Do Phosphatidylserines Transduce Cell-Penetrating Peptides by Electroporation?

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Short Abstract **— Cell-penetrating peptides (CPPs) such as TAT and polyarginine, rapidly pass through the plasma membranes of mammalian cells by an unknown mechanism called transduction. They may be biologically and medically useful when fused to well-chosen chains of fewer than about 35 amino acids. I offer a simple model of CPP transduction in which phosphatidylserines and CPPs effectively form two plates of a capacitor with a voltage sufficient to form transient pores (molecular electroporation). The model is consistent with experimental data on the transduction of a oligo-arginine into mouse C_2C_{12} myoblasts and makes testable predictions.**

Keywords **— Cell-penetrating paptides, transduction, molecular electroporation.**

In 1988, two groups [1, 2] working on HIV reported that the trans-activating transcriptional activator (TAT) of HIV-1 can cross cell membranes. The engine driving this 86-aa cell-penetrating peptide (CPP) is its residues 48–57 which carry a charge of $+8e$. Other CPPS were soon found. Antp is residues 43–58 of Antennapedia, a homeodomain of the fly; it carries a charge of $+7e$. R^n carries charge $+ne$. These and other polycations can penetrate the plasma membranes of live cells towing cargos that greatly exceed the 600 Da restriction barrier.

Many early experiments on CPPs were wrong because the cells were fixed or insufficiently washed or because the fluorescence varied with the (sub)cellular conditions and the fluorophores [3]. Yet some clarity is emerging: TAT carries cargos across cell membranes with high efficiency by at least two functionally distinct mechanisms according to whether the cargo is big or small [4]. Big cargos, such as proteins or quantum dots, enter via caveolae endocytosis and macropinocytosis [5, 6], and relatively few escape the cytoplasmic vesicles in which they then are trapped [4]. Small cargos, such as peptides of fewer than 30–40 amino acids, enter both slowly by endocytosis and rapidly by an unknown mechanism, called transduction, that uses the membrane potential [4, 7–9]. Peptides fused to TAT enter cells within seconds [10] and pervade all intracellular compartments [4].

I review some therapeutic applications of CPPs and some facts about plasma membranes and then construct a simple model of transduction in which CPPs on the outer leaflet and phosphatidylserines on the inner leaflet form a kind of capacitor with a voltage sufficient to form transient pores (molecular electroporation). The model is consistent with measurements made by Tünnemann *et al.* [11] on the transduction oligoarginines into mouse myoblasts. The model makes two testable predictions.

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