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Noradrenergic alpha-2 agonists have anxiolytic-like actions on stress-related behavior and mesoprefrontal dopamine biochemistry.

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Clonidine (CLON), an alpha-2 agonist, has anxiolytic-like actions on the response of mesoprefrontal dopamine (DA) neurons to aversive stimuli in addition to some fear-related behavioral responses. We hypothesized that the anxiolytic-like actions of clonidine could be mimicked by stimulation of alpha-2 receptors on the mesoprefrontal dopamine neurons. Here, we test this hypothesis using clonidine or guanfacine (GFC), another alpha-2 agonist, in a model of aversive conditioning that selectively activates the mesoprefrontal dopamine neurons. One day prior to testing with drugs, rats were conditioned to fear a soft tone by pairing it with a footshock. During testing, the animals were subjected to the tones alone after drugs were administered systemically, or by local infusion into the regions containing the cell bodies and terminals of the mesoprefrontal dopamine neurons, namely, the ventral tegmental area (VTA) and the prelimbic (PL) cortex. Systemic administration of guanfacine blocked the increase in immobility in response to the conditioned tone and prevented the stress-associated increase in dopamine turnover in the prelimbic cortex. Systemic clonidine also prevented the stress-associated increase in dopamine turnover but caused sedation preventing behavioral measures. Guanfacine was then used in all local injection studies. The local application of guanfacine into either the prelimbic cortex or the ventral tegmental area did not prevent the conditioned fear induced increase in dopamine turnover or the increase in immobility in response to the conditioned tones. We conclude that the anxiolytic-like actions of alpha-2 agonists are not due to binding to alpha-2 receptors on the stress-sensitive mesoprefrontal dopamine neurons.

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