AChE and RACK1 promote the anti-inflammatory properties of fluoxetine.

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Abstract:

Selective serotonin reuptake inhibitors (SSRIs) show anti-inflammatory effects, suggesting a possible interaction with both Toll-like-receptor 4 (TLR4) responses and cholinergic signaling through as yet unclear molecular mechanism(s). Our results of structural modeling support the concept that the antidepressant fluoxetine physically interacts with the TLR4-myeloid differentiation factor-2 complex at the same site as bacterial lipopolysaccharide (LPS). We also demonstrate reduced LPS-induced pro-inflammatory interleukin-6 and tumor necrosis factor alpha in human peripheral blood mononuclear cells preincubated with fluoxetine. Furthermore, we show that fluoxetine intercepts the LPS-induced decreases in intracellular acetylcholinesterase (AChE-S) and that AChE-S interacts with the nuclear factor kappa B (NF?B)-activating intracellular receptor for activated C kinase 1 (RACK1). This interaction may prevent NF?B activation by residual RACK1 and its interacting protein kinase PKC?II. Our findings attribute the anti-inflammatory properties of SSRI to surface membrane interference with leukocyte TLR4 activation accompanied by intracellular limitation of pathogen-inducible changes in AChE-S, RACK1, and PKC?II.

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