MECHANISM FOR THE ENHANCEMENT OF CISPLATIN ANTITUMOR EFFECT BY CAFFEINE
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It has been reported that caffeine enhances the antitumor effect of cisplatin on osteosarcoma. There are several in vitro studies for the combination effect of caffeine with cisplatin. However, because caffeine is a stimulator of central nervous systems, its toxic reaction may be observed above 30 µg/mL in plasma level. The purpose of this study is to investigate the appropriate concentration for caffeine-assisted chemotherapy and to elucidate the mechanism for the enhancement of antitumor effect of cisplatin by caffeine in vivo, using osteosarcoma C-SLM-bearing rats. C-SLM cells were transplanted on the back of male Fischer rats (7 weeks-old), and the antitumor effect of cisplatin was examined with or without caffeine for two weeks. Cisplatin reduced tumor size to 1/3 of untreated control, and this antitumor effect was further enhanced by coadministration of caffeine at 100, 60, 60 mg/kg intraperitoneally every 8 hours. Furthermore, this effect was also plasma concentration dependent like in vitro study. Cisplatin concentration in tumor was significantly increased in 48 hours after caffeine coadministration, while there was no change in plasma, kidney, liver and muscle. The mrp3 mRNA level in tumor was significantly decreased by caffeine. It was suggested that cisplatin efflux from tumor was inhibited and intracellular cisplatin concentration was increased. In conclusion, caffeine-assisted chemotherapy can be expected to be very effective on osteosarcoma, but because its effect needs high plasma concentration, appropriate plasma concentration should be controlled for efficacy and safety.