ANTI-HYPERTENSIVE EFFECTS OF PROPRANOLOL UNALTERED BY 6-HYDROXYDOPAMINE GIVEN INTRAVENTRICULARY TO SHR

Takao KUBO and Yoshimi MISU
Department of Pharmacology, Yokohama City University School of Medicine, Yokohama 232, Japan
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The beta adrenergic blocking drug, propranolol, has been used effectively in the therapy of hypertension, but its mechanism of antihypertensive action is still controversial. Several investigators have suggested that an action on the central nervous system may be important in the hypotensive action of this drug (1–4).

There is now considerable evidence that central catecholaminergic (particularly noradrenergic) neurons are involved in central cardiovascular regulation (5, 6). Both single and repeated administration of propranolol produces changes in the content of brain noradrenaline and tyrosine hydroxylase activity in rats (1, 7). Thus, the antihypertensive action of propranolol may indeed be mediated via an action on central noradrenergic neurons. To examine this hypothesis, we studied the effects of intraventricular 6-hydroxydopamine (6-OH-DA) on the hypertensive action of propranolol in spontaneously hypertensive rats (SHR).

Five-month-old female SHR (Okamoto-Aoki strain) were given 6-OH-DA into the lateral brain ventricle using a stereotaxic technique. The rats had been anaesthetized with sodium pentobarbitone, 40 mg/kg i.p. These rats were given 2 injections of 6-OH-DA (each 250 μg) at 3 day intervals. The injection volume was 10 μl. Other rats received the same volume of the vehicle solution. One week after the pretreatment with intraventricular 6-OH-DA or vehicle, the rats were given propranolol (ca. 16 and 64 mg/kg/day) in the diet (8) for 12 weeks or were used as untreated controls. Each group included 10 rats. The blood pressure and heart rate were measured in conscious rats by an indirect tail-cuff method using a programmed electrosphygmomanometer (PE-300, Narco Bio-Systems, INC.). dl-Propranolol hydrochloride and 6-hydroxydopamine hydrobromide were obtained from Sigma Chemical Corp. 6-OH-DA was dissolved immediately before use in saline with 0.1% ascorbic acid. Data were reported as means±standard errors and levels of significance were determined by Student’s t-test.

Figure 1 summarizes the influence of chronic oral propranolol administration on systolic blood pressure and heart rate in SHR pretreated with intraventricular vehicle or 6-OH-DA. In the vehicle-pretreated animals, propranolol produced a dose-dependent fall in blood pressure. When compared with untreated control, the blood pressure was significantly lower at 10 and 12 weeks of treatment with propranolol (16 mg/kg) and significantly lower from 6 to 12 weeks of treatment with propranolol (64 mg/kg). In the intraventricular 6-OH-DA-pretreated animals, blood pressure was also lowered dose-dependently after propranolol. There was no significant difference between the intraventricular vehicle-pretreated and 6-OH-DA-pretreated animals regarding blood pressures of untreated control, propranolol (16
mg/kg)-treated and propranolol (64 mg/kg)-treated groups.

Heart rate was also reduced dose-dependently after propranolol administration in intraventricular vehicle-pretreated animals (Fig. 1). Intraventricular 6-OH-DA consistently produced a significant decrease in heart rate in those rats not treated with propranolol (P<0.05). Propranolol produced a further significant reduction in heart rate in the 6-OH-DA-pretreated animals.

In spontaneously hypertensive rats, pretreatment with intraventricular 6-OH-DA did not alter the hypotensive effect following chronic oral propranolol administration. We have previously shown that the application of 6-OH-DA (250 \( \mu \)g x 2) by the same route produces a marked reduction in noradrenaline of SHR brain (9). These data may indicate that central noradrenergic neurons do not mediate the hypotensive response produced by propranolol. This finding is in general agreement with the recently published results of Sugawara and Ozaki (10) showing that an acute hypotensive effect induced with propranolol was not inhibited by lateral ventricle injection of 6-OH-DA in conscious rats. In contrast, Meyers et al. (3) demonstrated that pretreatment with intracisternal 6-OH-DA abolished the depressor response following intravenous and intraventricular administration of propranolol in conscious rabbits. More recently, Montastruc and Montastruc (11) have shown that the hypotensive action of intravenous and intracisternal propranolol is suppressed by pretreatment with intracisternally administered 6-OH-DA in anaesthetized hypertensive dogs. The
differences between these two studies with rabbits and dogs, and these two studies with rats may be due to species differences, anaesthesia or differences in experimental protocols. 6-OH-DA administered intraventricularly produced a consistent decrease in heart rate in control rats not given propranolol and such may be due to a reduction in central catecholamines. Propranolol lowered heart rate much to the same extent in both intraventricular vehicle-pretreated and 6-OH-DA-pretreated animals. Thus, it appears likely that the bradycardic action of propranolol is not mediated via an action on central noradrenergic neurons.

Nevertheless, the involvement of central beta adrenergic mechanisms in the cardiovascular effects of propranolol cannot be completely ruled out. In addition to the noradrenergic neurons, recent studies have demonstrated the presence of adrenaline-containing neurons in the brain. Reid et al. (12) suggested that the central adrenergic neurons are little affected by 6-OH-DA administered centrally. Whether the central adrenergic neurons actually do participate in the cardiovascular responses to propranolol is the subject of ongoing studies.

REFERENCES