Simvastatin protects Sertoli cells against cisplatin cytotoxicity through enhanced gap junction intercellular communication

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Abstract. Cisplatin, an important chemotherapeutic agent against testicular germ cell cancer, induces testicular toxicity on Leydig and Sertoli cells, leading to serious side-effects such as azoospermia and infertility. In a previous study, it was found that simvastatin enhanced the sensitivity of Leydig tumor cells to chemotherapeutic toxicity through the enhancement of gap junction functions. In the present study, the effect of simvastatin on the sensitivity of normal Sertoli cells to cisplatin and the role of gap junctions in such effects was investigated. The results showed that, simvastatin attenuated cisplatin toxicity only when cells exhibited high-density culture where gap junctional formation was possible. When gap junction function was decreased by the gap junction inhibitor or by siRNA targeting connexin 43, the protective effect of simvastatin to cisplatin toxicity was substantially attenuated. Simvastatin also enhanced gap junction functions between Sertoli cells. This effect was mediated by the reduction of PKC-mediated connexin phosphorylation, thereby increasing connexin 43 membrane localization. Thus, simvastatin-induced enhancement of gap junction-mediated intercellular communication attenuated cisplatin toxicity on Sertoli cells. This result indicated that enhancement of gap junction function by simvastatin may have bilateral beneficial effects on cisplatin-based chemotherapy, enhancing cisplatin killing on cancer while ameliorating the reproduction toxicity.

Introduction

The incidence of testicular cancer has been on the increase over the last few decades due to increasing environmental toxicants (1). Testicular germ cell cancer is a curable cancer and cisplatin is the potent chemotherapeutic agent used to combat this disease. However, cisplatin also affects germ, Sertoli and Leydig cells during chemotherapy, which results in a 30-50% infertility rate for testicular cancer survivors (2,3). Identification of a strategy to attenuate cisplatin-induced testicular toxicity without affecting the killing of cancer cells largely improves long-term quality of life for testicular cancer patients.

Gap junction-mediated intercellular communication (GJIC) is reported to have enhancing effects on the toxicity of chemotherapeutic agents such as cisplatin and etoposide (4,5) to cancer cells. Gap junction (GJ) is formed by the docking of two hemichannels from neighbouring cells. Each hemichannel is composed of six homogenous or heterogeneous connexins (Cx). The connexin family comprises 20 members in mouse and 21 in human, in which connexin 43 (Cx43) is a predominant Cx member that expressed in human testicular tissues and testicular cancer cells (6,7).

Gap junctions provide a direct pathway for the rapid inter-cytoplasmic diffusion of hydrophilic metabolites and signaling molecules between adjacent cells. Accumulated evidence suggests that various death signals triggered by anti-tumor agents propagated through gap junctions from target cells to neighbouring cells, thereby promoting antineoplastic efficacy in cancer cells (4,8). This ‘bystander’ effect is not limited to death signals. Previous findings have demonstrated that the protective signal may spread through gap junctions between normal cells in response to oxidative stress and ischemic injury (9-11). Hong et al reported that gap junctions between testicular cancer cells communicated predominantly toxic effects and increasing cisplatin toxicity, while gap junctions between normal testicular cells communicated predominantly protective effects, decreasing cisplatin toxicity to Sertoli and Leydig cells (12). This finding suggests that an...
increase in GJIC enhances cisplatin-induced toxic effect on cancer cells while protecting normal testicular cells against cisplatin-induced injury.

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. They reduce plasma cholesterol levels and are widely used for cardiovascular disease resulting from hypercholesterolemia. There is considerable interest concerning the therapeutic utilization of statins in antineoplastic and antioxidation treatment (13,14). Our previous results showed that simvastatin increased GJ function in Leydig tumor cells and increased endopodite cytotoxicity to these cells (15). Nevertheless, to the best of our knowledge, there is no evidence to demonstrate the effect of simvastatin on GJIC between normal testicular cells and whether this interaction is involved in the effect of simvastatin on the response of testicular normal cells to chemotherapeutic compounds.

In the present study, we confirmed that GJ protected TM4 Sertoli cells against cisplatin toxicity. Simvastatin attenuated cisplatin toxicity, which was decreased when GJIC was inhibited by a chemical inhibitor or Cx43-siRNA. Moreover, we revealed that simvastatin induced enhancing effects on the gap junction through the downregulation of phosphorylated Cx43. Our results indicated that the inhibitory effect of simvastatin on cisplatin toxicity in TM4 cells may be attributed to an increase of GJIC by decreasing Cx43 phosphorylation. Simvastatin, a sensitizer of testicular tumor cells to the antineoplastic agent demonstrated in our previous study, protects normal testicular cells from cisplatin toxicity.

Materials and methods

Materials. Cisplatin was purchased from Sigma-Aldrich, St. Louis, MO, USA, and was dissolved in phosphate-buffered saline (PBS) for a stock concentration. Cell culture reagents were all obtained from Invitrogen Life Technologies (Carlsbad, CA, USA). Simvastatin was purchased from Sigma-Aldrich. Simvastatin (20 mg), which is a lactone prodrug, was diluted in 0.5 ml 100% ethanol, followed by the addition of 0.75 ml 0.1 M NaOH and heating at 50˚C for 2 h. The solution was neutralized with 0.1 M HCl to pH 7.2 and adjusted with PBS to a final concentration of 5 mM, sterilized by filtration and aliquots were stored at -20˚C.

Cell lines and cell culture. The mouse Sertoli cell line (TM4) was obtained from the American Type Culture Collection (ATCC; Manassas, VA, USA). TM4 cells were cultured in Dulbecco's modified Eagle’s medium (DMEM)/F-12 supplemented with 5% horse serum and 2.5% fetal bovine serum, 100 U/ml penicillin and 100 g/ml streptomycin. The cells were grown at 37˚C in an atmosphere of 5% CO₂ in air.

RNA interference. RNA interference of Cx43 expression was performed by stable cell lines endogenously expressing shRNA. pSilencer 2.1-U6 neo plasmids expressing shRNA targeting Cx43 (target sequence, 5'-GCTCACGTGTTCTATGTA-3') or pSilencer 2.1-U6 negative control plasmids (both from Ambion Europe, UK) were transfected into cells, and stable cell lines were selected by 0.1 mg/ml G418 and identified by western blotting and by parachute dye transfer assay (12).

Standard colony-forming assay. Cell survival was assayed by a standard colony-forming assay, adapted for use at high and low cell density, corresponding to conditions in which junctional channel formation was permitted or not, respectively (8). In the high-density condition, the cells were seeded at 3x10⁴ cells/cm² such that cultures were 70-100% confluent at the time of cisplatin exposure. The cells were treated with cisplatin for 1 h in the dark, then washed with PBS, harvested by trypsinization, counted, diluted and seeded in 6-well dishes (100 cells/well). Colony formation was assessed 5-7 days later by fixation and staining with crystal violet. Colonies containing ≥50 cells were scored. In the low-density condition, the cells were directly seeded at a density of 500 cells/cm² in 6-well plates and treated with cisplatin for 1 h after attachment. The plates were rinsed and assessed for colony formation as previously described. Colony formation was normalized to the colony-forming efficiency of non-cisplatin-treated cells. There was no significant difference in the plating efficiency between the low- and high-density cultures in the untreated samples (data not shown). Simvastatin was added to the culture medium 3 h prior to cisplatin treatment.

Evaluation of the GJIC capacity. To evaluate GJIC capacity, we performed ‘Parachute’ dye-coupling assay as described by Goldberg et al (15). Donor and receiver TM4 cells were grown to 80-90% confluency. The donor cells were double-labeled with 10 µM CM-DiI, a membrane dye that cannot spread to coupled cells, and 10 µM calcein-AM (both from Invitrogen Life Technologies), which is converted intercellularly into the gap junction-permeable dye calcein. The donor cells were washed, trypsinized and then resuspended with serum-free medium and seeded onto the receiver cells at a 1:150 donor/receiver ratio. Simvastatin was added in the donor cell suspension at the same time. The donor cells were allowed to attach for 4 h at 37˚C to form gap junctions with receiver cells, followed by examination with a fluorescence microscope. For each experimental condition, the average number of receiver cells containing dye calcein around one donor cell was determined and normalized to that of the control.

Western blotting. Protein extractions were carried out by direct dissolution of cells in protein lysis buffer containing protease inhibitors (Sigma-Aldrich). Protein concentrations were determined using Bio-Rad Dc protein assay reagent (Bio-Rad, Hercules, CA, USA). Approximately 20 µg of lysate protein was separated on the 10% SDS-PAGE gel, then electrically transferred to polyvinylidene difluoride (PVDF) membranes (Bio-Rad) and blocked with 5% skim milk TBST. Individual membranes were probed with monoclonal anti-Cx43 antibody produced in mouse (1:4,000; Sigma-Aldrich) and monoclonal antibodies against p-Cx43 (ser368) (Cell Signaling Technology, Beverly, MA, USA). The membranes were incubated with horseradish peroxidase (HRP)-conjugated secondary antibodies (GE Healthcare, Pittsburgh, PA, USA). The immuno reactive bands were visualized by ECL plus western blotting detection system (GE Healthcare). Blots were re-probed with an anti β-tubulin antibody (Sigma-Aldrich) and developed in an identical manner for assessing β-tubulin protein levels. The intensities were quantified by Quantity One software on GS-800 densitometer (Bio-Rad).
Immunofluorescent staining. TM4 cells were plated on glass coverslips in 24-well plates and treated with 10 µM simvastatin when 80% confluency was reached. The cells were fixed in 4% paraformaldehyde at room temperature, washed and blocked with 5% BSA for 30 min at room temperature. This process was followed by incubation with monoclonal anti-mouse Cx43 antibody (1:1,500; Sigma-Aldrich) dissolved in 5% BSA. The cells were incubated with the goat anti-mouse secondary antibody conjugated with fluorescein isothiocyanate (1/400; Invitrogen Life Technologies), washed and mounted with a solution containing P-phenylenediamine + glycerol + PBS at the proportions 29:9:1. Fluorescence was viewed and images were captured with a fluorescence microscope.

PKC activity assay. The total protein kinase C activity of TM4 cells was determined using the PepTag non-radioactive PKC assay kit (Promega, Madison, WI, USA), according to the manufacturer’s instructions. The PepTag assay uses fluoro-rescent peptide substrate which is highly specific for PKC. Phosphorylation of this substrate by PKC alters the peptides net charge from +1 to -1. This change in the net charge of the substrate allows the phosphorylated and non-phosphorylated versions of the substrate to be rapidly separated on an agarose gel (0.8%). The phosphorylated species migrates towards the positive electrode, while the non-phosphorylated substrate migrates towards the negative electrode. The bands were then visualized under UV light and excised from the gel, and heated at 95°C until the gel was sectioned. The bands were melted and mixed with Gel solubilization solution, glacial acetic acid and distilled water. Absorbency was read at 570 nm using a spectrophotometer in a 96-well plate.

Statistical analysis. Data were statistically analyzed using the unpaired Student’s t-test at a significance level of P<0.05. Data are presented as means ± SEM unless otherwise indicated using SigmaPlot (Jandel Scientific, San Rafael, CA, USA).

Results

Gap junctions in TM4 cells attenuate cisplatin cytotoxicity. TM4 cells expressing Cx43 were cultured under conditions where gap junction formation was not possible (low-density; 100 cells/cm²; cells not in direct contact with each other) and where gap junction formation was possible (high-density; 3x10⁴ cells/cm²). The cells were treated with cisplatin for 1 h and then cell survival was assessed as described in Materials and methods. As shown in Fig. 1A, treatment with cisplatin reduced the clonogenic survival of TM4 cell at low and high density in a concentration-dependent manner. The toxic effect of cisplatin was much less at a high cell density than at a low cell density.

To investigate the role of GJIC in the density-dependence of cisplatin response in TM4 cells, the gap junction function was regulated by two methods: pharmacological inhibition on junctional channels by TPA and downregulation of Cx43 expression by siRNA. TPA is a well-recognized chemical inhibitor for Cx43 channels. Fig. 2 shows that, TPA significantly suppressed the dye spread through junctional channels in TM4 cells. At high cell density, pretreatment of TM4 cells with TPA increased cisplatin toxicity, and manifested a reduction in survival fraction from 68 to 43%. By contrast, TPA had no effect on cisplatin cytotoxicity when the cells were cultured at a low cell density (Fig. 1B). Cx43 protein expression and junctional coupling were downregulated in TM4 cells stably transfected with Cx43 siRNA (Fig. 2). Consistent with the TPA results, cisplatin toxicity in siRNA-transfected cells was greater than that of the untransfected cells at high cell density. Columns, mean for five experiments; bars, SEM. *, Significantly different from control, P<0.05; †, significantly different from the cisplatin bar in (B) and from the untransfected cells bar in (C), P<0.05.

Simvastatin reduces cisplatin cytotoxicity in TM4 cells. We examined the effect of simvastatin on cisplatin cytotoxicity in
TM4 cells. TM4 cells were pretreated with 10 µM simvastatin for 3 h and exposed to simvastatin and cisplatin for another 1 h. As shown in Fig. 3A, simvastatin itself had no toxic effect on TM4 cells at high and low density. At high density, the inhibition of clonogenic survival by cisplatin was attenuated by simvastatin. However, simvastatin exerted no effect on cisplatin toxicity at low density. As shown in Fig. 3B the simvastatin-induced suppression of cisplatin toxicity in TM4 cells was concentration-dependent. The cytotoxicity of cisplatin was reduced with increasing concentrations of simvastatin. Simvastatin-induced suppression of cisplatin cytotoxicity is reversed by GJIC reduction.

To investigate whether the density-dependent simvastatin effects were mediated by GJIC, Cx43-siRNA stably transfected cells were used. In Fig. 3C, simvastatin-induced reduction in cisplatin toxicity was markedly attenuated in Cx43-siRNA stably transfected cells at a high density. At low cell density where gap junction rarely formed, there was no difference between the control and Cx43-siRNA-transfected cells. These results indicated that the simvastatin-induced decrease of cisplatin cytotoxicity was reversed by GJIC reduction.

**Effect of simvastatin on GJIC and Cx43 membrane localization in TM4 cells.** The results described above support that the inhibitory effect of simvastatin on cisplatin cytotoxicity requires functional gap junctions, indicating that simvastatin may regulate gap junction activity. At high cell density when gap junction is formed, simvastatin may enhance GJIC, which mediated the transfer of possible protection signals among normal testicular cells thereby reducing cisplatin toxicity. To confirm this hypothesis, we examined the effect of simvastatin on junctional coupling between TM4 cells. Fig. 4A shows that the cells that have been treated with simvastatin for 4 h have a marked increase in calcein dye diffusion through gap junctions. The dye coupling was gradually enhanced with increasing concentrations of simvastatin from 0.5 to 25 µM.

**Simvastatin inhibits PKC-mediated Cx43 phosphorylation.** In order to investigate the mechanism by which simvastatin enhanced GJIC, western blotting was performed to examine the expression of constituent Cx43 in simvastatin-treated cells. As shown in Fig. 5A, simvastatin did not alter the level of total Cx43.

Cx43 phosphorylation is known to play an important role in gap junction disassembly and internalization from the cell surface (17). Our previous study on Leydig tumor cells raises...
the possibility of targeting PKC as a regulatory signal for simvastin to induce Cx43 dephosphorylation (15). We then investigated the effect of simvastatin on the phosphorylation status of Cx43. In Fig. 5B, the amount of phosphorylated Cx43 at serine 368 (ser368) which was identified to be a specific phosphorylation site for PKC was markedly reduced in cells pretreated with simvastatin. This reduction was enhanced with increasing simvastatin concentrations. The expression of phosphorylated Cx43 in Sertoli cells was almost 50% of control after simvastatin treatment for 4 h.

As shown in Fig. 6, simvastatin markedly reduced PKC expression. The decrease of PKC expression occurred at 30 min and peaked in 4 h. Consistent with the alteration of PKC expression, PKC activity was also reduced in a time-dependent manner in simvastatin-treated cells (Fig. 6B). To investigate that PKC-mediated connexin phosphorylation...
Figure 5. Effects of simvastatin on Cx43 expression and p-Cx43 (ser368) expression. (A) Western blot analysis of Cx43 expression in cells treated with varying concentrations of simvastatin. (B) Western blotting showing p-Cx43 (ser368) levels in cells following treatment with 10 µM simvastatin for varying time periods. Bar graphs are derived from the densitometric scanning of the blots and shows a comparison of the level of Cx to β-tubulin density ratio. Columns, mean from four experiments; bars, SEM. * Significantly different from control.

Figure 6. Role of PKC activity on simvastatin-induced enhancement of gap junction communication. (A) Western blotting showing levels of PKC in TM4 cells treated with 10 µM simvastatin for the indicated time period. (B) The cells treated with simvastatin for the indicated time periods were subjected to a non-radioactive PKC assay described in Materials and methods. PKC activity is expressed as absorbance at a wavelength of 570 nm. (C) Comparison of dye spread through cells treated with GF109203X (1 µM) or TPA (50 nM) for 4 h with and without simvastatin (10 µM). (A and B) Columns, mean from four experiments; bars, SEM. * Significantly different from control.
was associated with the simvastatin-induced enhancement of GJIC, dye spread of Sertoli cells was then assessed in the cells treated with simvastatin and GF109203X, a specific PKC inhibitor or TPA, a PKC activator. GF109203X increased the dye spread of Sertoli cells through GJ, while TPA markedly decreased the dye spread. The simvastatin-induced increase of GJIC in Sertoli cells was slightly affected by simultaneous pretreatment with GF109203X. TPA exerted a significant suppression effect on the simvastatin-induced enhancement of dye spread through GJ.

**Discussion**

Infertility is one of the most serious late adverse consequences after cisplatin-based chemotherapy treatment (2,18). Cisplatin induces toxicity in germ cells and in Sertoli and Leydig cells, and eventually results in long-lasting azoospermia and testicular atrophy in male adults (19). Disruption of the cell junction has been identified between Sertoli cells in rats after intraperitoneal injection with cisplatin (20). Investigation into cultured cells has also demonstrated that cisplatin reduced the production of transferrin, androgen-binding protein, lactate and estradiol in Sertoli cells (21). In concordance with this observation, we found that cisplatin induced cytotoxicity in Sertoli cells, with clonogenic survivals decreasing 32% in controls after incubation with cisplatin for 1 h.

The concentration of cisplatin used in the present study was lower relative to some *in vitro* models, but was approximately the peak plasma concentration during chemotherapy (22). Our paradigm allowed the GJIC-mechanism observed in the present study to be applied. Thus, a much higher concentration than that used in our text led to extensive cell death and no GJIC-mediated effects were identified. Investigators have shown that the inter-Sertoli cell junctions constituting the blood-testis barrier become leaky even at low-cisplatin doses (3). Clinically, normal cells are less sensitive to anti-tumor agents compared with cancer cells. Thus, long-lasting continuous cisplatin exposure in testicular tumor patients produces toxicity on Sertoli cells.

Cx43 is the predominately expressed Cx in testis. It is localized between Sertoli and Germ cells in seminiferous epithelium as well as in Leydig cells (23). Cx43 is not associated with the physiological functions of Leydig cells. However, Cx43 is critical for the formation of junctions and coordination of junctional communication between Sertoli and Germ cells and plays a vital role in the processes of Sertoli proliferation as well as Germ cell proliferation and differentiation (23). Cx43 in Sertoli cells is considered important in spermatogenesis (7). It has been revealed that Cx43 expression was significantly reduced in testes of infertile patients with secretory azoospermia. In Sertoli cell-only syndrome rat, Cx43 expression in Sertoli cells was undetected and the GJIC between them was impaired. Sridharan et al and Günther et al have confirmed that lack of Cx43 solely in Sertoli cells was sufficient to induce the arrest of spermatogenesis (24,25). By contrast, environment chemicals have been found to affect Sertoli cell interactions through junctional proteins, and specifically Cx43 exerted deleterious effects on spermatogenesis (26). In light of those findings, an extensive exploitation of drugs or biologic approach to restore Cx43 expression and increase GJIC in Sertoli cells is of considerable value for improving reproduction. Our studies therefore suggest that future investigations in the putative therapeutic roles of simvastatin in decreasing reproduction toxicity among male patients should be performed.

Statins, classical cholesterol-lowering drugs, exert pleiotropic effects on osteoporosis, inflammation and other diseases generated by different issues (27,28). Cx43 also plays essential roles in coordinating activities in the majority of organs. To the best of our knowledge, GJIC, which we demonstrated to be enhanced by simvastatin in the present study, seems to provide a probable mechanism as evidence for pleiotropic actions. An increase of GJ conductance protects heart from life-threatening arrhythmia (29). The antiarrhythmic ability of simvastatin thus seems due to its action on GJ (30). Furthermore, whether simvastatin-induced effects on GJIC ameliorate cisplatin-induced cardiovascular toxicity, which was also shown to be associated with Cx43 merit future investigation.

Phosphorylation is critically involved in Cx disassembly, degradation and internalization. It therefore altered the amounts of constituent Cxs localized on membrane and GJ function. Cx43 is the most easily phosphorylated Cx subtype, containing 12 or more serine or tyrosine residues at carboxyl terminal that can be extensively phosphorylated by a multiplicity of phosphorylation protein kinases (17,31). Simvastatin is a lipophilic statin that permeates through plasma membrane by passive diffusion. It has been observed that simvastatin inhibits the activation of different kinases such as PKC or MAPKs in various cell culture (15,32). Li et al focused on Sertoli cells, showing that PKC played a crucial role in regulating tight junctions during spermatogenesis (33). Our findings confirm that simvastatin induced a significant decrease in PKC activity and the simvastatin-induced increase of junctional dye transfer was abolished by TPA (a PKC activator) and imitated by GF109203X (a PKC inhibitor). Therefore, our results suggest that PKC is a regulatory signal for simvastin to induce Cx43 dephosphorylation in Sertoli cells.

The GJIC-mediated protection effect in normal cells has also been confirmed by other authors showing that neuronal vulnerability to oxidative stress and ischemia was significantly increased by the inhibition of astrocytic gap junctions (11,34), and that Cx43 exerted a protective effect against oxidative stress-induced cell death in human retinal pigment epithelial cells and in cultured primary osteocytes (10,35). Cx43 itself has been suggested to contribute to the activation of a major cytoprotective signaling pathway in cardiomyocytes (36). The cells exposed to cisplatin usually produce apoptosis by the formation of crosslinks, including intra- and inter-DNA crosslinks. It has also been demonstrated that cisplatin toxicity in rat liver epithelial cells was enhanced by GJIC (8). However, in normal testicular cells, cisplatin-induced DNA crosslinks were increased when GJIC was blocked by 18-GA or siRNA. GJIC is believed to communicate predominantly protective signals in normal testicular cells through gap junction in response to cisplatin (12). Nevertheless, which and how protective signals were triggered after cisplatin exposure have not been identified and whether it directly or indirectly induces the decrease of DNA crosslinks remains to be investigated. Glutathione is speculated to be a likely candidate.
Glutathione (GSH) is a tripeptide with a molecular weight of 307 Da and is permeable to gap junctions. As reported by Nakamura et al (37), metabolic coupling of GSH between mouse and quail myocytes through gap junctions played an essential role in resistance of mouse myocytes to oxidative stress. Hepatotoxicity induced by acetaminophen was more higher in Cx32-KO mice and this was associated with a lower level of cellular GSH concentration. That study identified the protective effect of GSH transmission between neighboring cells through GJIC (38).

To the best of our knowledge, the present study is the first to demonstrate that the enhancement effect of simvastatin on GJ has a protective effect against cisplatin-induced toxicity on Sertoli cells. The beneficial role of GJ in cisplatin-based chemotherapy therefore is bidirectional. An increase of GJIC by simvastatin has synergistically toxic effects on tumor cells, while the increase of GJIC on Sertoli cells alleviated their sensitivity to antineoplastic agents and therefore improved reproductive potency in male adults. The present study provides an update on the pharmacologic intervention of GJ or connexins and highlights the importance of basic cell biology in decreasing reproduction toxicity caused by exposure to chemotherapy.

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