Long-term effects of propranolol on tyrosine hydroxylase and dopamine-β-hydroxylase in the superior cervical ganglia of the rabbit

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The beta-adrenoceptor antagonist propranolol is well-established as an effective antihypertensive in man, but the mechanism of its hypotensive action has not been fully explained. Experimental studies have established that the immediate effects of propranolol treatment include a reduction in cardiac output and in plasma renin activity. However, this cannot explain the therapeutic effect since the hypotensive action of propranolol is delayed in onset (Prichard & Gillam, 1969). The present study was designed to test the hypothesis that chronic propranolol treatment causes a slow-onset reduction in sympathetic nervous system activity. One reflection of changes in the activity of sympathetic neurons is now considered to be the concentration of tyrosine hydroxylase and dopamine-β-hydroxylase contained within the cells (Thoenen, 1972). We have estimated the amount of these two enzymes in the superior cervical ganglia of rabbits after different lengths of treatment with propranolol.

Eighteen rabbits weighing 2–3 kg were injected subcutaneously twice daily with either saline (controls, 1 mg/kg of a 0.9% w/v NaCl solution, $n=6$) or (±)-propranolol (4 mg/kg for 3 days, $n=4$; 6 days, $n=4$ or 12 days, $n=4$). Fifteen hours after cessation of treatment the left and right superior cervical ganglia were removed and homogenized separately in 1 ml of 0.3M sucrose. Tyrosine hydroxylase activity was determined using the method of Levitt, Gibb, Daly, Lipton & Udenfriend (1967) and dopamine-β-hydroxylase (DBH) activity by that of Molinoff, Weinshilboum & Axelrod (1971). The results are summarized in Table 1.

Prolonged β-adrenoceptor blockade with propranolol induced a gradual reduction in activity of tyrosine hydroxylase. A delayed fall in DBH activity followed, highly significant after 12 days of treatment. These results can be interpreted as indicating a decreased activity of the sympathetic nervous system in response to this drug treatment. This suggestion is supported by the observations of Lewis & Hausler (1975) that propranolol infusion decreases preganglionic sympathetic activity.

Tyrosine hydroxylase is the rate-limiting enzyme in the biosynthesis of noradrenaline (Levitt *et al.*, 1965), and DBH activity has been used as an estimate of the size of the noradrenergic vesicle pool (De Potter & Chubb, 1971). Therefore, it is suggested that the gradual decrease in the concentration of these two enzymes indicates a decreased release of noradrenaline in response to chronic β-adrenoceptor blockade. This could explain the gradual decrease in blood pressure which is a well-established effect of treatment with propranolol.

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Table 1 Tyrosine hydroxylase and dopamine β-hydroxylase (DBH) activities of rabbit superior cervical ganglia (SCG)

		SCG tyrosine hydroxylase activity (nmol 15 min^{-1} mg protein^{-1})	*SCG DBH activity (nmol h^{-1} mg protein^{-1})*
Controls	($n=12$)	1.74 ± 0.12	185 ± 5
Propranolol 4 mg/kg. bd.	3 days ($n=8$)	1.62 ± 0.14	196 ± 7
Propranolol	6 days ($n=8$)	1.29 ± 0.11†	152 ± 10*
Propranolol	12 days ($n=8$)	1.34 ± 0.10*	139 ± 8‡

* $P<0.05$; † $P<0.02$; ‡ $P<0.001$.