Methylxanthines and the Kidney

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Contents

Abstract This chapter describes the effects of the natural methylxanthines caffeine and theophylline on kidney function. Theophylline in particular was used traditionally to increase urine out put until more potent diuretics became available in the middle of the last century. The mildly diuretic actions of both methylxanthines are mainly the result of inhibition of tubular fluid reabsorption along the renal proximal

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tubule. Based upon the use of specific adenosine receptor antagonists and the observation of a complete loss of diuresis in mice with targeted deletion of the A1AR gene, transport inhibition by methylxanthines is mediated mainly by antagonism of adenosine A1 receptors (A1AR) in the proximal tubule. Methylxanthines are weak renal vasodilators, and they act as competitive antagonists against adenosine-induced preglomerular vasoconstriction. Caffeine and theophylline stimulate the secretion of renin by inhibition of adenosine receptors and removal of the general inhibitory brake function of endogenous adenosine. Since enhanced intrarenal adenosine levels lead to reduced glomerular filtration rate in several pathological conditions theophylline has been tested for its therapeutic potential in the renal impairment following administration of nephrotoxic substances such as radiocontrast media, cisplatin, calcineurin inhibitors or following ischemia-reperfusion injury. In experimental animals functional improvements have been observed in all of these conditions, but available clinical data in humans are insufficient to affirm a definite therapeutic efficacy of methylxanthines in the prevention of nephrotoxic or postischemic renal injury.

1 Introduction

The plant constituents caffeine and theophylline have been known to alter kidney function since the demonstration in 1864 that caffeine can increase urine production in patients with congestive heart failure and edema (Koschlakoff 1864). Interest in the renal actions of methylxanthines has remained acute although the clinical use of theophylline is largely restricted to the treatment of extra-renal diseases such as asthma. The focus of this chapter is a description of the renal effects of the natural methylxanthines, mainly of caffeine and theophylline, and a discussion of current understanding of the mechanisms underlying these effects. Important progress in mechanistic thinking has been made by using modified methylxanthines, and it will therefore sometimes be necessary to include data obtained with synthetic xanthine derivatives when this permits discrimination between the different targets of the natural compounds. This is especially relevant in the case of methylxanthines as antagonists of adenosine receptors, a predominant mechanism in many renal actions of methylxanthines. Nevertheless, a broad discussion of adenosine and its interaction with adenosine receptors is not the goal of this review, and adenosine will only be discussed in the context of understanding methylxanthine actions. We also will make reference to nonnatural xanthine compounds in cases where their actions are in conflict with those of caffeine or theophylline or where they shed light on likely mechanisms of action.

2 Diuresis

The natural methylxanthines caffeine and theophylline were used traditionally to increase urine output until more potent diuretics became available in the middle of the last century. In numerous studies in animal and humans the order of diuretic potency of the natural methylxanthines was found to be theophylline > caffeine > paraxanthine > theobromine. The actions of methylxanthines as diuretics have been extensively reviewed in an excellent chapter in the *Handbook of Experimental Pharmacology* in which the literature prior to 1970 was summarized and discussed in full detail (Fulgraff 1969). In the period since then, it has been confirmed repeatedly that caffeine and other methylxanthines can induce an increase in urine flow in humans and experimental animals. The dose of caffeine that elicits a significant acute diuresis has been reported to be on the order of 300 mg, the equivalent of about four to five cups of coffee (Grandjean et al. 2000; Passmore et al. 1987; Riesenhuber et al. 2006). As determined by impedance analysis, an acute intake of 642 mg of caffeine without a change in total fluid intake caused a measurable decrease in body weight corresponding to a 2.7% reduction of total body water (Neuhauser et al. 1997). Furthermore, a positive fluid balance prior to methylxanthine administration enhanced the diuretic efficacy of methylxanthines, while a negative fluid balance reduced the diuretic response (Fulgraff 1969). The diuretic potency of caffeine appears to be also modulated by age and habituation, with old age and previous exposure to caffeine causing further decreases in the diuretic effectiveness of caffeine (Izzo et al. 1983).

Overall, the relatively modest potency of caffeine to enhance water excretion and cause net water loss is consistent with studies in which caffeine (up to 6 mg/kg) given for 11 days did not affect 24-h urine volume and was not associated with symptoms of negative fluid balance (Armstrong et al. 2005). The same conclusion was drawn in a study where the diuretic effects of caffeinated and noncaffeinated electrolyte drinks were compared in individuals at rest and during moderate exercise (Wemple et al. 1997). While the ingestion of caffeine (25 mg/dl at 35 ml/kg) caused a higher urine flow in individuals at rest compared with ingestion of caffeine-free fluid, urine flow was reduced to the same level during exercise and this was associated with identical increments of plasma catecholamine concentrations. In a smaller study, consumption of tea as the major fluid source did not cause noticeable differences in hydration status compared with nontea fluid intake in a group of mountaineers at high altitude (Scott et al. 2004). Thus, the general advice against using caffeinated drinks for volume replacement may need to be qualified in that beverages containing moderate amounts of caffeine do not appear to cause significant fluid losses (Armstrong 2002).

Caffeine in high concentration supplied in a calcium-free medium has been shown to prevent the increase in calcium level caused by vasopressin in rat renal papillary collecting duct cells and this may blunt the increase of cyclic AMP (cAMP) level and the effect of vasopressin on water permeability (Ishikawa et al. 1992). Caffeine appears to exert this effect by depletion of endoplasmic calcium

stores, suggesting that its action may be caused by interaction with ryanodine-sensitive calcium-release channels. Nevertheless, there is no evidence in support of the notion that methylxanthines in lower concentrations inhibit solute-free water absorption in the distal part of the nephron. In fact, theophylline has been observed to mimic the effect of vasopressin on water permeability in isolated perfused collecting ducts and in the bladder of the toad (Grantham and Orloff 1968; Orloff and Handler 1962). Both vasopressin and theophylline increased cellular cAMP levels, indicating that the theophylline effects are mediated by inhibition of phosphodiesterase (PDE) (Handler et al. 1965). Caffeine is unlikely to reduce collecting duct water reabsorption through inhibition of adenosine receptors since in perfused and nonperfused collecting ducts adenosine has been shown to inhibit AVP-stimulated water permeability through activation of A_1 adenosine receptors (Edwards and Spielman 1994; Yagil 1990). Since A_2-adenosine-receptor-mediated effects have not been identified (Edwards and Spielman 1994; Yagil 1990), caffeine would thus be expected to enhance, not inhibit, collecting duct water transport, just as inhibition of cAMP degradation by possible methylxanthine effects on PDE would not be predicted to inhibit water transport. Furthermore, there does not seem to be a direct effect of caffeine on vasopressin secretion since plasma vasopressin levels have been reported to be unaltered after caffeine ingestion (Izzo et al. 1983; Nussberger et al. 1990). One would conclude that the type of diuresis caused by methylxanthines is mostly or exclusively a solute diuresis.

3 Natriuresis

Increased urine flow caused by methylxanthines is accompanied by increased excretion of sodium, chloride, calcium, phosphate, magnesium, and other urinary solutes. Although methylxanthines have in some studies been found to increase the tubular sodium load, significant natriuresis can occur without changes in glomerular filtration rate (GFR) or renal blood flow (RBF), clearly indicating that the natriuresis caused by methylxanthines is predominantly the result of inhibition of tubular salt transport (Davis and Shock 1949; Ludens et al. 1970; Shirley et al. 2002). Natriuresis without hemodynamic changes was also caused by methylxanthines in premature infants and newborn rabbits (Gouyon and Guignard 1987; Mazkereth et al. 1997). The increased excretion of calcium caused by caffeine may have implications for calcium homeostasis. Abstinence from moderate daily caffeine consumption (200 mg or less) has been noted to significantly increase plasma concentrations of ionized calcium and to reduce PTH levels in women with a relatively low dietary calcium intake (Massey et al. 1994; Wise et al. 1996).

In addition to causing natriuresis and diuresis, the administration of theophylline to conscious rats (10–50 mg/kg oral) or anesthetized rabbits (15 mg/kg intravenously) was accompanied by increased urinary excretion of prostaglandin E_2 (PGE_2) and cAMP (Baer et al. 1983; Oliw et al. 1977). Pretreatment with indomethacin or meclofenamate prevented the natriuretic action of theophylline, and

conversely, theophylline caused a transient reversal of the antinatriuresis and antidiuresis elicited by indomethacin in patients with rheumatic diseases (Oliw et al. 1977; Seideman et al. 1987). The possibility that some effects of methylxanthines on urine excretion could be indirect is also supported by the observation that plasma and kidney atrial natriuretic factor (ANF) activity increased following prolonged caffeine ingestion (Eggertsen et al. 1993; Lee et al. 2002). Nevertheless, no change in plasma ANF was seen 2 h after an oral intake of a single 250 mg dose of caffeine (Nussberger et al. 1990). That the natriuretic effect of methylxanthines is probably not strictly dependent on ANF is also suggested by the observation that prior exposure to theophylline did not modify the natriuretic action of ANF (Beutler et al. 1990).

There is considerable evidence to indicate that methylxanthine-induced natriuresis is predominantly a consequence of inhibition of salt transport along the proximal convoluted tubule. Administration of 400 mg of caffeine to healthy human subjects caused an about 1.5-fold increase in sodium excretion and this was associated with an increase in the clearance of lithium (Shirley et al. 2002). A reduction of proximal solute reabsorption in humans as assessed by lithium clearance was also caused by theophylline and aminophylline (Beutler et al. 1990; Brater et al. 1983). At the level of the single tubule, systemic administration of theophylline (20 mg/kg subcutaneously) caused an about 20% reduction in proximal tubular reabsorptive capacity as determined with the split-droplet technique in the rat (Fulgraff 1969). Tubular microperfusion of the loop of Henle with solutions containing theophylline or 3-isobutyl-1-methylxanthine did not significantly alter chloride reabsorption, indicating that methylxanthines do not affect salt absorption along proximal straight tubules and thick ascending limbs (Schnermann et al. 1977). The effect of methylxanthines on sodium transport in tubular segments beyond the proximal tubule and the loop of Henle has not been explored in detail, although on the basis of indirect evidence an inhibitory action in more distal parts of the tubule has been proposed (Brater et al. 1983; Shirley et al. 2002).

The mechanism by which methylxanthines inhibit proximal NaCl reabsorption is related to their properties as antagonists of adenosine receptors. Xanthine derivatives such as doxofylline and enprofylline with low affinity for adenosine receptors, but similar ability to inhibit PDE, have been noted to exert only marginal effects on natriuresis compared with aminophylline or theophylline, suggesting that inhibition of adenosine receptors is critical for the natriuretic action (Andersson et al. 1984; Cirillo et al. 1989; Franzone et al. 1988). Strong experimental evidence indicates that it is the A_1 adenosine receptor subtype whose inhibition results in natriuresis. In mice with targeted deletion of A_1 adenosine receptors, the diuretic and natriuretic effect of caffeine (45 mg/kg) or theophylline (45 mg/kg) was entirely absent (Rieg et al. 2005). The natriuresis caused by systemic administration of xanthine derivatives designed to selectively inhibit A_1 adenosine receptors such as CVT-124, 1,3-dipropyl-8-cyclopentylxanthine (DPCPX), and KW-3902 has been shown by lithium clearance and renal tubular micropuncture approaches to be accompanied by inhibition of proximal tubular fluid reabsorption (Knight et al. 1993; Kost et al. 2000; Mizumoto and Karasawa 1993; Wilcox et al. 1999).

DPCPX-induced natriuresis can be prevented by pertussis toxin, consistent with an involvement of the Gi-coupled A_1 adenosine receptors (Kost et al. 2000).

In view of the dominant role of Na/H exchange for sodium reabsorption in the proximal tubule, it is not surprising that modulation of NHE3 has been implicated in adenosine-dependent modulation of sodium reabsorption. In opossum kidney cells, low concentrations of an A_1 adenosine receptor agonist (less than 10^{-8} M) do in fact activate NHE3, an effect that is blocked by A_1 adenosine receptor antagonists and apparently mediated by inactivation of adenylyl cyclase (Di Sole et al. 2003). Downregulation of NHE3 and of α_1/β_1-NaKATPase protein expression was observed following a 1-day treatment with caffeine in rats (Lee et al. 2002). On the other hand, theophylline (1 mM) did not affect HCO_3 flux as assessed from the pH recovery in stationary microperfusion studies in the rat (Bailey 2004). In renal proximal tubular cell cultures and opossum kidney cells, A_1 adenosine receptor activation stimulated and inhibition of A_1 adenosine receptors by DPCPX or KW-3902 inhibited apical sodium/phosphate (Cai et al. 1994, 1995; Coulson et al. 1991) and Na/glucose cotransport (Coulson et al. 1991, 1996). Inhibition of phosphate uptake by A_1 adenosine receptor antagonists was associated with a dose-dependent increase of cellular cAMP production as well as an increase in protein kinase C activity (Cai et al. 1995; Coulson et al. 1991, 1996). Theophylline and A_1-adenosine-receptor- selective xanthine derivatives inhibited basolateral HCO_3 conductance in microperfused rabbit proximal convoluted tubules and this effect was mimicked by forskolin and chlorophenylthio-cAMP, suggesting that methylxanthines inhibit Na/HCO_3 cotransport activity by increasing intracellular cAMP levels (Takeda et al. 1993). To the extent that caffeine causes an increase in arterial blood pressure, a potential direct role of blood pressure in inhibiting tubular reabsorption and altering NHE3 distribution needs to be considered (Nussberger et al. 1990; Rachima-Maoz et al. 1998; Rakic et al. 1999). Finally, it should be pointed out that administration of methylxanthines only explores the impact of a reduction in adenosine-mediated effects, and that the consistent stimulatory effect of adenosine suggested by this intervention is therefore not in conflict with the possibility that high concentrations of adenosine may elicit inhibition of proximal tubular transport (Di Sole 2008; Di Sole et al. 2003).

4   Hemodynamics

Several studies in anesthetized dogs agree that the intrarenal infusion of methyl-xanthines does not affect RBF significantly, although renal vascular tone may decrease slightly because of small blood pressure reductions (Ibarrola et al. 1991; Osswald 1975; Premen et al. 1985). Furthermore, theophylline or caffeine do not alter renal plasma flow in humans to an extent that could be detected by clearance techniques (Beutler et al. 1990; Brater et al. 1983; Brown et al. 1993; Passmore et al. 1987). Changes of GFR in response to methylxanthines are sometimes more pronounced than those of RBF causing increases of filtration fraction (Fulgraff

1969). On the other hand, theophylline consistently inhibited adenosine-induced reductions of GFR and RBF in dogs and rats (Osswald 1975; Osswald et al. 1977; Pawlowska et al. 1987; Spielman 1984). Similarly, the vasodilator response of medullary blood flow to adenosine was blocked by 8-phenyltheophylline (Dinour and Brezis 1991). Thus, methylxanthines can affect renal hemodynamics by blocking the vascular actions of adenosine, at least in the range of supranormal adenosine levels. The absence of major effects of methylxanthines on renal hemodynamics could be due to low resting levels of adenosine. However, this seems unlikely since renal interstitial adenosine levels as determined by microdialysis are on the order of 50–200 nM, a range in which both A_1 and A_{2a} adenosine receptors should be partially occupied (Baranowski and Westenfelder 1994; Nishiyama et al. 2001; Siragy and Linden 1996; Zou et al. 1999). Thus, renal vascular tone under basal conditions appears to represent a state of balanced activation of A_1 and A_{2a} adenosine receptors. Vascular actions of theophylline could also result from a reduction of the inhibitory effect of adenosine on catecholamine release from renal sympathetic nerve terminals (Hedqvist and Fredholm 1976). In isolated perfused rabbit kidneys, theophylline did not affect norepinephrine release or RBF under basal conditions, presumably a reflection of the absence of a basal sympathetic tone (Hedqvist et al. 1978). However, the increased norepinephrine release following renal nerve stimulation was slightly potentiated by theophylline, and this was accompanied by a decrease in the vasoconstrictor response to nerve stimulation (Hedqvist et al. 1978). Similarly, theophylline attenuated the vasoconstrictor response to exogenous norepinephrine (Hedqvist et al. 1978; Yoneda et al. 1990). Finally, the reduction of GFR following dipyridamole and indomethacin administration in rheumatic patients was fully reversed by theophylline, suggesting that some of the vascular effects of indomethacin may be adenosine-mediated (Seideman et al. 1987).

In contrast to the negligible effects of methylxanthines on global renal vascular tone, theophylline has been found to fully inhibit the local tubuloglomerular feedback (TGF) response to changes of NaCl concentration in individual nephrons. Intratubular and intravenous administration of theophylline or 1,3-dipropyl-8-*p*-sulfophenylxanthine caused a dose-dependent blockade of the afferent arteriolar constriction induced by increases in NaCl concentration in the tubular fluid passing the macula densa segment (Franco et al. 1989; Osswald et al. 1980; Schnermann et al. 1977). This effect is the result of inhibition of A_1 adenosine receptors since the effect of theophylline on TGF was fully mimicked by subtype-specific adenosine receptor antagonists (Kawabata et al. 1998; Ren et al. 2002; Schnermann et al. 1990; Thomson et al. 2000; Wilcox et al. 1999). Infusion of hypertonic saline into the renal artery of anesthetized dogs has been shown to cause sustained vasoconstriction, and this has been considered a model of "whole kidney TGF" (Gerkens et al. 1983). Like single nephron TGF, vasoconstriction caused by hypertonic saline was inhibited by theophylline or aminophylline (Gerber and Nies 1986; Gerkens et al. 1983). Extracellular conversion of released cAMP by ectophosphodiesterases and 5′-nucleotidase has been suggested to constitute a significant source of adenosine in the kidney (Jackson et al. 1997). Thus, the PDE-inhibitory effects of

xanthines may contribute to inhibition of TGF by reducing the interstitial adenosine levels (Mi et al. 1994).

5 Renin Secretion

It is remarkable that methylxanthines are able to cause natriuresis despite the fact that they also stimulate the strongly antinatriuretic renin–angiotensin system. Theophylline increased plasma renin activity in dogs, and this increase was shown to occur without changes in blood pressure or in the plasma levels of epinephrine and norepinephrine, indicating that it was not mediated by the renal baroreceptor mechanism or by adrenergic receptors (Reid et al. 1972). In fact, theophylline stimulated renin release even in dogs treated with propranolol. Likewise, oral administration of caffeine in rats for 10 days was associated with a marked rise of renin secretion (Tofovic and Jackson 1999). Even though it was thought that the theophylline effect may be mediated by inhibition of PDE and the resulting increase in cellular cAMP levels (Reid et al. 1972), it now seems likely that stimulation of renin by methylxanthines is at least in part, but probably predominantly, a consequence of inhibition of adenosine receptors. Inhibition of A_1 adenosine receptors by the selective antagonist FK-453 caused a significant increase of plasma renin levels (Balakrishnan et al. 1993), and DPCPX partially inhibited the stimulation of renin release caused by low NaCl concentration in a microperfused juxtaglomerular apparatus preparation (Weihprecht et al. 1990). Furthermore, infusion of caffeine or theophylline at a dose that did not change renal cortical cAMP levels has been reported to abolish the inhibitory effect of intrarenally infused adenosine on renin secretion, and this effect could be dissociated from hemodynamic changes (Arend et al. 1987; Choi et al. 1993; Spielman 1984). In support of the notion that endogenous adenosine exerts a general inhibitory "brake" function in renin release, caffeine or theophylline as well as specific A_1 adenosine receptor antagonistic xanthines have been reported to augment the renin-stimulatory effects of a low renal artery pressure, a low-sodium diet, furosemide, isoproterenol, and vasodilators such as diazoxide and hydralazine (Brown et al. 1991; Langard et al. 1983; Paul et al. 1989; Pfeifer et al. 1995; Tofovic et al. 1991; Tseng et al. 1993). Despite the convincing effect of methylxanthines in experimental animals, studies in normotensive human subjects examining the effect of caffeine (250 mg) or coffee drinking have reported plasma renin concentration to increase, decrease, or remain unchanged, indicating that caffeine in moderate doses may not consistently induce the plasma caffeine levels needed to stimulate renin release (Nussberger et al. 1990; Robertson et al. 1978; Smits et al. 1983). Similarly, no increases of plasma renin concentration were observed in response to caffeine or coffee drinking in hypertensive patients (Eggertsen et al. 1993; Palatini et al. 1996; Robertson et al. 1984) or in patients with autonomic failure (Onrot et al. 1985).

6 Disease and Therapeutic Aspects

6.1 Polycystic Kidney Disease

Generation of cAMP has been shown to play a role in the secretion of fluid that is thought to be partly responsible for the accumulation of fluid in renal cystic disease (Belibi et al. 2002). Thus, by augmenting cAMP levels, methylxanthines could contribute to the progression of cyst formation. In fact, in primary cultures of renal cysts from patients with autosomal dominant polycystic kidney disease (ADPKD), caffeine (10–1,000 μM) increased levels of cellular cAMP and this was associated with an increase of transepithelial chloride secretion. Furthermore, caffeine greatly potentiated the augmentation of cAMP induced by Gs-coupled agonists such as vasopressin and PGE$_2$. The increase of cAMP levels by caffeine was in part mediated by inhibition of PDE since rolipram, a PDE inhibitor that does not interact with adenosine receptors, also caused a marked elevation of cAMP levels. However, an elevation in cAMP level was also seen with adenosine (10 mM), and this effect was attenuated, but not fully blocked by caffeine, suggesting that stimulation of A$_2$ adenosine receptors contributed to the accumulation of cAMP in cyst cells (Belibi et al. 2002). Cyst formation has also been related to impaired mechanosensation by primary cilia since both polycystin 1 (PC1) and polycystin 2 (PC2) are found in association with cilia. In fact, the increase in cytosolic calcium concentration caused by a flow stimulus in renal cells of wild-type mice was not seen in cells from PC1- or PC2-deficient mice or after treatment of wild-type cells with blocking antibodies against PC2 (Nauli et al. 2003). The increase in cytosolic calcium concentration by flow was blocked by high concentrations of caffeine, suggesting that it was caused by release of stored calcium across ryanodine-sensitive receptors in response to an initial calcium entry through PC2 cation channels. Nevertheless, caffeine ingestion did not accelerate cyst formation in the Han–Sprague-Dawley rat model of ADPKD although it was associated with the generation of hypertension (Tanner and Tanner 2001).

6.2 Nephropathies

In several experimental disease models, chronic caffeine administration has been found to exacerbate the development of hypertension and renal disease, perhaps through the effect of caffeine on renin secretion. For example, the presence of caffeine (0.1%) in the drinking water of rats augmented the blood pressure increase caused by renal arterial constriction and this was associated with a greater increase of plasma renin concentration (Choi et al. 1993; Kost et al. 1994; Ohnishi et al. 1986). Similarly, a 10-day caffeine exposure enhanced renin secretion to a markedly greater extent in spontaneously hypertensive heart failure (SHHF/Mcc-fa) rats than in control rats (Tofovic et al. 1999). In association with the increase of renin

secretion, prolonged caffeine ingestion caused a faster decline of renal function and a significant enhancement of urinary protein excretion (Tofovic and Jackson 1999). An adverse effect of chronic caffeine intake on renal function was also observed in puromycin aminonucleoside induced nephrosis in rats. Both the decline of renal function assessed as creatinine clearance and the increase of renin secretion were enhanced in puromycin-treated rats receiving caffeine in comparison with nephrotic rats receiving tap water (Tofovic et al. 2000). In addition, caffeine potentiated the development of interstitial fibrosis and glomerulosclerosis caused by puromycin (Tofovic et al. 2000). Finally, long-term treatment with caffeine reduced renal function and augmented proteinuria in obese diabetic ZSF1 rats despite improving glucose tolerance. Caffeine-induced renal deterioration was paralleled by enhanced fibrosis, proliferation, and inflammation (Tofovic et al. 2002, 2007). In addition to stimulating the release of renin, the effects of caffeine may be mediated through interference with the direct anti-inflammatory effects of adenosine (Tofovic et al. 2007).

In view of this solid body of evidence in support of caffeine as a risk factor in renal disease it is unexpected that the methylxanthine pentoxifylline has been found to produce exactly opposite outcomes. Pentoxifylline has only a low affinity for adenosine receptors and is generally considered a PDE inhibitor with some selectivity for PDE4 (Daly 2007). In animal studies, pentoxifylline markedly reduced the functional decline, proteinuria, fibrosis, and inflammation in rats following 5/6 nephrectomy or treatment with anti-GBM antiserum, and this was associated with an attenuation of the stimulated expression of mitogenic and profibrotic gene products (Chen et al. 2004; Lin et al. 2002). This effect was probably independent of the renin–angiotensin system since a combination of pentoxifylline with an ACE inhibitor further diminished disease progression (Lin et al. 2002), and since the plasma renin level was found to be unchanged in a human study (Chen et al. 2006). Furthermore, pentoxifylline protected against endotoxin-induced renal failure in mice and reduced plasma levels of TNF-α, IL-1β, and nitric oxide (Wang et al. 2006). In relatively small human trials, pentoxifylline reduced proteinuria and slowed the GFR decline in patients with chronic renal failure (Lin et al. 2008; Perkins et al. 2009), and it reduced proteinuria in patients with primary glomerular diseases in association with a reduction of urinary MCP-1 excretion (Chen et al. 2006). In nonhypertensive type 2 diabetic subjects pentoxifylline was as effective in reducing microalbuminuria as the ACE inhibitor captopril (Rodriguez-Moran and Guerrero-Romero 2005). A meta-analysis of ten randomized controlled studies in adult patients with diabetic kidney disease suggested comparable efficacies of pentoxifylline and captopril in reducing proteinuria (McCormick et al. 2008). The mechanism of action of the protective effects of pentoxifylline or its metabolite lisofylline is unclear.

6.3   Radiocontrast Nephropathy

Iodinated radiocontrast agents used in a number of radiological imaging procedures can cause acute renal failure. The incidence is very low in the absence of

complicating factors, but it increases considerably in patients with pre-existing renal conditions or in other circumstances that represent a risk factor for developing acute renal failure in general, such as dehydration or low cardiac output. Since radiocontrast-induced renal failure is accompanied by a reduction of RBF and GFR, methylxanthines have been among a number of vasodilator agents that have been assessed in regard to their preventive potential. In sodium-depleted dogs, radiocontrast agents reduced RBF and GFR, and both of these effects were attenuated by prior administration of theophylline (Arend et al. 1987; Deray et al. 1990). Furthermore, theophylline partially prevented the reduction of medullary blood flow induced by iodixanol (Lancelot et al. 2002). Thus, theophylline appears to act by antagonizing vasoconstriction mediated by A_1 adenosine receptor activation, and this hypothesis was corroborated in studies in which the A_1-adenosine-receptor-selective antagonist KW-3902 was even more effective than theophylline in attenuating iohexol-induced renal functional impairment in dogs with pre-existing renal insufficiency (Arakawa et al. 1996). Acute renal failure and cytotoxicity following iohexol administration were found to be more pronounced in wild-type than in A_1-adenosine-receptor-deficient mice, and a similar protective effect could be seen when wild-type mice were pretreated with the A_1-adenosine-receptor-selective antagonist DPCPX (Lee et al. 2006). In rats pretreated chronically with N^ω-nitro-L-arginine methyl ester, but not in control rats, sodium diatrizoate caused a decrease of GFR and RBF that could be fully prevented by pretreatment with theophylline, DPCPX, or KW-3902 (Erley et al. 1997; Yao et al. 2001). It could also be prevented by extracellular volume expansion, the standard preventive strategy (Yao et al. 2001). In the majority of studies, prophylactic administration of theophylline or aminophylline has also been reported to provide protection against radiocontrast renal failure in humans (Erley et al. 1994; Huber et al. 2001, 2003; Kapoor et al. 2002; Katholi et al. 1995; Kolonko et al. 1998). Protection by theophylline was similar to that afforded by oral or intravenous hydration (Erley et al. 1999). Two recent meta-analyses, one including 480 patients and the other including 585 patients, concluded that theophylline or aminophylline appear to attenuate the radiocontrast-induced decline of renal function (Bagshaw and Ghali 2005; Ix et al. 2004). On the other hand, an analysis of 41 studies that used radiocontrast agents in combination with theophylline, N-acetylcysteine, fenoldopam, dopamine, iloprost, statins, furosemide or mannitol showed that only N-acetylcysteine provided significant renoprotection, whereas the risk reduction provided by theophylline was not significant (Kelly et al. 2008). Greater protection by N-acetylcysteine than by theophylline was also observed in a study in dehydrated rats (Efrati et al. 2009). Exactly how methylxanthines exert their limited protective effect is unclear in view of the well-recognized multifactorial pathophysiological mechanisms of radiocontrast-induced nephropathy (Cox and Tsikouris 2004; Persson et al. 2005). Because of similar effects of other vasoactive agents such as ANP, dopamine, endothelin antagonists, calcium channel blockers, and PGE_2, nonspecific vasodilatation of the renal vascular bed is likely to play a major contributory role. Nevertheless, despite some promising results, the overall clinical experience does not support the

use of methylxanthines as a first-line defense against the induction of contrast nephropathy (Lin and Bonventre 2005).

6.4   Calcineurin Inhibitors

The main complication of immunosuppression by calcineurin inhibitors is nephrotoxicity manifesting itself as a decline of renal function associated with vasoconstriction and a reduction of RBF. In early studies in rats, theophylline failed to ameliorate cyclosporine-induced renal vasoconstriction, indicating that it was not caused by adenosine (Churchill et al. 1990). Subsequently however, caffeine, theophylline, and pentoxifylline were observed to reduce the acute contractile response to cyclosporine of isolated glomeruli and mesangial cells in culture (Potier et al. 1997). Furthermore, the acute reduction of GFR and RBF caused in rats by a single dose of tacrolimus was completely reversed by theophylline given 1 h after the drug (McLaughlin et al. 2003a). Concomitant chronic administration of theophylline together with tacrolimus prevented the decrease of creatinine clearance that was caused by tacrolimus in the control group (McLaughlin et al. 2003b). In contrast, chronic administration of theophylline did not protect against cyclosporine-induced renal failure in rabbits and even enhanced its cytotoxic effects, whereas functional recovery was seen when theophylline was given as a single dose following a 5-day treatment with cyclosporine (Prevot et al. 2002). Follow-up studies that would shed light on the reasons for these divergent observations are not available. In children with nonrenal transplants who showed signs of tacrolimus nephrotoxicity, such as an increase in serum creatinine levels and oliguria despite treatment with loop diuretics, a single dose of aminophylline (5 mg/kg) caused a doubling of urine flow rate and osmolar clearance as well as a moderate increase of renal function (McLaughlin and Abitbol 2005).

6.5   Cisplatin

Cisplatin-based chemotherapy is another treatment modality that is often associated with nephrotoxicity. In a placebo-controlled trial on 36 patients, the administration of theophylline before and for 5 days following cisplatin treatment completely prevented the fall of inulin clearance that was seen in the placebo group, in which GFR fell by 21% (Benoehr et al. 2005). This study in humans is thus consistent with observations in rats in which aminophylline ameliorated cisplatin-induced renal failure when given in the maintenance phase although it did not prevent the decline of renal function when administered prophylactically (Heidemann et al. 1989). Since enprofylline did not mimic the protective action of aminophylline, adenosine receptor activation is the likely cause for the decline of renal function (Heidemann et al. 1989). Specifically, the protective action seems related to inhibition of A_1 adenosine receptors because the A_1-adenosine-receptor-specific antagonists

DPCPX and KW-3902 were effective both in preventing and in treating the nephrotoxic effects of cisplatin (Knight et al. 1991; Nagashima et al. 1995). A higher dose of cisplatin in vivo as well as exposure of LLC-PK1 cells to cisplatin caused upregulation of A_1 adenosine receptor expression, and this was associated with cytoprotection on the basis of the finding that nonselective and A_1-adenosine-receptor-selective antagonists exacerbated cisplatin-induced nephrotoxicity (Bhat et al. 2002; Pingle et al. 2004; Saad et al. 2004). Thus, the potential of methylxanthines to exert both protective and injurious effects may be a reflection of the wide spectrum of adenosine actions in fundamental processes such as tissue oxygen supply and inflammation.

6.6   Glycerol

Theophylline and other methylxanthines have been consistently found to ameliorate the experimental acute renal failure caused by intramuscular injection of glycerol when treatment was started at the time of injury (Bidani and Churchill 1983; Bowmer et al. 1986, 1988). The protective effect appears to be a consequence of inhibition of A_1 adenosine receptors since subtype-specific antagonists mimic the action of the natural methylxanthines (Ishikawa et al. 1993; Panjehshahin et al. 1992; Suzuki et al. 1992) and since their effect can be seen in a dose range that has no discernible effect on renal PDE activity (Panjehshahin et al. 1992). In contrast to the protective action of methylxanthines in myoglobinuric acute renal failure, theophylline did not improve renal function in the renal failure caused by mercury chloride or gentamicin (Kellett et al. 1988; Rossi et al. 1990).

6.7   Ischemia–Reperfusion

Interest in the potential of methylxanthines to improve renal function following postischemic acute renal failure has arisen from the fact that ischemia is associated with increases of adenosine tissue content in the kidney as well as in other organs (Osswald et al. 1977). Thus, it was conceivable that methylxanthines may exert beneficial effects by preventing the renal vasoconstriction caused by excess adenosine. In rats, theophylline, administered as a single dose of 100 μmol/kg 10 min before the release of a 1-h renal artery occlusion, increased GFR and electrolyte excretion threefold to sixfold within 3 h of the postischemic period compared with vehicle-treated animals (Osswald et al. 1979), an observation that was later confirmed in both rats and rabbits (Gouyon and Guignard 1988; Lin et al. 1986). The protective mechanism of methylxanthines in the initiation phase of renal injury following ischemia–reperfusion is likely related at least in part to inhibition of vasoconstrictive adenosine receptors. Support for this notion comes from a recent study in which the A_1 adenosine receptor antagonist DPCPX infused prior to and following a 30-min period of bilateral renal artery obstruction was observed to

significantly improve creatinine clearance over the initial 4 h following reperfusion (Moosavi et al. 2009). Furthermore, the immediate postischemic reduction of GFR was enhanced by dipyridamole, an inhibitor of adenosine uptake through equilibrative nucleoside transporters, and this effect was abrogated by theophylline (Lin et al. 1987). In clinical studies, a single dose of theophylline given early after birth in asphyxiated full-term infants elicited beneficial effects by reducing the renal involvement and fall in GFR as determined over the first 5 days (Bakr 2005; Bhat et al. 2006; Eslami et al. 2009; Jenik et al. 2000).

The role of methylxanthines in the maintenance phase following renal ischemia is an area of considerable controversy. Early studies have shown that pretreatment of rats with a single dose of theophylline during a 30-min renal artery occlusion was associated with higher RBF and GFR during the maintenance phase of acute renal failure after 5 days, suggesting that theophylline administration in the acute phase affected the severity of renal failure in the maintenance phase (Lin et al. 1988). Furthermore, theophylline administered 5 days after ischemia acutely increased RBF and GFR in previously untreated rats (Lin et al. 1988). Theophylline also caused an increase of GFR measured 5 days after experimental renal transplantation in rats without affecting the inflammatory response (Grenz et al. 2006). On the other hand, in a small study with limited statistical power, theophylline was not found to afford protection against acute renal failure during cardiac surgery (Kramer et al. 2002). It is uncertain whether theophylline exerts these effects by antagonizing vasoconstrictor effects of adenosine. In fact, adenosine itself given immediately after a renal ischemia of 45 min provided renoprotection after 24 h, an effect mimicked by CGS-21680 and therefore apparently mediated by activation of A_{2a} adenosine receptors (Lee and Emala 2001). Similarly, the rise of serum creatinine level assessed 1 and 2 days following renal ischemia was found to be reduced by chronic administration of the selective A_{2a} agonist DWH-146 and enhanced in A_{2a}-adenosine-receptor-deficient mice (Day et al. 2003; Okusa et al. 1999). Relative renoprotection 24 h following renal ischemia was also provided by A_1 adenosine receptor agonists, and a worsening of the outcome was observed in A_1-adenosine-receptor-deficient mice (Kim et al. 2009; Lee et al. 2004a, b). Comparable renoprotective effects of A_{2a} and A_1 adenosine receptor activation suggest that the functional improvement after extended reperfusion is unrelated to the vascular actions of adenosine since the vascular effects of activating A_{2a} or A_1 adenosine receptors are opposite. The common denominator may be a dominant anti-inflammatory action of adenosine that is exerted by both receptor subtypes.

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