Arginine vasopressin receptors as therapeutic targets for castration-resistant prostate cancer

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BACKGROUND

Improved drugs to combat castration-resistant prostate cancer (CRPC) are needed. We identified the G protein-coupled receptor, arginine vasopressin receptor type 1A (AVPR1A) as a potential therapeutic target in CRPC. AVP is the ligand for AVPR1A and all AVPR subtypes. AVPR1A signals via Gq11 subunits to stimulate intracellular calcium release. AVPR1A mRNA levels are elevated in CRPC patients compared to primary PC and depletion of AVPR1A decreases CRPC cell proliferation. Safe and effective AVPR1A antagonists have been evaluated in clinical trials for non-cancer conditions. The AVPR1A selective antagonist, relcovaptan, inhibits CRPC tumor growth in vivo in three distinct preclinical settings: newly emergent, established and late stage growth in the bone metastatic niche. Because osteoblasts and osteoclasts express AVPR1A, we investigated possible autocrine and paracrine signaling by the ligand AVP. Since AVP stimulates all AVPRs including AVPR2, which is also expressed in CRPC, we investigated the effects of AVPR2 antagonism on PC cell proliferation.

METHODS

We examined AVP stimulated pathways using pharmacologic inhibitors, analyzed human PC datasets, and investigated AVP production by CRPC cell lines. We evaluated AVPR2 mRNA expression in PC cells and the combined effects of selective antagonists of AVPR1A and AVPR2 on CRPC cell proliferation.

RESULTS

Pre-provasopressin (the precursor to mature AVP) mRNA is present at higher levels in advanced PC patient datasets. We discovered that AVP was synthesized by several CRPC cell lines. AVP stimulates ERK phosphorylation leading to activation of CREB in CRPC and this pathway was blocked by a Gq11 inhibitor but was independent of calcium signaling. AVPR2 was co-expressed with AVPR1A in patient samples as well as in select CRPC cell lines. The combination of AVPR1A and AVPR2 antagonists inhibited CRPC cell proliferation and promoted apoptosis to a significantly greater extent than treatment with the individual antagonists.

CONCLUSION

These data reveal the potential for AVP autocrine and paracrine signaling in CRPC and suggest that AVP-mediated activation of both AVPR1A and AVPR2 may occur. These findings support the repurposing of drugs that target AVPRs in CRPC.