**TRICYCLIC PSYCHIATRIC ANTIDEPRESSANTS AS ALPHA2A ADRENERGIC RECEPTOR LIGANDS MODULATING RECEPTOR FUNCTION**

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High comorbidity between depression and cardiovascular diseases has been supported by numerous epidemiological studies. Tricyclic antidepressants, which modulate the noradrenergic activity, have been shown to induce adverse effects on cardiac functions. In this study, we have investigated potential effects of tricyclic drugs on the noradrenergic system by characterizing their interactions with and effects on alpha 2 adrenergic receptors (ARs), beginning with the primarily noradrenergic antidepressant desipramine (DMI). DMI was found to be an orthosteric arrestin-biased ligand at the alpha2A-AR, selectively inducing recruitment of arrestin (observed by FRET) but not activation of heterotrimeric G proteins. Arrestin recruitment results in DMI-driven downregulation of receptor expression with chronic exposure, a process which occurs for cortical alpha2AR in vivo in an arrestin-dependent fashion and likely underlies mechanistically unexplained neuroadaptive alterations in alpha2AR expression associated with DMI. Our findings provide novel insight into tricyclic pharmacology at alpha2ARs which could contribute its complex effects to the cardiovascular system.