Non-Canonical Effects of Ouabain and Digoxin on Vascular Smooth Muscle

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Inhibition of Na,K-ATPase activity is regarded as the primary mechanism of action for digitalis drugs (or cardiotonic steroids, CTS). This "lag hypothesis" has been recently called into question, as there is also a signaling cascade involved that may be unique to each subclass of CTS. Consistent with this, it has been hypothesized that the α2 Na,K-ATPase plays a specific role in regulating vascular function. We therefore examined the role of the α2 Na-K-ATPase in modulating the responsiveness of the renal vasculature to digoxin and ouabain using two experimental approaches: 1) in vivo measurements of renal pressure-flow relationships, and 2) ex vivo analysis of force generation in second order vessels dissected from mouse kidneys. Responses in wild type mice, expressing a CTS-sensitive α2 subunit ($\alpha2^{S/S}$), were compared to those in mutant mice, expressing a CTS-resistant α2 subunit ($\alpha2^{R/R}$).

Results: In experiment 1, blood flow responses to step-changes in renal perfusion pressure were evaluated at baseline and during treatment with escalating doses of ouabain or digoxin. In 14 mice (ouabain-treated: 3 $\alpha2^{R/R}$ and 3 $\alpha2^{S/S}$; digoxin-treated: 4 $\alpha2^{R/R}$ and 4 $\alpha2^{S/S}$), no differences in myogenic responses were found between the two drugs or between the two genotypes. In experiment 2, force generation in isolated renal vessels in response to PE was determine before and during treatment with increasing concentrations of ouabain or digoxin in 42 vessels from 13 mice (time-control: 9 $\alpha2^{R/R}$ and 10 $\alpha2^{S/S}$; ouabain-treated: 6 $\alpha2^{R/R}$ and 5 $\alpha2^{S/S}$; digoxin-treated, 6 $\alpha2^{R/R}$ and 10 $\alpha2^{S/S}$). There was no effect of either digoxin or ouabain on renal artery contractions in either of the two genotypes.

Conclusion: The lack of effect of CTS on renal vascular reactivity in either $\alpha2^{R/R}$ or $\alpha2^{S/S}$ mice was surprising, as it is a popular idea that binding of CTS specifically to the α2 Na-K-ATPase subunit can influence myogenic tone. These findings do not support the hypothesis that the α2 subunit plays a predominate role in regulating vascular smooth muscle responsiveness, and suggest that future investigations should focus on other isoforms, such as the widely expressed α1 subunit.