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Pertubation of G-protein coupled receptor-mediated transactivation of ErbB receptor tyrosine kinases by polyamidoamine dendrimer drug delivery systems

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Introduction G-protein coupled receptors such as those for Angiotensin II (Ang II) or Norephinephrine (NE) can transactivate members of the epidermal growth factor receptor (EGFR or ErbB) family of receptor tyrosine kinases including EGFR and ErbB2. Polyamidoamine (PAMAMs) dendrimers are a series of spherical, tree-like polymer structures that have defined chemical architecture and molecular size in the nano scale. Superfect (SF) and Polyfect (PF) are two commercially available PAMAM dendrimers that bear the same cationic (-NH2) surface chemistry but differ in their molecular architecture whereby PF is an intact and SF is a fractured dendrimer architecture. SF and PF are widely used as drug delivery systems including as transfection agents for genes and siRNA. We have previously shown that these drug delivery systems can modulate signal transduction pathways involving EGFR and MAP kinases. Here, we investigated the effect of SF and PF on GPCR-mediated transactivation of EGFR and/or ErbB2 in cultured primary rat aortic vascular smooth muscle cells (VSMC).

Method VSMC cultures, obtained by enzymatic dissociation of the rat thoracic aorta, were initially cultured in serum containing DMEM media until 60–70% confluence and then in serum-free media and/or treated with different doses of PF or SF PAMAM dendrimers for 4h. Alternatively, cells were either exposed to Ang II or NE for 30 mins with or without treatment with PF or SF for 4 hrs or in some cases pretreated with either Losartan or Prazosin.

Results Ang II and NE induced significant (approximately 2-fold) induction of EGFR and ErbB2 phosphorylation in VSMC that could be blocked with Losartan (an AT_1 receptor antagonist) and Prazosin (an $alpha_1$-adrenergic receptor antagonist) respectively ($p<0.05$; N=4). PF significantly attenuated both Ang II and NE-induced transactivation of ErbBs and downstream signalling via ERK1/2 (>80% inhibition, $p<0.05$; N=4). Surprisingly and in contrast to PF, SF significantly augmented Ang II and NE-mediated transactivation of ErbBs and subsequent downstream phosphorylation of ERK1/2 ((>150%, $p<0.05$; N=4).

Conclusions These data suggest that PAMAM dendrimers are novel modulators of GPCR-mediated signalling via ErbB receptor tyrosine kinases and that their exact signalling effects are dependent on their molecular architecture. These findings could have important implications for the use of PAMAMs in delivering genes and siRNA into cells where, aside from their drug delivery properties, their ability to modulate signal transduction pathways needs to be accounted for.