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Possible effects of nanosecond pulsed electric fields on proteins

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Most, if not all, effects of pulsed electric fields are analyzed in terms of electrical charging of plasma membranes for conventional electroporation pulses with micro- to milli-second durations and for charging plasma membranes and intracellular membranes for pulses with sub-microsecond durations. However, not all cell responses from nanosecond pulsed electric fields (nsPEFs) are fully explained by poration of cell membranes. Observations that nsPEF-induced a Ca2+-dependent dissipation of the mitochondria membrane potential ($\Delta\Psi$m), which was enhanced when high frequency components were present in fast rise-fall waveforms, are not compatible with a poration event. Since most if not all Ca2+-regulated events are mediated by proteins, actions of nsPEFs on proteins appear likely in this context. Inhibitors of possible components of the mitochondrial permeability transition pore complex had no effect nsPEF-induced dissipation of $\Delta\Psi$m, indicating that nsPEFs have different effects on $\Delta\Psi$m than known modulators such as cyclosporin A, bongkrekic acid and DIDS (disodium 4,4′-diisothio-cyanatostilbene-2,2′-disulfonate). In a direct test to determine possible effects on proteins, we analyzed nsPEF effects on the catalytic activity of the prototypic protein kinase – the catalytic (C) subunit of protein kinase A (PKA) or the cAMP-dependent protein kinase, which transfers the gamma-phosphate from ATP to protein substrates, thereby modifying their regulatory functions, subcellular localization and/or stability. In one approach, one and ten pulses with 60 ns and 300 ns durations were applied to the enzyme with electric fields that were matched for energy density (60 kV/cm and 26 kV/cm, respectively). PKA C-subunit catalytic activity linearly decreased across all conditions of pulse number, duration and electric field according to a scaling formula that defines charging effects on rod-shaped molecules – $E\tau(\frac{1}{2}n)^{0.5}$, where E = electric field, τ = pulse duration and n = pulse number. Inaction did not scale linearly when using a formula for effects of energy deposition into the molecule ($E^2\tau n$). Because effects on the kinase prototype PKA C-subunit can be generalized to other kinases and because protein kinases regulate a broad range of physiological and pathological functions, nsPEF-induced modulation of protein kinase activity can have considerable impact on kinase structure and functional relationships and cell signal transduction. Because effects on the kinase prototype PKA catalytic subunit can be generalized to other kinases and because protein kinases regulate a broad range of physiological and pathological functions, nsPEF-induced modulation of protein kinase activity can have considerable impact on kinase structure and functional relationships and cell signal transduction.