other hand, prostate cancer risk seems to be reduced in diabetic patients, probably due to lower testosterone level [5,13,74,85]. In Asian countries, however, diabetes was associated with an increased risk of prostate cancer [90]. The association between diabetes and cancer most probably arises from hyperinsulinemia, hyperglycemia, and inflammation. Impaired insulin signaling shifts the balance between two counteracting pathways, anabolic mTOR (mammalian target of rapamycin) and catabolic AMPK (adenosine monophosphate-activated protein kinase), toward mTOR, which eventually stimulates cell

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proliferation [33,66,70,145]. As the incidence of type 2 diabetes is rising, more attention should be paid to possibilities how to reduce cancer risk in these patients.

Glitazones in diabetes treatment

Glitazones (thiazolidinediones) are relatively new antidiabetic drugs used in type 2 diabetes treatments. The first one, troglitazone (Rezulin), was introduced in Britain and in USA in 1997 but was withdrawn from the market in the same year in Britain and in 2000 in USA [138] because of hepatotoxicity. The next glitazone, rosiglitazone (Avandia TM, GlaxoSmithKline), was approved in USA in 1999 and in Europe in 2000, but was suspended from the European market in September 2010 because of cardiovascular risk [47]. In the USA, however, rosiglitazone is still available but only through a restricted access program (Avandia-Rosiglitazone Medicines Access Program) [136]. Therefore, pioglitazone (Actos TM, Eli Lilly) remains the only glitazone which is now used in Europe. Unfortunately, higher risk of bladder cancer in pioglitazone users (which will be discussed further) was reported, and as a result, pioglitazone was withdrawn from the market in France in July 2011 [131], and Germany and Luxembourg recommended not starting new patients on pioglitazone [45]. In October 2011, the European Medicines Agency concluded that pioglitazone should remain available as a treatment option provided a careful selection and monitoring of patients were made [44]. U.S. Food and Drug Administration has recommended to prescribe pioglitazone with caution in patients with a previous history of bladder cancer and not to use it in patients with active bladder cancer [137]. A new glitazone, rivoglitazone, is currently undergoing research for use. Preliminary data obtained from a 26-week, placebo- and pioglitazone-controlled monotherapy study showed that rivoglitazone was efficient in hyperglycemia reduction and insulin sensitivity improvement, and the safety profile appeared similar to that of pioglitazone [25].

Mechanism of action of glitazones

Glitazones are synthetic ligands of peroxisome proliferator-activated receptor γ (PPAR-γ). PPAR-γ and other two isotypes (α, β/δ) belong to nuclear receptor superfamily comprising steroid, retinoid, and thyroid hormone receptors [105]. PPARs (peroxisome proliferator-activated receptors) contain a ligand-binding domain that recognizes and binds specific PPAR agonists, and a DNA-binding domain that interacts with specific peroxisome proliferator-response elements (PPREs) within the genome. PPARs form heterodimers with retinoid X receptor (RXR) which bind to PPREs in the promoter region and regulate the transcription of various target genes [50,79,120]. PPAR-α is expressed mainly in the liver, kidney, heart, skeletal muscle, brown adipose tissue, and intestines [16,78,109], controls expression of multiple genes and is involved in inflammation regulation [35,87]. PPAR-β/δ is expressed ubiquitously [16,43] and is involved in the control of lipid metabolism and placental development [6,96]. PPAR-γ exists in two isoforms, PPAR-γ1 and PPAR-γ2 (with additional 28 amino acids at the N-terminal compared to PPAR-γ1) [40,155]. PPAR-γ1 is expressed in a number of tissues, including heart, brain, skeletal muscle, kidney, pancreas, epithelial tissues, such as urothelium and intestine, and in specific kinds of immune and inflammatory cells [7,95,96,134]. PPAR-γ expression was also detected in tumors originating from various organs [38,96,98]. PPAR-γ2 is expressed mainly in adipose tissue [134]. PPAR-γ is crucial for adipocyte differentiation and adipogenesis, and also plays important roles in glucose and lipid metabolism, energy homeostasis, inflammation, and cancer [48,49,141]. Glitazones improve insulin activity through several mechanisms including: stimulation of the expression of genes that increase fat oxidation and lower plasma free fatty acid levels; increased expression, synthesis, and release of adiponectin; and stimulation of adipocyte differentiation [9,32,123]. So far, the exact mechanism of their action is not fully understood but they may exert their effects through PPAR-γ independent ways too, *e.g.* by AMPK activation [56,115] or apoptosis regulation [144].

Preclinical data on glitazone effects in carcinogenesis

As PPAR-γ receptors are expressed not only in normal but also in cancer cells [38,49,98], their ligands may alter tumor growth and progression. Numerous (mostly *in vitro*) reports showed that glitazones inhibit cancer cell growth, but some data are contradictory and indicate enhancement of carcinogenesis by PPAR-γ activation [86,148]. PPAR-γ ligands may inhibit carcinogenesis through cell cycle arrest and apoptosis induction [41,126,128], angiogenesis suppression [8,111], and anti-inflammatory actions [53,97]. Pioglitazone inhibited glioma growth both *in vitro* [61,110] and *in vivo* [61,110,140]; rosiglitazone reduced glioma growth [142] and cell invasiveness *in vitro* [72]. Rosiglitazone inhibited tumor growth in a human neuroblastoma xenograft [18], but another study by Krieger-Hinck et al. [82] showed only a minor effect on neuroblastoma in a metastatic xenograft mouse model. Pioglitazone inhibited human gastric cancer cell proliferation *in vitro* [126], rosiglitazone suppressed cell invasion and metastasis in human gastric cell lines [22]. Pancreatic cancer cell proliferation was inhibited by pioglitazone [71,132], and rosiglitazone [36] both *in vitro* and *in vivo.* Pioglitazone [14,63] and rosiglitazone [63] suppressed early carcinogenic transformation in chemically induced liver carcinogenesis in rats; rosiglitazone inhibited hepatocellular carcinoma metastases both *in vitro* and *in vivo* [117]. Troglitazone induced cell cycle arrest and apoptosis of hepatocellular carcinoma cell lines [152]. Pioglitazone and rosiglitazone inhibited chemically induced colon carcinogenesis in mice [108] and pheochromocytoma cell growth [75]. Glitazones may exert oncostatic effects through PPAR-γ-independent pathway too, as was shown in report by Fujita et al. [58]. Pioglitazone and another PPAR-γ ligand 15-deoxy-D12,14-prostaglandin J2 (15d-PGJ2) were reported to suppress the production of angiogenic factors in human renal cell carcinoma *in vitro* [154], the latter substance induced apoptosis in human hepatoma cells [30] and human oral squamous cell carcinomas too [59]. Pioglitazone attenuated colon cancer liver metastasis in immunodeficient mice [127] and ovarian tumor xenograft growth in nude mice [119]. Pioglitazone and rosiglitazone suppressed growth of human adrenocortical cell line [52]; rosiglitazone diminished adrenocortical carcinoma proliferation in a xenograft mouse model [92]. Rosiglitazone prevented the progression of preinvasive lung cancer in the A/J mouse model [93]. Another PPAR-γ agonist, ciglitazone (which was developed in early 1980s but was never introduced to the market), induced apoptosis in melanoma cells both *in vitro* [15,54] and *in vivo* [15]. Pioglitazone, troglitazone, and ciglitazone inhibited human ovarian cancer cell growth [76]; ciglitazone enhanced inhibitory effects of cisplatin on growth of human ovarian xenografts [150]. Ciglitazone was also effective in inhibition of high grade bladder cancer xenograft development [113]. Troglitazone and 15d-PGJ2 suppressed bladder carcinoma cell growth [19]; troglitazone [4,19,83,100] and 15d-PGJ2 [19,100] inhibited growth of prostate cancer cell lines; troglitazone also inhibited growth of prostate tumor xenografts in BNX mice [83]. Colon cancer cell growth was inhibited by pioglitazone and 15d-PGJ2 [118]; the same effect was reported for rosiglitazone [147] and troglitazone [3]. PPAR-γ agonists may also be effective in early stages of colon tumorigenesis as troglitazone and pioglitazone inhibited chemically induced colitis and