A Membrane Interaction Mechanism for Polynuclear Platinum Complex Uptake in Cells

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Cell uptake is the first step of platinum drug action in tumor cells and may contribute to cisplatin resistance. However little is known about the mechanism of cellular uptake while much attention has been paid to the interaction of platinum anticancer drugs with the final target DNA and other biomolecules such as Human Serum Albumin. Polynuclear platinum drugs which contain two or three platinum centers linked by diamine chains BBR 3571 and BBR 3464 show different binding with DNA compared to cisplatin and other "classical" mononuclear platinum drugs due to the high positive charge and hydrogen bonding in the centrally-linked diamine. BBR3571, a spermidine-linked dinuclear platinum compound, is the prototype of a 2nd-generation BBR3464. Both BBR3571 and BBR3464 have high cellular uptake, despite their high charge. The strong electrostatic interaction between BBR 3464 and DNA has been previously shown and this work examines the interaction with phospholipids, which are the major constituent of biological membranes.

Liposomes have been applied as a model membrane to study drug interaction with phospholipid bilayers. The phospholipids DPPS, DPPA, DPPE, DPPG and DPPC were studied for the membrane uptake mechanism of BBR3571 and BBR3464. Differential Scanning Calorimetry (DSC) experiments show that interaction occurs between all negatively charged phospholipids DPPS, DPPA and DPPG with platinum drugs BBR3464/BBR3571 even in the solution of 100 mM NaCl, and none for the zwitterionic phospholipid DPPC and DPPE. Both electrostatic and covalent bond formation was observed by ^{31}P NMR after incubation of the negatively charged liposomes DPPA, DPPS and DPPG with BBR 3464 and BBR3571. ICP results show that in presence of 100 mM NaCl buffer, DPPA liposome has higher uptake than DPPS for BBR3464/BBR3571. In absence of chloride, the uptake of DPPA and DPPS are higher than the solution of 100 mM NaCl, but not big different. HSQC [^{1}H, ^{15}N] results show slow covalent bond formation in 100 mM NaCl solution for DHPS and DHPA (which have short alkyl chains and good solubility in water compared to DPPS and DPPA) with ^{15}N labeled BBR 3464. The results indicate that the electrostatic interaction is more important than covalent bond formation in the uptake by these liposomes. The phospholipid interaction follows the same trend as cellular uptake, suggesting that a "phospholipid" shuttle is a viable mechanism of cell uptake for these charged compounds.

References

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