

**P024** Influence of the peptide structure upon the biological activity of PNA-peptide conjugates in cells with natural nucleic acid level and transfected cells.

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PNA being complementary to the nociceptin/orphanin FQ receptor mRNA (PNA-1) or to the cryptic splice site of the modified luciferase gene pLuc/705 (PNA-2) were covalently bound to the cell-penetrating  $\alpha$ -helical amphipathic model peptide KLALKLALKALKAAKLKLA-NH<sub>2</sub> (MAP) and derivatives thereof showing systematically altered structure forming properties, charge and size. Pretreatment of spontaneously beating neonatal rat cardiomyocytes with the PNA-1 constructs significantly reduced the positive chronotropic effect on the beating rate exerted by the neuropeptide nociceptin irrespective of the structural properties of the peptide moieties already at the 100 nM range. By contrast, only the PNA-2 construct with the parent peptide MAP was able to restore correct splicing in stably transfected HeLa pLuc 705 cells after at least 1  $\mu$ M incubations. Uptake studies based on capillary electrophoresis with laser-induced fluorescence detection revealed similar uptake for all conjugates. Size-exclusion-chromatography provided evidence for the existence of the conjugates nearly exclusively in aggregated forms in physiological buffer at concentrations higher than 500 nM. In conclusion our findings suggest factors additional to a facilitation of the membrane penetration. to have crucial importance for the biological activity of PNA-peptide conjugates. One of such possibilities could consist of the aggregation propensity of the conjugates in conjunction with a consequent nonendocytic or endocytic mode of uptake.