Kidney & Blood Pressure Research

N-Acetylcysteine Attenuates Iodine Contrast Agent-Induced Nephropathy in 5/6-Nephrectomized Rats

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Abstract
Aims: In the present study we tested the efficacy of N-acetylcysteine (NAC) to minimize nephrotoxic effects of iodine contrast agents in intact rats as well as in 5/6-nephrectomized (5/6-Nx) rats. *Methods:* Rats were allocated to a group of intact rats (n = 42) and a group of 5/6-Nx rats (n = 42). After 1 month of recovery from surgery, 5/6-Nx rats and intact (sham-operated) animals received either 6 ml/kg body weight (b.w.) meglumine ioxithalamate (Telebrix 350) or 6 ml/kg b.w. iohexol (Omnipaque 350) intravenously with or without pretreatment with 100 mg/kg b.w. NAC. Plasma and urinary concentrations of creatinine, sodium and protein in 24-hour urine collections were determined prior to and on days 1, 3 and 7 after drug administration. *Results:* In intact animals, contrast agents caused no significant changes in kidney function throughout the duration of the experiment. In contrast, significant increases in plasma creatinine levels and decreases in creatinine clearance were induced by both contrast agents in 5/6-Nx rats. These changes were significantly attenuated by NAC pretreatment. *Conclusion:* The results of the present study demonstrate that iodine contrast agent-induced nephropathy in 5/6-Nx rats is significantly attenuated by intravenous pretreatment with NAC.

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Introduction

Radiographic diagnostics using iodinated contrast medium have been considered fairly safe and are widely used in patients. However, there are many reports indicating serious risks of developing contrast-induced nephropathy (CIN) that represents one type of acute kidney injury [1], i.e. mostly non-oliguric acute renal failure. Although the incidence and pathophysiology of CIN still remains unclear, the most plausible mechanism for the onset and development of CIN might be renal vasoconstriction and ischemia combined with an enhanced activity of oxygen radicals in the kidney. This process closely resembles ischemia-reperfusion injury and is aggravated

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by hypovolemia [2, 3]. Previous studies have demonstrated that a decrease in renal tissue perfusion after administration of iodinated radiographic contrast media presents a serious risk to renal tubular integrity and function due to decreasing oxygen supply, especially in the outer renal medullary region. It has been proposed that this is the trigger mechanism mainly responsible for contrast-medium-induced acute renal failure [4–6]. Moreover, it has been shown that the impaired renal tissue perfusion is associated with increased production of vasoconstrictor agents including adenosine and endothelin, whereas the counter-regulatory action of endogenous vasodilatory compounds, primarily of nitric oxide (NO) and prostaglandins, is reduced [7–11]. Thus, it is likely that multiple interactions are involved in the development of CIN.

Although in the majority of cases the application of contrast media produces no significant adverse reactions, it has been noted that CIN is more likely to develop in patients with preexisting renal impairment associated with concomitant diseases such as chronic inflammatory kidney disease, diabetes mellitus, hypertension or heart failure [12, 13].

The incidence of adverse reactions varies with the type of contrast media used. Based on these observations, nephrotoxicity of different contrast media and strategies to potentially protect against CIN have been evaluated [14–17]. These include administration of saline-bicarbonate solutions, diuretics or antioxidants [18–22]. From these latter compounds, sulfhydryl donors such as N-acetylcysteine (NAC) or thiosalicylic acid were shown to decrease the level of oxygen radicals and to exhibit a protective effect against vascular dysfunction, mostly by increasing NO bioavailability [23, 24]. In the earlier studies we reported that ischemia-reperfusion injury in dogs and humans with myocardial infarction can be successfully managed with NAC [25, 26]. Furthermore, we and others have shown beneficial effects of NAC also in patients with renal insufficiency [22, 24, 27] and ischemic renal failure [28]. Thus, in the present study we tested the potential of NAC to prevent or minimize the nephrotoxic effects of contrast agents in intact rats as well as in 5/6-nephrectomized (5/6-Nx) rats – a model of chronic renal insufficiency [29, 30]. Since the differences in production of adverse effects between administration of the standard high-osmolar ionic monomer sodium-meglumine-ioxithalamate contrast medium (Telebrix) and the low-osmolar non-ionic contrast medium iohexol (Omnipaque) are still controversial in clinical practice [17, 31–33], we evaluated whether any differences in the development of CIN can be revealed when either Telebrix or Omnipaque were employed.

Animals and Methods

The present study was performed in male Wistar rats (Charles River Laboratories, Germany) in accordance with guidelines and practices established by the Institute for Clinical and Experimental Medicine Animal Care and Use Committee. All animals were housed in facilities accredited by the Czech Association for Accreditation of Laboratory Animal Care. Rats [initial body weight (b.w.) 230–270 g] were randomly allocated into an intact group (n = 42) and a 5/6-Nx group (n = 42). In this latter group, 5/6-nephrectomy was performed under anesthesia (tiletamine + zolazepam, Virbac SA, Carros, France, 8 mg/kg, and xylasine, Spofa, Prague, Czech Republic, 4 mg/kg i.m.) as described previously [28]. An abdominal midline incision was performed to expose the kidneys. The right kidney and both poles of the left kidney were removed surgically in order to remove 5/6 of renal parenchyma as estimated according to kidney weight. The abdominal wall and the skin were sutured. The animals were then allowed to recover from surgery for 1 month and to adapt to the 5/6-nephrectomy. In sham-operated control rats only an abdominal midline incision was performed.

After 1 month of recovery from surgery, 24-hour urine collections in metabolic cages were performed and blood samples were taken from the tail vein to determine basal levels of creatinine and sodium in plasma and urine as well as urinary protein [30, 34]. On the day before the contrast agent was administered, drinking water with the addition of furosemide (40 mg/l) and potassium chloride (500 mg/l) was given for 12 h. The animals were then deprived of water for 12 h to mimic a hypovolemic state. On the following day, in intact and 5/6-Nx rats a cannula (PE50) was inserted into the femoral vein under the usual anesthesia. The following solutions were given intravenously via the implanted femoral vein catheter: 3.5 ml of sterile saline or 3.5 ml of saline with NAC 100 mg/kg (b.w) (ACC Injekt; Hexal AG, Holzkirchen, Germany). Additional groups of intact and 5/6-Nx rats received saline or saline + NAC followed by an intravenous injection of either 6 ml/kg b.w. high-osmolar (1,860 mosm/l) ionic monomer sodium-meglumine-ioxithalamate (MIO, Telebrix 350; Guerbet, Roissy, France) or 6 ml/kg b.w. low-osmolar (780 mosm/l) non-ionic iohexol (IOH, Omnipaque 350; Amersham Health, Cork, Ireland). As iodinated contrast agent, one of the most commonly used ionic contrast medium (MIO) and one of the currently used nonionic medium (IOH) were selected. The dose of contrast medium exceeded the average routinely applied dose to possibly aggravate the renal insult. Based on the infused agents, the animals were allocated into the following six groups of intact rats: (1) control group (n = 7), (2) NAC group (n = 7), (3) MIO group (n = 7), (4) MIO + NAC group (n = 7), (5) IOH group (n = 7), and (6) IOH + NAC group (n = 7) and into the following six groups of 5/6-Nx rats: (1) control group (n = 6), (2) NAC group (n = 6), (3) MIO group (n = 8), (4) MIO + NAC group (n = 8), (5) IOH group (n = 7), and (6) IOH + NAC group (n = 7).

24-hour urine collections and blood sampling were repeatedly performed before and after drug administration on days 1, 3, and 7.

The creatinine concentration in plasma and urine samples was determined by a commercial kinetic colorimetric assay (Roche Diagnostics Corp., Indianapolis, Ind., USA) and creatinine clearance was calculated to estimate glomerular filtration rate which was expressed per gram of kidney weight. Protein concentration

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Table 1. Basal parameters in intact Wistar rats prior to water restriction and contrast agent administration

Group	n	UV ml/day	$U_{Na}V$ mmol/day	P_{Cr} µmol/l	Cr clearance ml·day^{-1}·g KW^{-1}	P_{Urea} µmol/l	Urea clearance ml·day^{-1}·g KW^{-1}	Proteinuria mg/day
Control	7	36 ± 4	1.3 ± 0.4	55 ± 4	708 ± 40	9.2 ± 0.5	155 ± 16	3.8 ± 0.4
NAC	7	34 ± 3	1.1 ± 0.2	54 ± 2	751 ± 42	8.6 ± 0.5	161 ± 22	3.3 ± 0.2
MIO	7	34 ± 3	1.2 ± 0.3	56 ± 3	732 ± 54	9.3 ± 0.4	153 ± 11	2.8 ± 0.5
MIO + NAC	7	36 ± 2	1.4 ± 0.3	55 ± 2	763 ± 71	9.1 ± 0.3	160 ± 11	3.6 ± 0.3
IOH	7	35 ± 4	1.1 ± 0.2	55 ± 3	735 ± 44	9.2 ± 0.4	152 ± 14	2.9 ± 0.4
IOH + NAC	7	34 ± 3	1.3 ± 0.2	54 ± 2	723 ± 33	9.0 ± 0.3	151 ± 12	3.3 ± 0.5

There were no differences between groups. NAC = N-acetylcysteine; MIO = meglumine ioxithalamate; IOH = iohexol; UV = urine volume; $U_{Na}V$ = absolute sodium excretion; P_{Cr} = plasma creatinine; Cr clearance= clearance of endogenous creatinine – expressed per gram of kidney weight (KW); P_{Urea} = plasma urea concentration.

Table 2. Basal parameters in 5/6-Nx Wistar rats prior to water restriction and contrast agent administration

Group	n	UV ml/day	$U_{Na}V$ mmol/day	P_{Cr} µmol/l	Cr clearance ml·day^{-1}·g KW^{-1}	P_{Urea} µmol/l	Urea clearance ml·day^{-1}·g KW^{-1}	Proteinuria mg/day
Control	6	27 ± 3	1.7 ± 0.5	67 ± 4	756 ± 21	13.9 ± 1.1	115 ± 11	12.4 ± 2.4
NAC	6	26 ± 2	1.5 ± 0.4	66 ± 2	747 ± 32	12.5 ± 0.5	110 ± 8	13.6 ± 2.7
MIO	8	25 ± 3	1.4 ± 0.4	65 ± 3	762 ± 50	13.1 ± 0.7	115 ± 8	11.8 ± 2.5
MIO + NAC	7	26 ± 2	1.4 ± 0.5	66 ± 3	741 ± 24	14.2 ± 0.6	120 ± 14	12.1 ± 3.3
IOH	8	28 ± 2	1.8 ± 0.5	64 ± 2	764 ± 31	14.1 ± 0.5	110 ± 7	11.6 ± 3.1
IOH + NAC	7	26 ± 3	1.6 ± 0.4	65 ± 4	762 ± 20	13.5 ± 0.5	115 ± 17	12.8 ± 2.9

There were no differences between groups. NAC = N-acetylcysteine; MIO = meglumine ioxithalamate; IOH = iohexol; UV = urine volume; $U_{Na}V$ = absolute sodium excretion; P_{Cr} = plasma creatinine; Cr clearance = clearance of endogenous creatinine – expressed per gram of kidney weight (KW); P_{Urea} = plasma urea concentration.

in urine samples was measured by the Biuret method using a commercially available kit (Lachema, Brno, Czech Republic). The concentration of sodium was determined by flame photometry.

Statistical Analysis

Results are expressed as means ± SEM. Statistical comparisons within groups were conducted by the use of ANOVA for repeated measurements, followed by Newman-Keuls test. Two-way ANOVA followed by post-hoc test was used for comparisons between groups for each time point of the study. Statistical significance is defined at a value of $p < 0.05$.

Results

Basal values of the clearances of endogenous creatinine, urea, urinary volume, sodium excretion and proteinuria in intact rats prior to water restriction and contrast media administration are summarized in table 1.

There were no significant differences among experimental groups of intact rats. In all groups of intact rats, administration of the two types of iodinated contrast agents (MIO or IOH) caused no significant changes in plasma creatinine and urea levels (fig. 1) or in creatinine and urea clearances (fig. 2) during the experimental period of 7 days. Proteinuria or urinary sodium excretion were also unchanged in these rats. We noticed a slightly lower plasma creatinine level and increased creatinine clearance in the NAC group on day 1, which, however, did not reach statistical significance.

Basal values of the clearances of endogenous creatinine, urea, urine volume, sodium excretion and proteinuria in 5/6-Nx rats prior to water restriction and contrast media administration are summarized in table 2. There were no significant differences among experimental groups of 5/6-Nx rats. 5/6-Nx rats exhibited higher basal plasma creatinine and urea levels ($p < 0.05$). They also
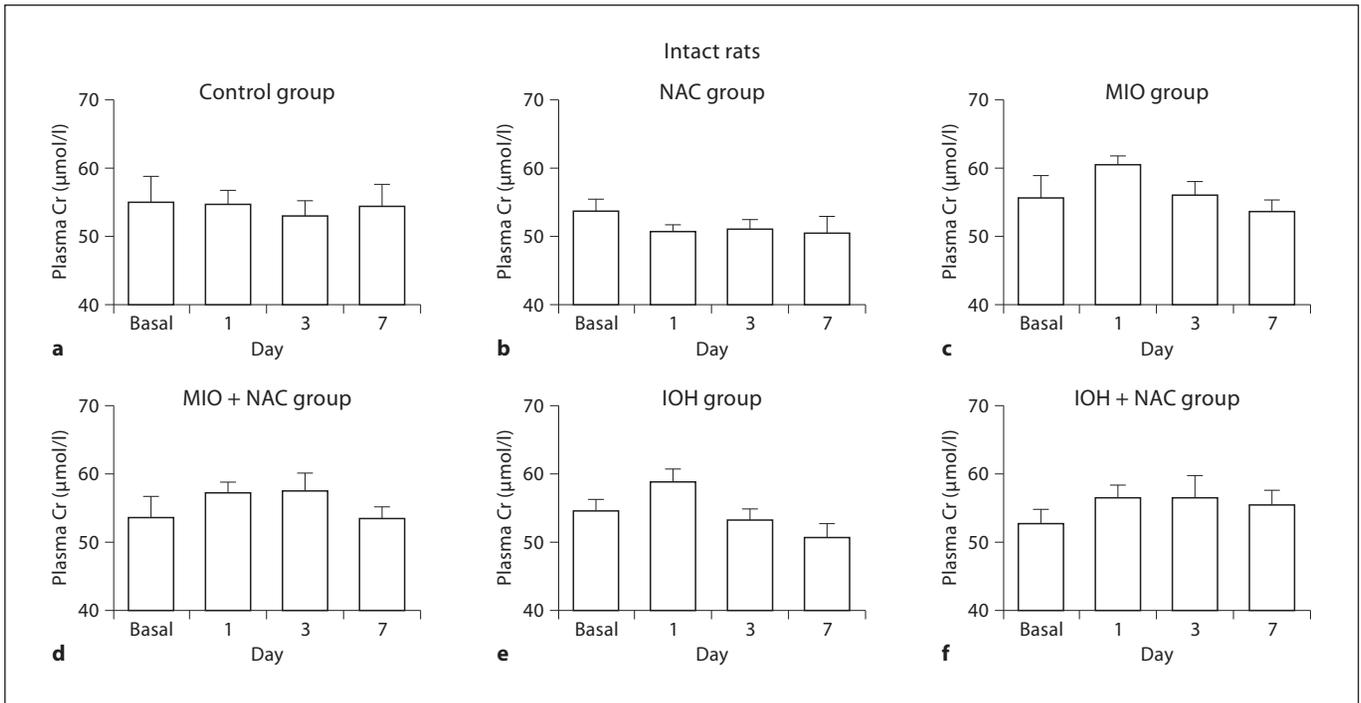
Fig. 1. a–f Time course of responses of plasma creatinine to contrast medium administration in water-restricted intact Wistar rats. Cr = Creatinine; NAC = N-acetylcysteine; MIO = meglumine-ioxithalamate; IOH = iohexol. Data represent mean values ± SEM.
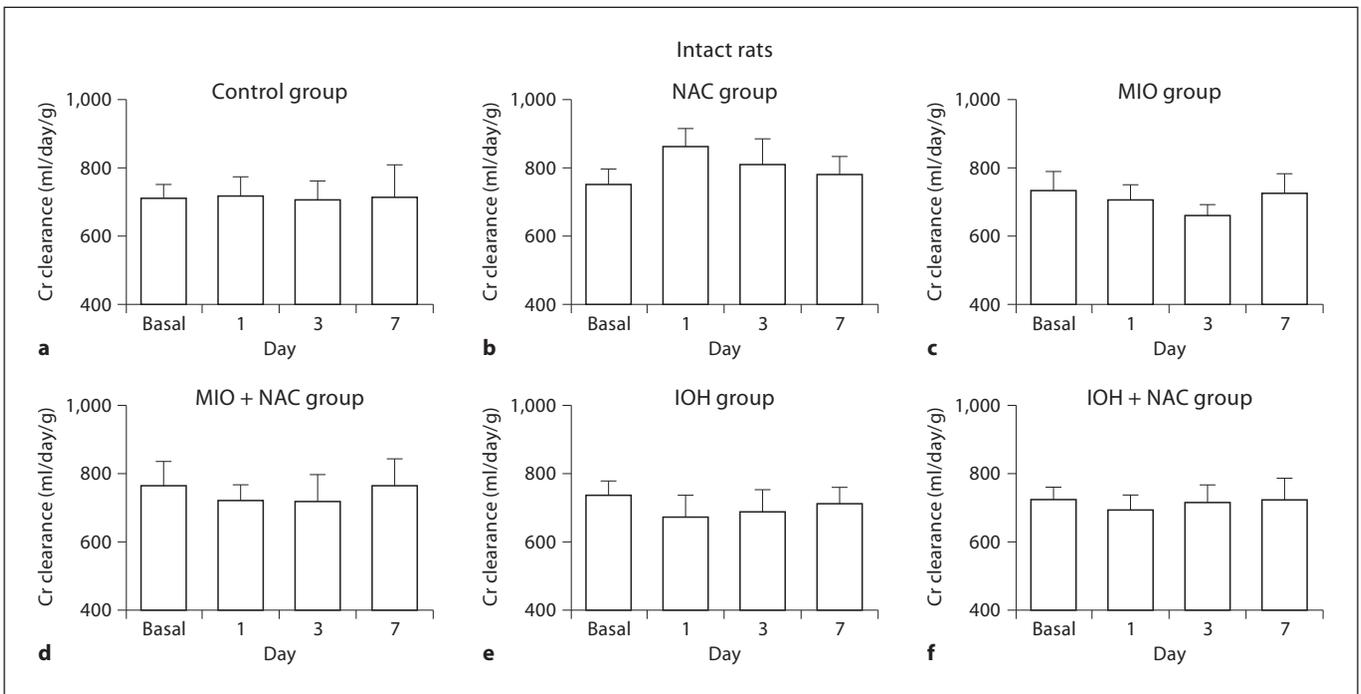

Fig. 2. a–f Time course of responses of creatinine clearance to contrast medium administration in water-restricted intact Wistar rats. See figure 1 for abbreviations. Data represent mean values ± SEM.
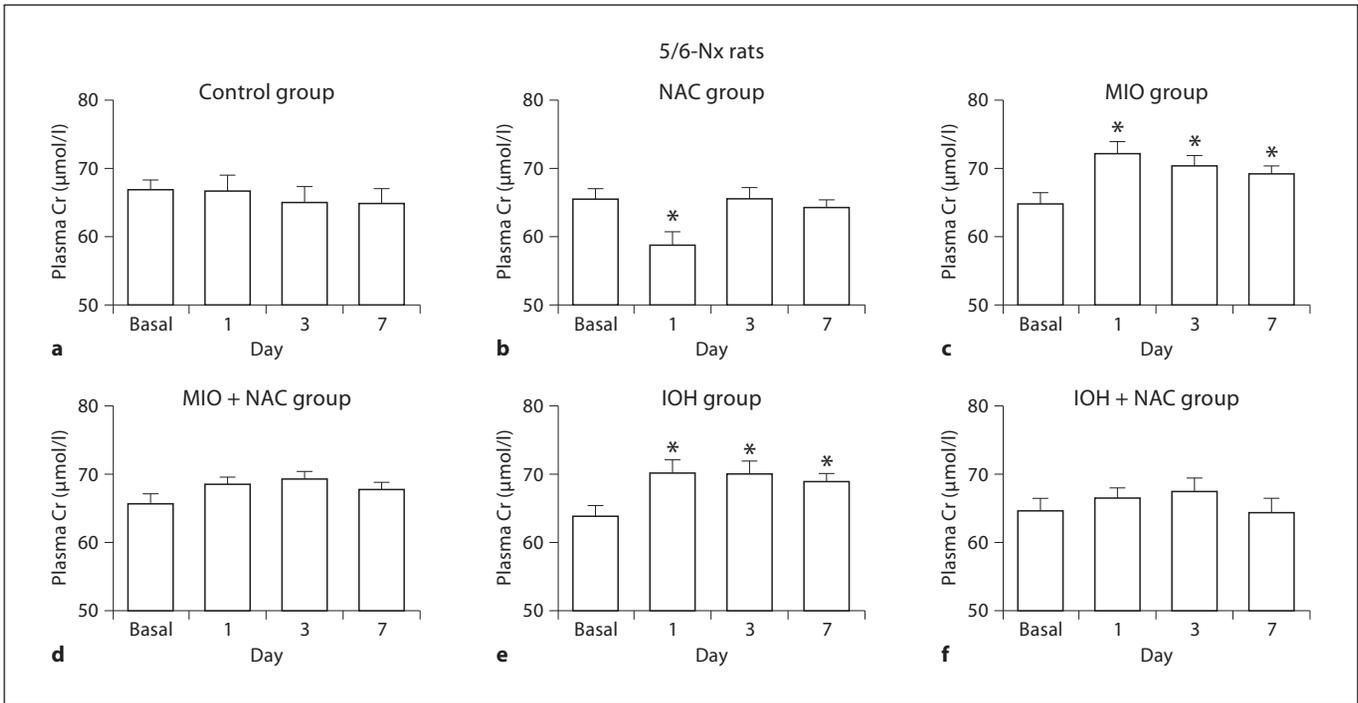
Fig. 3. a–f Time course of responses of plasma creatinine to contrast medium administration in water-restricted 5/6-Nx Wistar rats. See figure 1 for abbreviations. Data represent mean values $\pm$ SEM. * $p < 0.05$ vs. basal values.
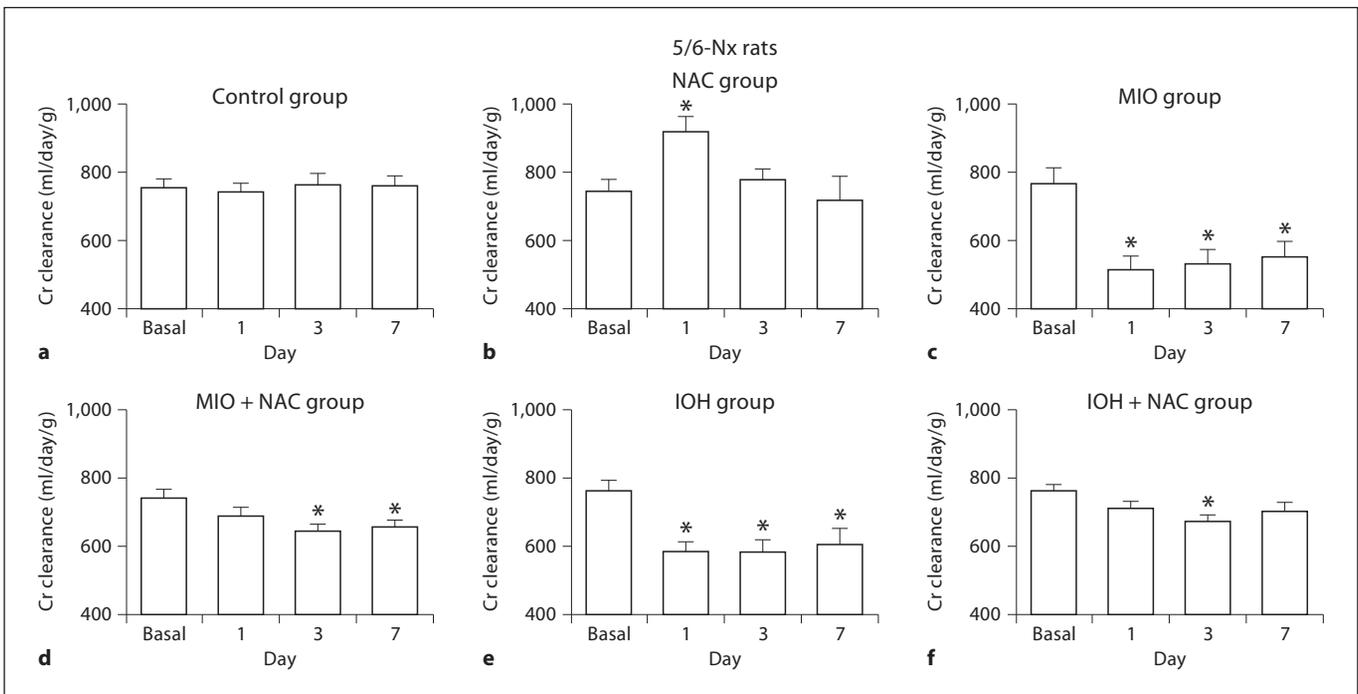

Fig. 4. a–f Time course of responses of creatinine clearance to contrast medium administration in water-restricted 5/6-Nx Wistar rats. See figure 1 for abbreviations. Data represent mean values $\pm$ SEM. * $p < 0.05$ vs. basal values.

showed similar, but lower (p < 0.05) creatinine and urea clearances and greater proteinuria (p < 0.05) compared to intact animals. Administration of either contrast agent MIO or IOH caused significant increases in plasma creatinine level (fig. 3) and urea (not shown), and decreases in creatinine (fig. 4) and urea clearances (not shown). Infusion of contrast media did not further alter proteinuria and had no effect on absolute and fractional sodium excretion in 5/6-Nx rats.

Administration of NAC bolus alone induced a transient decrease in plasma creatinine and urea levels (fig. 3b) and an increase in creatinine clearance (fig. 4b), whereas sodium excretion rate and proteinuria remained unaffected. Pretreatment with NAC prevented the rise in plasma creatinine (fig. 3) and significantly attenuated the decline in creatinine clearance induced by the administration of contrast media (fig. 4). Plasma urea level and urea clearance exhibited a similar pattern of changes as creatinine level and creatinine clearance (data not shown).

Discussion

The first major finding of this study indicates that iodinated contrast medium-induced increases in plasma creatinine level and reductions in glomerular filtration rate occurred only in 5/6-Nx rats but not in intact animals.

The second finding suggests that impairment of kidney function produced by the administration of contrast agent can be attenuated by a single prophylactic bolus of NAC in this model of chronic renal insufficiency. The present study is in agreement with previous observations that the administration of contrast media alone does not lead to the development of CIN in animals with normal renal function [35, 36], but strongly indicates that preexisting renal impairment may be a major factor in the incidence of CIN.

Third, our present data do not reveal any significant differences between the administration of the contrast agents MIO or IOH in 5/6-Nx rats, indicating that there are no differences in the adverse effects on renal function following administration of high-osmolar or low-osmolar contrast media.

We are aware that the 5/6-nephrectomy model – 1 month after renal mass reduction – does not fully meet the criteria of chronic renal disease and does not entirely correspond to the conditions characteristic for diabetes, hypertension or generalized atherosclerosis. However, after renal mass reduction the remaining nephrons undergo hypertrophy and increase their function [37, 38] and thus this rat model of chronic renal insufficiency remains useful and is widely studied [39].

Our present findings show that hypovolemia in 5/6-Nx rats is only a marginal factor for the development of CIN. Thus, our data further support previous studies demonstrating the beneficial effects of NAC in renal failure and end-stage renal disease [24, 28, 40, 41] and support the prophylactic value of the administration of NAC as a potential preventive strategy against CIN in subjects with chronic renal insufficiency. In addition, our present findings are in accordance with the recent report by Marenzi et al. [42] who demonstrated that NAC reduced the severity of CIN in patients with acute myocardial infarction treated with primary angioplasty and had a more profound protective effect against CIN in patients with impaired renal function before the intervention and in patients with severely impaired left ventricular function.

Several studies have suggested that the changes in renal hemodynamics, which follow the application of contrast media, exert regional effects within the kidney [5, 36, 43–45]. A selective reduction in outer medullary blood flow has been demonstrated in salt-depleted uninephrectomized rats and in streptozotocin-induced diabetic rats [36, 47]. As the outer medulla is especially susceptible to ischemic injury, it has also been suggested that the resulting hypoxia leads to tubular damage and thus contributes to the pathophysiology of CIN [44]. In contrast, others reported that tubular function did not significantly contribute to the overall changes in renal function during contrast-induced glomerular vasoconstriction [4, 11, 46]. In agreement with this suggestion, we did not observe significant changes in fractional sodium excretion after infusion of contrast media. The discrepancy of results may be related to differences in experimental conditions and in the actual renal functional state depending on the state of hydration. Finally, it is generally agreed that fractional sodium excretion should be interpreted with caution since it is too variable to be used as a reliable marker of CIN [44], also under clinical conditions.

The pathogenesis of CIN remains poorly understood. In this type of acute renal failure a complex interaction of multiple pathophysiologic mechanisms may be involved. However, increasing evidence indicates that oxidative stress significantly contributes to renal failure which follows contrast medium administration [13, 44, 47]. As hypoperfusion of tissues generates reactive oxygen species, the ability to attenuate oxidant injury depends on the capacity of endogenously produced antioxidants which de-

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creases with age [44]. Moreover, increased oxidative stress is present in most chronic cardiovascular and renal diseases [40]. There is also a close correlation with the decrease of NO bioavailability; it should be emphasized that contrast agents can directly alter NO production or, via oxidative stress, further diminish NO bioavailability [48]. This is in accord with the importance of renal vasoconstriction and of the impairment of renal autoregulation, characteristic features of CIN [49] after contrast medium administration. Taken together, a number of specific factors contribute to the increased risk to develop CIN [32, 44].

As a preventive measure, NAC is presently often used in individuals with renal impairment or cardiac surgery to protect against acute renal failure [47, 50, 51]. In this context – because of its antioxidative actions with a subsequent rise in NO bioavailability – NAC has been proposed as a valuable tool to improve renal perfusion [49, 52]. Our observation of a transient reduction in plasma creatinine level and an increased creatinine clearance in 5/6-Nx rats resulting from a single intravenous infusion of NAC is in good agreement with previous investigations demonstrating that NAC has protective properties in renal insufficiency [27, 52] and ischemic renal failure [24, 49, 53]. Nevertheless, conflicting results were reported regarding the efficacy of NAC in humans [54, 55]. The exact roles of factors such as the dose of the drug, the efficiency of absorption after oral administration, body hydration or the role of coexisting diseases have not yet been identi-

fied. Despite these controversies, in our view, NAC administered intravenously at a relatively high dose has a beneficial effect on the diseased kidney, regardless of whether or not contrast agents were administered [27]. In conclusion, our present data demonstrate that iodine contrast agent-induced nephropathy in 5/6-Nx rats is significantly attenuated by intravenous pretreatment with NAC and thus further support the value of preventive high-dose NAC administration in an effort to reduce the incidence of CIN. Further comprehensive studies are needed to define an optimal protective dosage of NAC in different states of cardiovascular and kidney diseases.

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