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Phosphodiesterase 5A inhibitors improve functional recovery after stroke in rats: optimized dosing regimen with implications for mechanism.

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Phosphodiesterase 5A (PDE5A) inhibitors improve functional recovery after middle cerebral artery occlusion (MCA-o) in rats. We used the PDE5A inhibitor 3-(4-(2-hydroxyethyl)piperazin-1-yl)-7-(6-methoxypyridin-3-yl)-1-(2-propoxyethyl) pyrido[3,4-b]pyrazin-2(1H)-one hydrochloride (PF-5) to determine the timing, duration, and degree of inhibition that yields maximum efficacy. We also investigated the localization of PDE5A to determine the tissues and cells that would be targets for PDE5 inhibition and that may mediate efficacy. Nearly complete inhibition of PDE5A, starting 24 h after MCA-o and continued for 7 days, resulted in nearly complete recovery of sensorimotor function that was sustained for 3 months. Delaying administration until 72 h after MCA-o resulted in equivalent efficacy, whereas delaying treatment for 14 days was ineffective. Treatment for 7 days was equivalently efficacious to 28 or 84 days of treatment, whereas treatment for 1 day was less effective. In the normal forebrain, PDE5A immunoreactivity was prominent in smooth muscle of meningeal arteries and a few smaller blood vessels, with weak staining in a few widely scattered cortical neurons and glia. At 24 and 48 h after MCA-o, the number and intensity of blood vessel staining increased in the infarcted cortex and striatum. PDE5A immunoreactivity also was increased at 48 h in putative microglia in penumbra, whereas there was no change in staining of the scattered cortical neurons. Given the window for efficacy and the PDE5A distribution, we hypothesize that efficacy results from an effect on vasculature, and perhaps modulation of microglial function, both of which may facilitate recovery of neuronal function.

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