A functional cross-talk between alpha1-adrenergic receptors and mGlu7 metabotropic glutamate receptors may pay a role in stress-related psychiatric disorders

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The role of adrenergic signalling in the modulation of mood and depression-related behaviour has been pointed out both in clinical studies and in animal models, as alpha1A-adrenergic receptor (AR) signalling, but not alpha1B-AR signalling, produces antidepressant-like behaviour in the mouse and that prolonged stimulation of alpha1A-AR induces a reduction in anxious and depressive behaviour in animals (Doze et al, 2009; Doze et al, 2011). However, recent evidence suggests that also metabotropic glutamate (mGlu) receptors, including mGlu7, may play a role in the pathophysiology of stress-related psychiatric disorders such as anxiety and major depression. Accordingly, mGlu7 receptor knockout mice show an antidepressant-like behaviour and altered response to stress. We therefore investigated whether a cross-talk between alpha1A-AR and mGlu7 receptors may physiologically occur and whether this can be relevant to the clinic. We first performed experiments in HEK293 cells that were transiently transfected with alpha1A-AR and mGlu7 receptors, and we found that phenylephrine (PE)-induced polyphosphoinositide (PI)-hydrolysis was significantly reduced by both L-2-amino-4-phosphonobutanoate (L-AP4) and L-serine-O-phosphate (L-SOP), which activate mGlu7 receptors at high concentrations. The mGlu7-mediated effect was prevented by co-expression of the 2 receptors with the GRK2 C-terminal tail, suggesting that the mGlu7 effect on alpha1A-AR signalling is mediated by Gβγ. We have also shown that the mechanism of mGlu7 inhibition of alpha1A-AR-signalling requires MAPK activation, as it can be reduced in the presence of both UO126 and PD98059. To further investigate this mechanism, we used brain slices from the mouse cerebral cortex, in which we fully confirmed the ability of high concentrations of L-AP4 and L-SOP to inhibit noradrenaline-stimulated PI hydrolysis. Finally, to assess whether this cross-talk may be relevant to pathology, we performed behavioural and endocrinological experiments. When injected i.c.v., PE induced an anti-depressant behaviour in rats, as measured by the forced swimming test, and this effect was reduced by L-SOP administration. We also assessed the responsiveness of the HPA axis, by collecting trunk blood to measure plasma corticosterone levels, 30 min after i.c.v. injection of PE or L-SOP + PE. L-SOP strongly reduced the increase in corticosterone levels induced by PE. We therefore conclude that mGlu7 receptors negatively modulate alpha1A-AR signalling and that the interplay between these 2 receptor systems may play a role in the pathophysiology of mood disorders.

Doze et al (2009) *Brain Res*, 1285:148-157.
Doze et al (2011) *Mol Pharmacol*, 80:747-758.