Naunyn-Schmied Arch Pharmacol (2009) 380:473–477
DOI 10.1007/s00210-009-0462-4

EDITORIAL

Apoptosis induction by doxazosin and other quinazoline α_1-adrenoceptor antagonists: a new mechanism for cancer treatment?

Natasha Kyprianou · Taylor B. Vaughan · Martin C. Michel

Received: 1 October 2009 / Accepted: 1 October 2009 / Published online: 11 November 2009

Abstract Doxazosin and related, quinazoline-based α_1-adrenoceptor antagonists can induce apoptosis in prostate and various other normal, benign, smooth muscle, endothelial and malignant cells. Such apoptosis-inducing effects occur independently of α_1-adrenoceptor antagonism and typically require much high concentrations than those required for receptor occupancy. Several studies have invested efforts towards the elucidation of the molecular mechanisms underlying doxazosin-induced apoptosis. These include various tumor cells, cardiomyocytes, endothelial cells and bladder smooth muscle cells. While the high concentrations of doxazosin required to induce apoptosis challenge the use of this and related drugs for clinical optimization of apoptosis induction, such quinazoline structure may represent chemical starting points to develop more potent apoptosis-inducing agents free of α_1-adrenoceptor antagonistic action and suitable for cancer treatment with minimal and well-tolerated side effects.

Keywords Doxazosin · Apoptosis · Quinazoline

N. Kyprianou (✉) · T. B. Vaughan
Division of Urology, Department of Surgery,
University of Kentucky Medical Center and Markey Cancer Center,
Combs Building, Room 306, 800 Rose Street,
Lexington, KY 40536, USA
e-mail: nkypr2@email.uky.edu

N. Kyprianou
Department of Molecular and Cellular Biochemistry,
University of Kentucky Medical Center and Markey Cancer Center,
Combs Building, Room 306, 800 Rose Street,
Lexington, KY 40536, USA

M. C. Michel
Department of Pharmacology and Pharmacotherapy,
Academic Medical Center,
Amsterdam, The Netherlands

α_1-Adrenoceptor antagonists have originally been used for the treatment of arterial hypertension. However, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated that the α_1-antagonist doxazosin provided less protection from cardiovascular events than the diuretic chlorthalidone (ALLHAT Research Group 2000). Additionally, in the Vasodilator Heart Failure Trial 1, prazosin was shown to be associated with greater mortality among heart failure patients vs those treated with other vasodilators (Cohn et al. 1986). Therefore, α_1-antagonists are no longer considered to be a first-line treatment in cardiovascular medicine. On the other hand, this class of drugs has later been introduced to treat voiding symptoms attributed to benign prostatic hyperplasia (BPH) where they have become the most widely used option of medical therapy. Initially, the therapeutic success of this drug class was assumed only to be a direct result of α_1-adrenoceptor blockade resulting in smooth muscle relaxation within the prostate. In this model, smooth muscle relaxation, in turn, provides relief from obstructive lower urinary tract symptoms caused by the enlarged prostate (Kirby 1995). Since the late 1990s, rapidly growing evidence has mounted to support the paradigm shift concept that certain α_1-antagonists not only have action on smooth muscle but also have α_1-adrenoceptor-independent effects including apoptosis induction and suppression of tissue vascularity.

Early studies in mice showed that doxazosin, an α_1-adrenoceptor antagonist with a quinazoline-based structure, induced apoptosis in murine prostatic stromal and epithelial cells (Yang et al. 1997). Small retrospective cohort studies in humans provided the initial evidence that the therapeutic benefit of doxazosin in BPH patients may involve an apoptotic action against both prostate stromal and epithelial cells (Kyprianou et al. 1998). A series of subsequent studies

have confirmed the proapoptotic activity of quinazoline α_1-antagonists including doxazosin, terazosin (Chon et al. 1999), and more recently, prazosin (Lin et al. 2007) in normal and malignant prostate cells. While the induction of apoptosis by doxazosin and chemically related compounds was initially shown in prostate cells and most of the subsequent work has also been conducted in such cells, later studies demonstrated doxazosin-induced apoptosis to also occur in a range of other normal and tumor cells, indicating that this may be a global effect that is not cell type-dependent. Such other cell types include cardiac myocytes (Rodriguez-Feo et al. 2000; Eiras et al. 2006) and the H9C2 cell line derived thereof (Yang et al. 2009), vascular endothelial cells (Keledjian et al. 2005), bladder smooth muscle cells (Austin et al. 2004), urothelial cancer cells (Siddiqui et al. 2005), pituitary adenoma cells (Fernando and Heaney 2005), breast cancer cells (Hui et al. 2008), colon cancer cells, and HeLa cells (Gan et al. 2008).

One of the most interesting aspects of this effect is the fact that apoptosis induction occurs independently of the α_1-antagonistic properties of these drugs (Kyprianou and Benning 2000; Anglin et al. 2002). Support for this concept emerges from evidence suggesting a significantly increased apoptotic index in prostatic cells exposed to doxazosin and terazosin (quinazoline-based α_1-antagonists) but not following tamsulosin treatment (a sulfonamide-based α_1-antagonist). Furthermore, the irreversible α_1-antagonist phenoxybenzamine had no effect on the antigrowth action of doxazosin or terazosin (Kyprianou and Benning 2000). Finally, it should be noted that doxazosin and related quinazoline α_1-adrenoceptor antagonists block all subtypes of those receptors in the nanomolar range (Michel et al. 1995) whereas micromolar concentrations of these drugs are required to induced apoptosis in vitro (Kyprianou and Benning 2000; Benning and Kyprianou 2002). In some animal studies, the induction of apoptosis in response to doxazosin treatment in vivo was achieved at relatively high concentrations and supratherapeutic doses (Yang et al. 1997; Benning and Kyprianou 2002). Despite the initial reservations regarding this issue, one must recognize that the retrospective human studies have reported quinazoline-induced apoptosis in the prostate upon exposure to therapeutically relevant doses (Kyprianou et al. 1998; Chon et al. 1999). While the reason for this discrepancy is not fully clear, it should be noted that many of those human in vivo studies have largely relied on the terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick-end labeling (TUNEL) technique as an apoptosis marker, which may yield false-positive results in some cases (see below). Moreover, multiple large placebo-controlled studies have failed to detect reduction of prostate size upon long-term treatment with, e.g., doxazosin (McConnell et al. 2003) or alfuzosin (Roehrborn 2006), which would argue against a clinically relevant degree of apoptosis induction upon standard therapeutic doses of these drugs.

Several studies have attempted to elucidate the cellular and molecular mechanisms underlying the apoptosis-inducing effects of doxazosin and related quinazolines. While in vitro approaches with cultured cell lines initially demonstrated that at least part of these effects occur directly by an interaction of the quinazolines with their target cells (Anglin et al. 2002; Partin et al. 2003), subsequent studies in more complex models indicate additional indirect effects. For example, some experimental studies have identified anoikis (programmed cell death initiated by loss of cell–cell or cell–matrix adhesion; Frisch and Screaton 2001; Rennebeck et al. 2005) as one of the apoptotic mechanisms responsible for the suppression of prostate tumor growth and vascularity by the quinazoline α_1-adrenoceptor antagonists, doxazosin and terazosin, independent of effects on cell proliferation (Tahmatzopoulos et al. 2004, 2005). Human bladder tumors exposed to terazosin also had a significant increase in apoptosis and decrease in tissue vascularity (Tahmatzopoulos et al. 2005). Apoptosis induction in many tumor cell types along with the combination of direct and indirect (anoikis, reduced vascularity) cell death-promoting effects raises the possibility that quinazolines may be a drug class with clinically useful anticancer effects.

In this issue of the journal, Yang et al. (2009) have explored potential mechanisms of quinazoline-induced apoptosis. They report on a functional contribution of transforming growth factor-β (TGF-β) type I receptor/ALK5-p38 MAPK phosphorylation signaling cascade in doxazosin-induced apoptosis in rat embryonic ventricular myoblasts. This represents a new signaling pathway for the "cell-killing action" of doxazosin and its quinazoline-based derivatives. However, this is not the first indication of the involvement of this multifunctional growth factor, TGF-β, in doxazosin's apoptotic effects. Indeed, the ligand itself, TGF-β, has been previously implicated in doxazosin-induced apoptosis in prostate tumor epithelial cells and smooth muscle fibroblasts (Yang et al. 1997; Anglin et al. 2002; Partin et al. 2003). The dissection of the type I TGF-β receptor as the primary upstream "executioner" in the apoptotic cascade triggered by doxazosin carries much promise and initiates momentum for the identification of the downstream effectors. The characterization of the signaling network operated by TGF-β via Smad-dependent and Smad-independent mechanisms in conjunction with branches of MAP kinase pathways enables the therapeutic exploitation of this multifaceted growth factor during cancer progression. The challenge remains to identify effective therapeutic modalities that do not interfere with the positive effects of TGF-β as a tumor suppressor at the onset of tumorigenic growth while inhibiting the

dysfunctional TGF-β in advanced cancer. Considering this ill-fated alliance between TGF-β and tumors, the temporal targeting of the TGF-β pathway should be implemented during the transition from tumor suppressor to tumor promoter and prior to its involvement in the metastatic process in the context of the tumor microenvironment. The biological repertoire of epithelial, stromal fibroblasts and endothelial cells linked to anoikis provides attractive targets for doxazosin's action during prostate tumor metastasis via the ability of the drug to engage TGF-β signaling.

While recognizing that the proapoptotic properties of α_1-antagonists are exciting in the context of identification of novel cancer molecular therapeutics, one must also consider the negative effects that may result if these properties extend to other cell types. In vitro evidence indicated that doxazosin induced apoptosis in a time-dependent and dose-dependent (1–40 μM) manner in HL-1 cells (continuously dividing, spontaneously contracting mouse cardiomyocytes). Other quinazoline α_1-antagonists, terazosin and prazosin, in addition to doxazosin, were also linked to in vitro K^+ channel blockage in a 2004 study. In this study, all three quinazoline α_1-antagonists blocked human ether-a-go-go-related gene (HERG) K^+ channels, which are located in human cardiomyocytes and some adenocarcinomas. Blockage of current in HERG channels was demonstrated in both human embryonic kidney (HEK) cells and *Xenopus* oocytes in a concentration-dependent manner (Thomas et al. 2004). HERG channel-blocking agents have previously been shown to have antiproliferative effects in tumor cells (Smith et al. 2002) but carry the risk for QT intervals and hence arrhythmias (Kiehn et al. 1999). Furthermore, it was recently shown that HERG K^+ channel blockage induced by doxazosin directly results in HEK cell apoptosis (Thomas et al. 2008). It should be noted, however, that, while quinazoline α_1-antagonists have been associated with apoptosis induction (Yang et al. 1997; Kyprianou et al. 1998; Chon et al. 1999; Anglin et al. 2002; Lin et al. 2007), they have not been implicated as having direct proarrhythmic potential (Thomas et al. 2004) possibly because clinically used doses of these drugs are insufficient to act on HERG channels to a relevant degree.

Apoptosis overinterpretation

Controversy and inconsistency has surrounded the apoptosis research as mediated by alpha blockers in target cells. Most would agree that the gold standard of apoptosis detection would be a detailed morphological analysis of each cell in a section by an expert microscopist. As this process would be user-dependent and not feasible for high-throughput quantitative assessment, other methods are commonly used. Much of the quinazoline α_1-antagonist work, as stated above, has been driven by prostate histopathological studies in which the TUNEL technique has most frequently been the method of apoptotic index assessment. The technique, straightforward in its conception, involves labeling fragmented DNA in cells from histologic sections undergoing apoptosis by using TdT to transfer biotin UTP to the free 3′-OH broken end. The newly biotin-labeled sites are then visualized under fluorescence microscopy after reaction with fluorescein-conjugated avidin. Other commonly used methods of apoptosis detection include, but are not limited to, DNA fragmentation assay using gel electrophoresis (Gan et al. 2008), Hoechst nuclear staining with direct fluorescence microscopy, flow cytometry assessment (Gan et al. 2008), activated caspase-3 assay (Gan et al. 2008), MTT cell viability assay (Gonzalez-Juanatey et al. 2003), caspase-cleaved cytokeratin 18 (CK18) assay (Duan et al. 2003), and several others.

Proposed faults of the TUNEL technique attest that all nicks or breaks in DNA are labeled, whether resulting from apoptosis or other processes including active transcription, cell necrosis, or improper tissue preparation and handling (Gavrieli et al. 1992; Grasl-Kraupp et al. 1995; Yasuda et al. 1995; Kockx et al. 1998). As a result, the TUNEL assay has proven to be adequately sensitive, but the possibility of false positives has left the specificity to be challenged. Subsequent study has found TUNEL assay specificity to exceed 87% (Kelly et al. 2003) and to also yield results strongly correlated with caspase-3 activation and caspase-cleaved CK18 prostate assays (Duan et al. 2003). Thus, of current apoptosis assays, TUNEL is adequately apoptosis specific in prostate section analysis while producing results consistent with other common assays (Duan et al. 2003).

Translational significance

Throughout the last decade, emerging knowledge has defined quinazoline α_1-antagonists to have α_1-independent, proapoptotic properties in multiple laboratory and clinical settings. In recent years, much progress has been made to better understand the clinical relevance of this information. Recent research regarding structural variants of the quinazoline α_1-antagonists has yielded exciting anticancer pharmacologic potential. While the studies with known quinazolines have been important to establish this principle, doxazosin and related existing drugs are probably unsuitable for clinical apoptosis induction due to their α_1-antagonist properties. However, they may be useful as starting points for the synthesis of more potent compounds. A recent pharmacologic exploitation of the doxazosin structure led to two structural variants of doxazosin that

exhibit greater apoptosis-inducing action at lower concentrations (~1–2 μM) than their parent compound (Shaw et al. 2004; Garrison and Kyprianou 2006). Additional studies showed a lead doxazosin derivative to reduce endothelial cell viability, thus impeding tumor vascularity, in PC-3 and DU-145 prostate cancer xenografts (Garrison et al. 2007). Quinazoline α_1-antagonists might be responsible for additional α_1-independent growth-suppressing mechanisms including the activation of anoikis (loss of cellular adhesion to the extracellular matrix) via death receptor-signaling pathway and prevention of tumor cell invasion and migration (Tahmatzopoulos et al. 2004; Keledjian et al. 2005). Further translational application of the antitumor potential of quinazoline α_1-antagonists has shown the class to have synergistic effects with ionizing radiation in prostate cancer treatment (Cuellar et al. 2002) and to decrease the incidence of prostate cancer in patients previously treated with drugs from the class (Harris et al. 2007).

Tumor malignancy is dependent upon the continued ability to grow and spread to new tissues. These properties necessitate anoikis avoidance and continued angiogenesis. In turn, restoring or facilitating anoikis and inhibiting angiogenesis are two targets of anticancer therapy. Quinazoline-based drugs terazosin and doxazosin have been shown to facilitate anoikis in prostate cells by death receptor-mediated mechanisms involving death-inducing signaling complex formation/caspase-8 activation and inhibition of Akt survival signaling, consequential to the disruption of cell attachment to the extracellular matrix via targeting integrins (Shaw et al. 2004; Garrison and Kyprianou 2006; Garrison et al. 2007). These mechanisms are intimately connected with the ability of terazosin and doxazosin to induce TGF-β1-mediated apoptosis independent of α_1-adrenoceptor action (Partin et al. 2003). Terazosin and doxazosin have also been shown to α1-independently downregulate the vascular endothelial growth factor in prostate tissue, thus impairing angiogenesis in malignant prostate tumors (Tahmatzopoulos and Kyprianou 2004).

In conclusion, quinazoline α_1-antagonists are effective options in managing BPH as well as hypertension. Research has recently shown drugs in this class to have multiple α_1-independent, anticancer properties. Future directions include continued detailed exploration of biochemical mechanisms responsible for the apoptotic effects exerted by the quinazolines and optimizing compounds that effectively demonstrate these effects in humans with limited side effects.

Acknowledgments Work on α_1-adrenoceptor antagonists in the authors' laboratories has been supported by Astellas (MCM), Boehringer Ingelheim (MCM), the Deutsche Forschungsgemeinschaft (MCM), the National Institutes of Health (NK), Pfizer Oncology (NK), Abbot Pharmaceutical (NK), and the American Urological Association Foundation (NK).

References

ALLHAT Research Group (2000) Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 283:1967–1975

Anglin IE, Glassman DT, Kyprianou N (2002) Induction of prostate apoptosis by alpha1-adrenoceptor antagonists: mechanistic significance of the quinazoline component. Prostate Cancer Prostatic Dis 5:88–95

Austin PF, Cook BL, Niederhoff RA, Manson SR, Coplen DE, Weintraub SJ (2004) Inhibition of mitogenic signaling and induction of apoptosis in human bladder smooth muscle cells treated with doxazosin. J Urol 172:1662–1665

Benning CM, Kyprianou N (2002) Quinazoline-derived α1-adrenoceptor antagonists induce prostate cancer cell apoptosis via an α1-adrenoceptor-independent action. Cancer Res 62:597–603

Chon JK, Borkowski A, Partin AW, Isaacs JT, Jacobs SC, Kyprianou N (1999) Alpha 1-adrenoceptor antagonists terazosin and doxazosin induce prostate apoptosis without affecting cell proliferation in patients with benign prostatic hyperplasia. J Urol 161:2002–2008

Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH et al (1986) Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med 314:1547–1552

Cuellar DC, Rhee J, Kyprianou N (2002) Alpha1-adrenoceptor antagonists radiosensitize prostate cancer cells via apoptosis induction. Anticancer Res 22:1673–1679

Duan WR, Garner DS, Williams SD, Funckes-Shippy CL, Spath IS, Blomme EA (2003) Comparison of immunohistochemistry for activated caspase-3 and cleaved cytokeratin 18 with the TUNEL method for quantification of apoptosis in histological sections of PC-3 subcutaneous xenografts. J Pathol 199:221–228

Eiras S, Fernandez P et al (2006) Doxazosin induces activation of GADD153 and cleavage of focal adhesion kinase in cardiomyocytes en route to apoptosis. Cardiovasc Res 71:118–128

Fernando MA, Heaney AP (2005) α_1-Adrenergic receptor antagonists: novel therapy for pituitary adenomas. Mol Endocrinol 19:3085–3096

Frisch SM, Screaton RA (2001) Anoikis mechanisms. Curr Opin Cell Biol 13:555–562

Gan L, Zhu D, Yang L, Liu R, Yan F, Zhang J (2008) Involvement of transcription factor activator protein-2α in doxazosin-induced HeLa cell apoptosis. Acta Pharmacol Sin 29:465–472

Garrison JB, Kyprianou N (2006) Doxazosin induces apoptosis of benign and malignant prostate cells via a death receptor-mediated pathway. Cancer Res 66:464–472

Garrison JB, Shaw YJ, Chen CS, Kyprianou N (2007) Novel quinazoline-based compounds impair prostate tumorigenesis by targeting tumor vascularity. Cancer Res 67:11344–11352

Gavrieli Y, Sherman Y, Ben-Sasson SA (1992) Identification of programmed cell death in situ via specific labeling of nuclear DNA fragmentation. J Cell Biol 119:493–501

Gonzalez-Juanatey JR, Iglesias MJ, Alcaide C, Piñeiro R, Lago F (2003) Doxazosin induces apoptosis in cardiomyocytes cultured in vitro by a mechanism that is independent of α1-adrenergic blockade. Circulation 107:127–131

Grasl-Kraupp B, Ruttkay-Nedecky B, Koudelka H, Bukowska K, Bursch W, Schulte-Hermann R (1995) In situ detection of fragmented DNA (TUNEL assay) fails to discriminate among apoptosis, necrosis, and autolytic cell death: a cautionary note. Hepatology 21:1465–1468

Harris AM, Warner BW, Wilson JM, Becker A, Rowland RG, Conner W, Lane M, Kimbler K, Durbin EB, Baron AT, Kyprianou N (2007) Effect of alpha1-adrenoceptor antagonist exposure on prostate cancer incidence: an observational cohort study. J Urol 178:2176–2180

Hui H, Fernando MA, Heaney AP (2008) The α_1-adrenergic receptor antagonist doxazosin inhibits EGFR and NF-κB signaling to induce breast cancer cell apoptosis. Eur J Cancer 44:160–166

Keledjian K, Garrison JB, Kyprianou N (2005) Doxazosin inhibits vascular endothelial cell adhesion, migration and invasion. J Cell Biochem 94:374–388

Kelly KJ, Sandoval RM, Dunn KW, Molitoris BA, Dagher PC (2003) A novel method to determine specificity and sensitivity of the TUNEL reaction in the quantitation of apoptosis. Am J Physiol Cell Physiol 284:C1309–C1318

Kiehn J, Thomas D, Karle CA, Schöls W, Kübler W (1999) Inhibitory effects of the class III antiarrhythmic drug amiodarone on cloned HERG potassium channels. Naunyn Schmiedebergs Arch Pharmacol 359:212–219

Kirby RS (1995) Doxazosin in benign prostatic hyperplasia: effects on blood pressure and urinary flow in normotensive and hypertensive men. Urology 46:182–186

Kockx MM, Muhring J, Knaapen MW, de Meyer GR (1998) RNA synthesis and splicing interferes with DNA in situ end labeling techniques used to detect apoptosis. Am J Pathol 152:885–888

Kyprianou N, Benning CM (2000) Suppression of human prostate cancer cell growth by alpha 1-adrenoceptor antagonists doxazosin and terazosin via induction of apoptosis. Cancer Res 60:4550–4555

Kyprianou N, Litvak JP, Barkowski A, Alexander R, Jacobs SC (1998) Induction of prostate apoptosis by doxazosin in benign prostatic hyperplasia. J Urol 159:1810–1815

Lin SC, Chueh SC, Hsiao CJ, Li TK, Chen TH, Liao CH, Lyu PC, Guh JH (2007) Prazosin displays anticancer activity against human prostate cancers: targeting DNA and cell cycle. Neoplasia 9:830–839

McConnell JD et al (2003) The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med 349:2387–2398

Michel MC, Kenny B, Schwinn DA (1995) Classification of alpha 1-adrenoceptor subtypes. Naunyn Schmiedebergs Arch Pharmacol 352:1–10

Partin JV, Anglin IE, Kyprianou N (2003) Quinazoline-based alpha1-adrenoceptor antagonists induce prostate cancer cell apoptosis via TGF-beta signaling and I kappa B alpha induction. Br J Cancer 88:1615–1621

Rennebeck G, Martelli M, Kyprianou N (2005) Anoikis and survival connections in the reactive tumor microenvironment: significance in prostate cancer metastasis. Cancer Res 63:11230–11235

Rodriguez-Feo JA, Forbes J et al (2000) Doxazosin modifies Bcl-2 and Bax protein expression in the left ventricle of spontaneously hypertensive rats. J Hypertens 18:307–315

Roehrborn CG (2006) Three months' treatment with the α_1-blocker alfuzosin does not affect total or transition zone volume of the prostate. Prostate Cancer Prostatic Dis 9:121–125

Shaw YJ, Yang YT, Garrison JB, Kyprianou N, Chen CS (2004) Pharmacological exploitation of the alpha1-adrenoreceptor antagonist doxazosin to develop a novel class of antitumor agents that block intracellular protein kinase B/Akt activation. J Med Chem 47:4453–4462

Siddiqui EJ, Shabbir M, Thompson CS, Mumtaz FH, Mikhailidis DP (2005) Growth inhibitory effect of doxazosin on prostate and bladder cancer cells. Is the serotonin receptor pathway involved? Anticancer Res 25:4281–4286

Smith GAM, Tsui HW, Newell EW, Jiang X, Zhu XP, Tsui FWL, Schlichter LC (2002) Functional up-regulation of HERG K+ channels in neoplastic hematopoietic cells. J Biol Chem 277:18528–18534

Tahmatzopoulos A, Kyprianou N (2004) Apoptotic impact of alpha1-blockers on prostate cancer growth: a myth or an inviting reality? Prostate 59:91–100

Tahmatzopoulos A, Rowland RG, Kyprianou N (2004) The role of alpha-blockers in the management of prostate cancer. Expert Opin Pharmacother 5:1279–1285

Tahmatzopoulos A, Lagrange CA, Zeng L, Mitchell BL, Conner WT, Kyprianou N (2005) Effect of terazosin on tissue vascularity and apoptosis in transitional cell carcinoma of bladder. Urology 65:1019–1023

Thomas D, Wimmer AB, Wu K, Hammerling BC, Ficker EK, Kuryshev YA, Kiehn J, Katus HA, Schoels W, Karle CA (2004) Inhibition of human ether-a-go-go-related gene potassium channels by α1-adrenoceptor antagonists prazosin, doxazosin, and terazosin. Naunyn Schmiedebergs Arch Pharmacol 369:462–472

Thomas D, Bloehs R, Koschny R, Ficker E, Sykora J, Kiehn J, Schlömer K, Gierten J, Kathöfer S, Zitron E, Scholz EP, Kiesecker C, Katus HA, Karle CA (2008) Doxazosin induces apoptosis of cells expressing hERG K+ channels. Eur J Pharmacol 579:98–103

Yang G, Timme TL, Park SH, Wu X, Wyllie MG, Thompson TC (1997) Transforming growth factor β1 transduced mouse prostate reconstitutions: II. Induction of apoptosis by doxazosin. Prostate 33:157–164

Yang Y-F, Wu C-C, Chen W-P, Su M-J (2009) Transforming growth factor-beta type I receptor/ALK5 contributes to doxazosin-induced apoptosis in H9C2 cells. Naunyn Schmiedebergs Arch Pharmacol (in press)

Yasuda M, Umemura S, Osamura RY, Kenjo T, Tsutsuni Y (1995) Apoptotic cells in the human endometrium and placental villi: pitfalls in applying the TUNEL method. Arch Histol Cytol 58:185–190