European Journal of Pharmacology 746 (2015) 132–137

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Cardiovascular pharmacology

The supplement–drug interaction of quercetin with tamsulosin on vasorelaxation

Misha F Vrolijk [a,*], Guido R M M Haenen [a,*], Antoon Opperhuizen [a,b], Eugène H J M Jansen [c], Paul M Schiffers [a], Aalt Bast [a]

[a] Department of Toxicology and Pharmacology, Maastricht University, Maastricht, The Netherlands
[b] Netherlands Food and Consumer Product Safety Authority (NVWA), Utrecht, The Netherlands
[c] National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

ARTICLE INFO

Article history:
Received 24 October 2014
Received in revised form
5 November 2014
Accepted 6 November 2014
Available online 15 November 2014

Chemical compounds studied in this article:
Tamsulosin (PubChem CID 129211)
Quercetin (PubChem CID 5280343)
Quercetin-3-glucuronide (PubChem CID 5274585)
4′O-methyl-quercetin (PubChem CID 5281699)

Keywords:
Quercetin
Tamsulosin
Vasorelaxation
Orthostatic hypotension
Supplement–drug interaction
Pharmacodynamics

ABSTRACT

The food supplement quercetin is used as self-medication for prostate disorders and is known to induce vasorelaxation. The drug tamsulosin is used in the treatment of benign prostatic hyperplasia. A major side effect of tamsulosin is orthostatic hypotension, mediated by vasorelaxation resulting from α_1-adrenoceptor blockade. The overlapping profile prompted us to investigate the pharmacodynamic interaction of quercetin with tamsulosin. Since quercetin is extensively metabolized in the intestines and the liver, the metabolites quercetin-3-glucuronide and 4′O-methyl-quercetin were also examined. Vasorelaxation induced by the compounds was tested in rat mesenteric arteries (average diameter: 360 ± μm) constricted by the α_1-adrenoceptor agonist phenylephrine. Tamsulosin (0.1 nM) decreased phenylephrine sensitivity 17-fold ($n=10$). Quercetin (5, 10 and 20 μM) also caused a decrease (2-, 4- and 6-fold respectively) of phenylephrine sensitivity, while 10 μM of quercetin-3-glucuronide and 4′O-methyl-quercetin decreased this sensitivity (1.5- and 2-fold) only slightly ($n=6$). The combination of tamsulosin with quercetin or quercetin metabolites proved to be far more potent than the compounds in isolation. The combination of quercetin, quercetin-3-glucuronide or 4′O-methyl-quercetin with tamsulosin decreased the phenylephrine sensitivity approximately 200-, 35- and 150-fold ($n=6$). The strong pharmacodynamic interaction between the food supplement quercetin and tamsulosin underlines the potential of the impact of supplement–drug interactions that warrant more research.

1. Introduction

Dietary supplements are used for all sorts of indications and have been linked to a wide variety of health benefits. Among these supplements, quercetin belongs to the best studied dietary flavonoids, a class of polyphenolic compounds that are abundantly present in vegetables and fruit (Boots et al., 2008a; Kuhnau, 1976; Perez-Vizcaino et al., 2002). It displays a multitude of activities, such as antioxidant, anti-inflammatory and anti-atherogenic activities (Bast and Haenen, 2013; Boots et al., 2008a; Boots et al., 2008b; Edwards et al., 2007; Kleemann et al., 2011). In addition, quercetin has been found to induce vasorelaxation of resistance arteries, which has been shown to potentially reduce blood pressure (Galindo et al., 2012; Khoo et al., 2010; Larson et al., 2012b; Perez-Vizcaino et al., 2002). The exact mechanism by which quercetin causes vasorelaxation is not fully elucidated. Quercetin is known to act as a signaling molecule by forming reactive intermediates (Boots et al., 2007; Choi et al., 2003; Williams et al., 2004). These reactive intermediates may activate particular signaling cascades. One example of such intermediate is H_2O_2, which is an important regulator of signal transduction, by which it induces endothelium-dependent vasorelaxation (Khoo et al., 2010). The formation of H_2O_2 has been implicated in the vasorelaxant effect of quercetin.

Among the indications of quercetin is prostate pain and swelling, chronic pelvic pain syndrome and chronic prostatitis (Ma et al., 2004; Shoskes et al., 1999). In contrast to the growing interest in the biological effects and the side effects of quercetin supplementation, the interaction of quercetin with drugs has gained remarkably little attention. Similar to drug–drug interactions, drug–nutrition interactions may be predicted from the overlap in their pharmacodynamic

Abbreviations: AKT, Protein Kinase B; BPH, benign prostatic hyperplasia; CCRC, cumulative concentration-response curve; DMSO, dimethyl sulfoxide; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated protein kinase; KRB, Krebs Ringer bicarbonate buffer; Q, quercetin; Q3G, quercetin-3-glucuronide; 4′O-met-Q, 4′O-methyl-quercetin

* Correspondence to: Department of Toxicology, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands. Tel.: +31 43 3881229
E-mail addresses: m.vrolijk@maastrichtuniversity.nl (M.F. Vrolijk), g.haenen@maastrichtuniversity.nl (G.R.M. Haenen).

http://dx.doi.org/10.1016/j.ejphar.2014.11.006
0014-2999/

profiles. This strategy revealed the potentially hazardous interaction of quercetin with the drug tamsulosin on vasorelaxation with orthostatic hypotension as primary threat.

Tamsulosin belongs to the α_1-adrenoceptor antagonists that are used to treat urine retention caused by benign prostatic hyperplasia (BPH) (Roehrborn and Schwinn, 2004). BPH has a prevalence of over 70% in men above the age of 60 (Djavan and Marberger, 1999; Steers and Zorn, 1995). Blocking α_1-adrenoceptors limits constriction of smooth muscles in the urinary tract and the prostate, facilitating urinary flow (Kumar and Khan, 2010).

Three subtypes of the α_1-adrenoceptor exist: α_{1A}, α_{1B} and α_{1D}. These adrenoceptors have a contractile role in the vasculature (Methven et al., 2009). Tamsulosin is an insurmountable antagonist for all three α_1-adrenoceptor subtypes, meaning that it depresses maximal effects of α_1-agonists (Noble et al., 1997). The selectivity of tamsulosin is generally considered to be $\alpha_{1A} > \alpha_{1D} > \alpha_{1B}$ (Taguchi et al., 1997). Blocking α_1-adrenoceptors in the vasculature causes vasorelaxation, potentially reducing the vasoconstrictor response of our body to maintain normal blood pressure after standing up. This might ultimately lead to an orthostatic drop in blood pressure (Nieminen et al., 2006; Piascik and Perez, 2001). A major side effect of tamsulosin therefore is orthostatic hypotension, i.e. a sudden fall in blood pressure when standing up (Djavan and Marberger, 1999). Especially in elderly, orthostatic hypotension is critical, since a sudden drop in blood pressure increases the risk of falling and fainting. Fall-induced injuries are the fifth leading cause of death worldwide in the elderly population (Kannus et al., 2000; Kannus et al., 2005; Tinetti et al., 1986).

The common pharmacodynamic profile, the use of both compounds in a group of frail patients and the major clinical impact prompted us to assess the potential interaction between the supplement quercetin and the drug tamsulosin on vasorelaxation. The supplement–drug interaction was assessed in rat mesenteric arteries constricted by the α_1-adrenoceptor agonist phenylephrine. Nourian et al. (2008) have shown a strong correlation between the in vivo orthostatic hypotensive effects of antipsychotic drugs in an animal model of orthostatic hypotension, with the in vitro effects of these drugs on α_1-adrenoceptors of mesenteric arteries in rats (Nourian et al., 2008). This corroborated the experimental strategy that α_1-adrenoceptors of mesenteric resistance arteries are responsible for the orthostatic hypotensive effects. Since quercetin is extensively metabolized in the intestine and the liver, the biological effects of quercetin are mainly mediated by its metabolites, the effects of the metabolites quercetin-3-glucuronide and 4′O-methyl-quercetin were also determined (Perez-Vizcaino et al., 2002). Here we show that quercetin and its metabolites 4′O-methyl-quercetin and quercetin-3-glucronide strongly augment the vasorelaxing effects of tamsulosin.

2. Materials and methods

2.1. Animal treatments

16 weeks old male Wistar Kyoto (WKY) rats (Charles River, Maastricht, the Netherlands), weighing 200–300 g, were housed in cages together and maintained at room temperature in a room with a 12- h light-dark cycle. Rats had free access to drinking water and standard chow. No adverse events were present in the study. All experiments were performed in accordance with the institutional guidelines and were approved by the Ethics Committee on Experimental Animal Welfare of the Maastricht University. A total of 30 animals was used in this study.

2.2. Chemicals

Phenylephrine (Sigma-Aldrich) was dissolved in Krebs Ringer bicarbonate buffer (KRB) containing (in mM): NaCl 118.5, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25.0 and glucose, 5.5. Quercetin (Sigma-Aldrich), 4′O-methyl-quercetin (Extrasynthese, France), glucuronidated quercetin (Sigma-Aldrich) and tamsulosin (Sigma-Aldrich) were all dissolved in dimethyl sulfoxide (DMSO). Ferrous ammonium sulfate (Sigma-Aldrich) and potassium thiocyanate (Sigma-Aldrich) were both dissolved in miliQ.

2.3. Vasorelaxation of mesenteric arteries

WKY rats were killed by CO_2-inhalation. The mesentery was excised and immediately submersed in KRB at room temperature. Second-order branches of the superior mesenteric artery were dissected and isolated, by removing fat and connective tissue around the artery. Then, the artery was cut into 2 mm long segments and these were mounted in wire myographs (DMT, Aarhus, Denmark), in which 5 ml KRB was maintained at 37 °C and aerated with 95% O_2 and 5% CO_2. One holder of the myograph organ bath served as anchor, while a second holder was connected to an isometric force transducer, which was coupled to a signal amplifier. The myograph organ bath is connected to a computer to record isometric tension. Vascular functions were assessed as following: the arterial segments were stretched to the diameter at which contractile response to 10 μM phenylephrine was observed to be the largest. This was done by increasing the arterial diameter in steps of 50 μm, which loaded the resting tension, and subsequently measuring the magnitude of the contractile response to 10 μM of phenylephrine. In this study, the optimal internal diameter of the arterial averaged 360 ± 8 μm and contractile responses to 10 μM phenylephrine averaged 3.4 ± 0.1 N m^{-1}.

After the optimal arterial diameter was determined, endothelial function was tested by adding 10 μM acetylcholine, which induced a complete endothelium-dependent relaxation of the arteries. Only arteries with intact endothelium have been used for our experiments. The resting tension of the arteries averaged 0.71 ± 0.08 N m^{-1}. Then the arterial mesentery segments were washed again and equilibrated for 30 min, after which a first constructing cumulative concentration–response curve (CCRC) of phenylephrine (10^{-7}–10^{-3} M in logarithmic half-units) was constructed. The contractile response to phenylephrine is regarded as the control CCRC. After wash-out with KRB, the vessel segments were equilibrated again for 15 min, after which 0.1 nM tamsulosin was added. Nine minutes later, a second CCRC of phenylephrine was constructed to determine the effect of tamsulosin on phenylephrine-induced contraction. After wash-out, vessels were incubated for 9 min with 0.1 nM tamsulosin in combination with 5, 10, or 20 μM quercetin. Hereafter, a third CCRC of phenylephrine was constructed to determine the effect of combination of quercetin and tamsulosin on phenylephrine-induced contraction.

In order to determine the effect of quercetin metabolites on tamsulosin function, vessels were incubated with 10 μM of either 4′O-methyl-quercetin or quercetin-3-glucuronide in combination with 0.1 nM tamsulosin for 9 min, after which the vessels were contracted by phenylephrine. The effects of quercetin, 4′O-methyl-quercetin and quercetin-3-glucuronide alone on phenylephrine-induced contractions were also determined. A possible reaction between quercetin and tamsulosin was checked spectrophotometrically. No reaction was found. Furthermore, as a control experiment, the effect of the vehicle (DMSO) was determined in the same concentration (max. 0.2%) as used in the experiments. DMSO was found to have no significant effect on phenylephrine-induced contractions. After each wash-out and equilibration period, the arterial tension returned back to baseline independent of treatment. Finally, time-control experiments were performed by repeating a dose–response curve with phenylephrine at the end of the experiment. The sensitivity of the arteries to phenylephrine had not been changed during time and exposures.