CLOZAPINE DIRECTLY RELAXES BOVINE RETINAL ARTERIES

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It has been suggested that the atypical antipsychotic drug clozapine might be helpful in the development of new antiglaucoma agents, since it combines lowering of the intra-ocular pressure after topical instillation with vasodilation. However, the vasoactive influence of clozapine on ocular blood vessels has never been analysed. Therefore, this study aimed to evaluate whether clozapine has direct vasodilatory effects in isolated bovine retinal arteries (BRA) and to characterise pharmacologically the mechanisms involved. Retinal arteries were isolated from bovine eyes and mounted in a wire-myograph for isometric tension recording. Concentration-response curves were generated by cumulative addition of clozapine (1 nM to 10 μM) to the organ bath. Clozapine elicited a concentration-dependent relaxation of the BRA. Removal of the endothelium of the BRA, inhibition of nitric oxide synthase with N^{ω}-nitro-L-arginine and inhibition of soluble guanylyl cyclase with ODQ (1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one) significantly attenuated the clozapine-response, whereas cyclo-oxygenase inhibition with indomethacin had no influence. The Ca2+ channel activator Bay k8644, the nonselective 5-hydroxytryptamine receptor antagonist methiothepin and the adenosine receptor antagonist 8-(p-sulfophenyl) theophylline also failed in affecting the clozapine-induced relaxations.
In conclusion, clozapine clearly relaxes bovine retinal arteries in a direct way. Endothelium-derived NO is involved in this response. However, prostanoids, calcium entry blockade, 5-HT7 receptor stimulation and adenosine receptor stimulation all seem to be not involved.