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Inhibition of PDE4 fails to reverse behavioural deficits induced by muscarinic receptor blockage.

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Blocking muscarinic receptors disrupts memory, via inhibition of adenylate cyclase activity and decreased cAMP concentration in the brain, whereas inhibition of phosphodiesterase (PDE4) increases cAMP concentration. We examined interaction of PDE4-muscarinic receptors on memory during a go/no-go task in rats, using rolipram, a PDE4 inhibitor, and scopolamine, a muscarinic antagonist. Rats were trained on a go/no-go task requiring a lever-press (go) when a cue was presented on the right, but the withholding of a lever-press (no-go) during cue-presentation on the left. Drug effects on correct responses were measured under four conditions: saline, scopolamine, rolipram, and rolipram+scopolamine. Compared to saline controls, scopolamine or rolipram alone increased incorrect responses on both go and no-go trials. Co-administration of rolipram and scopolamine markedly increased incorrect responses, indicating that rolipram failed to reverse scopolamine-induced deficits. Importantly, lever-presses during no-go trials increased following rolipram, scopolamine, or both. Our findings suggest that behavioural deficits reflected impaired memory, not a decrease in activity, and that there was no direct interaction between PDE4 inhibition and muscarinic receptor activation. Given that a go/no-go task depends on the prefrontal cortex, PDE4 inhibition may not directly mediate working memory, but may involve activation of a second messenger system.