Effect of Thyroxine on the Cardiac Uptake of Catecholamines* 

Chong Sup Yoo, Young Myong Chu and Woo Choo Lee

Department of Pharmacology, Yonsei University College of Medicine, Seoul, Korea

ABSTRACT

The influence of thyroxine upon the cardiac uptake of catecholamines was investigated in rabbits. A single injection of thyroxine (1.0m/kg) into rabbits did not affect the concentration of myocardial catecholamines. However, this dose of thyroxine greatly increased the cardiac uptake of catecholamine following injection of 2.0 mg of norepinephrine as compared to that of untreated normal animals and it remained elevated for several hours. Similarly thyroxine also enhanced the accumulation of myocardial catecholamines following administration of dopa (60−80mg/kg) and epinephrine (1.0−1.5mg/kg).

INTRODUCTION

Considerable information concerning the hyperresponsiveness of hyperthyroid animals to catecholamines has become available. On the basis of the findings provided by Spinks and Burn (1952) and Trendelenburg (1953) who showed that monoamine oxidase (MAO) activity varied with the level of thyroid function, MAO inhibition was initially thought to contribute to the prolongation of the actions of catecholamines in hyperthyroid animals. On the other hand, Bacq et al. (1957) and Axelrod and Laroche (1959) reported that inhibition of catechol-O-methyltransferase (COMT) potentiated the cardiovascular effects of epinephrine as well as those of sympathetic nerve stimulation (Wylie et al., 1960). D'Iorio and Leduc (1960) observed depressed hepatic COMT levels after the administration of large doses of thyroxine in rats. From these observations, the possibility was also considered that an inhibition of COMT might contribute to the hyperresponsiveness of hyperthyroid animals to catecholamines.

Recent investigations have demonstrated a rapid uptake of injected norepinephrine by various tissues (Muscholl, 1961; Kopin et al. 1962), and this uptake has been thought to be the most important mechanism of inactivation of this drug. The development of supersensitivity to catecholamines in the hyperthyroid animals has been explained on the basis of its ability to block catecholamine uptake in tissue. Dengler (1961) demonstrated that heart slices from hyperthyroid rats contain less H2-norepinephrine after incubation than those from normals and concluded that thyroxine, like cocaine, inhibited the uptake of catecholamines by the heart. Subsequent study of Wurtman et al. (1963)
also supported the above concept by showing that cardiovascular hyperresponsiveness to epinephrine in hyperthyroid animals appeared to be related to an increased delivery of the active catecholamine and a concomitant decrease in its inactivation and retention, by binding, and is unrelated to the enzymes involved in catecholamine metabolism. However, in contrast to the above findings, the present experiment demonstrated that a single injection of thyroxine into rabbits significantly increased the cardiac accumulation of injected norepinephrine and its analogues.

**METHODS**

Normal male albino rabbits weighing approximately 2.0 kg were used. Animals were given thyroxine (1.0 mg/kg) intraperitoneally. Twenty-four hours after the injection of thyroxine, the animals were killed and the concentration of their cardiac catecholamines was determined by the spectrophotofluorometric procedure described by Shore and Olin (1958). The left ventricle was weighed and homogenized in 2 volumes of 0.01N HCl. A 2 ml sample of the homogenate was transferred to a 35 ml glass-stoppered reaction vessel containing 2 g of sodium chloride and 20 ml of butanol. The remainder of the procedure did not differ significantly from that described by the above authors. L-norepinephrine bitartrate (2 mg/kg), L-epinephrine (1.0–1.5 mg/kg) and dopa (60–80 mg/kg) were administered intramuscularly.

**RESULTS AND DISCUSSION**

Following intramuscular injection of 2.0 mg of norepinephrine into rabbits, the total catecholamine content of the myocardium was greatly increased and remained at an elevated level for several hours (Fig. 1). This result is consistent with the earlier findings that the cardiac tissue can specifically accumulate large quantities of injected norepinephrine (Raab and Gigee, 1955; Stromblad and Nickerson, 1961; Axelrod, 1959; Bhagat, 1963).

A single injection of 1.0 mg thyroxine into rabbits did not affect the concentration of their myocardial catecholamines. Twenty-four hours after the injection of thyroxine, 2.0 mg of norepinephrine was injected intramuscularly and the myocardial catecholamines were compared with those observed in rabbits which were given the same dose of norepinephrine without pretreatment with thyroxine. As shown by Fig. 1, the peak
Effect of Thyroxine on the Cardiac Uptake of Catecholamines

Fig. 2. The concentrations of cardiac catecholamines in normal and thyroxine-treated rabbits following intramuscular injection of norepinephrine (2.0 mg/kg), dopa (60-80 mg/kg) and epinephrine (1.0-1.5 mg/kg). Each bar represents average value of 5-6 experiments.

level of total catecholamine concentrations of the hearts was attained one hour after the injection of norepinephrine in the thyroxine-treated and untreated animals, indicating the concentration of the former is approximately 42% higher than that of the latter. Thereafter the concentration of catecholamines in thyroxine-treated animals declined to a value of 2.57 ± 0.29 µg/gm at 4 hours after norepinephrine injection, remaining still at a higher level that seen in either untreated or normal rabbits. It is noticeable that the pattern of decline in catecholamine content in the hearts was relatively similar between thyroxine-treated and untreated animals.

Similarly, the treatment of rabbits with thyroxine also significantly enhanced the cardiac uptake of catecholamines following injections of epinephrine (1.0-1.5 mg/kg) or dopa (60-80 mg/kg). The results are depicted in Fig. 2.

Similar findings were reported by Raab (1943) and Leduc (1955) who observed an exaggerated deposition of injected epinephrine in the cardiac tissue of thyroid-treated animals. Recently, Goodkind (1966), by determining the uptake of H\(^1\)-norepinephrine in atrial and ventricular myocardium of paired normal and hyperthyroid guinea pigs after the intravenous administration of norepinephrine, showed that atrial myocardium from hyperthyroid animals had a higher H\(^1\)-norepinephrine concentration than normal controls and the pattern of distribution of myocardial H\(^1\)-norepinephrine in normal and hyperthyroid guinea pigs followed the same distribution as the sympathetic innervation to the heart. From this result he concluded that thyroxine administration is associated with an increase in endogenous norepinephrine stores.

It has been suggested that some of signs of the hyperthyroid state can be attributed to the increased activity of the sympathetic nervous system. The responses of the cardio-
vascular system to epinephrine and norepinephrine are exaggerated in hyperthyroid animals, which suggest that the appearance of sympathetic activity may be due to increased sensitivity to these catecholamines (Hoffmann et al., 1947; Schneckloth et al., 1953). In a previous report (Lee et al. 1965), thyroxine treatment was found to increase myocardial catecholamine concentration in rabbits and it was indicated that the cardiovascular hemodynamics of thyrotoxicosis was largely dependent upon the capacity of thyroxine to increase cardiac catecholamines. On the basis of the present experimental results, it appears that the increased myocardial catecholamine content in the thyroxine-treated rabbits is due to increased myocardial uptake of circulating catecholamines. Goodkind and Stilp (1965) also found increased myocardial norepinephrine concentration in thyrotoxic guinea pigs and suggested that the myocardial catecholamine stores might participate in the increased myocardial contractile activity of these animals.

In contrast to the above results, the hearts of hyperthyroid rats have been reported to have decreased ability to concentrate H+ norepinephrine (Dengler, 1961; Wurtman et al., 1963). There is a probable species specificity for the effects of thyroxine on catecholamines. No explanation for this species difference is available at the present time.

REFERENCES


