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Paradoxical Relationship between the Superior Cervical Ganglia and the Antihypertensive Action of Propranolol in the Spontaneous Hypertensive Rat[1]

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ABSTRACT

The effect of *dl*-propranolol (1.0 mg/kg/day i.p.) on heart rate and blood pressure in young and old normo- and hypertensive rats was studied before and after bilateral sympathectomy of the superior cervical ganglia. Denervation alone produced no significant changes in blood pressure or heart rate in the normo- or hypertensive rat of either age. Thirty-five consecutive days of propranolol treatment significantly lowered blood pressure in the older established spontaneous hypertensive rat and prevented the increases from occurring in the younger, developing hypertensive rat. Blood pressure was not modified in the normotensive Wistar-Kyoto rat by propranolol. Denervation of the superior cervical ganglia at the beginning of the propranolol treatment or midway through the protocol abolished the antihypertensive effects in the young and old spontaneous hypertensive rat. A close temporal association of denervation with the loss of the antihypertensive effect was demonstrated. Although propranolol administration continued after denervation, the antihypertensive effects of the drug did not reappear.

The carotid sinus is supplied with adrenergic postganglionic fibers from the SCG. These fibers may play a role in the control of sinus muscle tone and, indirectly, blood pressure (Floyd and Neil, 1952; Kezdi, 1954).

A number of studies suggests a collaborative relationship between the carotid sinus, its adrenergic innervation, and the depressor reflex. Thus, stimulation of the sympathetic trunk supplying the SCG was shown to enhance the depressor reflex or sinus nerve activity, resulting from mechanical or hemodynamic distension of the sinus (Kezdi, 1954; Sampson and Mills, 1970; Endy and Tuttle, 1980). Propranolol, in one of the studies (Endy and Tuttle, 1980), further intensified the depressor reflex, apparently by facilitating the effect of stimulation more than by producing a decrease in the sinus distensibility. In addition, in the hemodynamically isolated and perfused sinus, propranolol also has been shown to increase sinus nerve activity, possibly by decreasing sinus wall distensibility (Tuttle and McCleary, 1978). The significance of these studies in explaining the antihypertensive effects of *beta* adrenergic blockers remains questionable because direct actions, such as upon cardiac output (Lund-Johansen, 1980), would not be under sympathetic control. However, recognized central and peripheral effects of propranolol (Klevans, *et al.*, 1976; Dollery *et al.*, 1973) could be ruled out in those studies of sinus nerve activity and distensibility. Conclusions, concerning a mechanism to explain the antihypertensive action of propranolol, have been difficult to interpret (Coltart and Shand, 1970; Zacest and Koch-Wesser, 1972; Hansson *et al.*, 1974) due to the high dosages of propranolol used and to the acute nature of their administration.

Therefore, it seemed worthwhile to determine if denervation of the SCG had any effect upon blood pressure or heart rate in the normo- and hypertensive rat exposed to lower concentrations of propranolol over a longer period of time.

Preliminary studies suggested that the hypertensive history of the rat, long established or in the process of developing, might bear upon the relationship between the SCG and the antihypertensive effect of *dl*-propranolol. For this reason, we used both young and old SHR and WKY.

Methods

Thirty male (400–425 day) and an equal number of (100–125 day) hypertensive rats (SHR; Okamoto and Aoki, 1963), plus a similar number of normotensive (WKY) controls were divided by age and then into five groups of six SHR and six WKY per group. The tail-cuff, electrosphygmographic technique (Technilab Instruments, Pequannock, NJ) and oscillographic recorder (Grass Instruments, Quincy, MA) were used to record blood pressure and heart rate.

Group designation. Groups A and B were differentiated according to whether the SCG was denervated before propranolol treatment or at 21 days after exposure to propranolol. Group C, designated as sham-operated controls, received no drug. Group D received propranolol for 35 days and Group E were denervated at day 7 and received no drug.

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ABBREVIATIONS: SCG, superior cervical ganglion; SHR, spontaneously hypertensive rats; WKY, Wistar-Kyoto rats.

Denervations. Rats subjected to denervation of the SCG were anesthetized with pentobarbital sodium (50 mg/kg; Ft. Dodge Laboratories, Ft. Dodge, IA). Under a dissecting microscope, both ascending sympathetic trunks supplying the SCG were cut proximal to the ganglia. Care was taken not to damage the vagal or sinus nerves. The wound was closed with suture and 400,000 U of penicillin were given i.m. Sham-operated rats were treated similarly, except that the innervation of the SCG was left intact. No rats died as a result of this procedure; most resumed normal behavior within 2 to 4 hr.

Drugs. SHR and WKY received single daily i.p. injections of *dl*-propranolol (inderal; Ayerst Co., Montreal, Quebec, Canada) at a level of 1.0 mg/kg. Depending upon the protocol, this regimen began at day 7 and continued for 35 days (Groups B and D) or began with the denervation of the SCG at the 21st day and continued for the duration of the 21 days (Group A).

Two adrenergic agonists, phenylephrine-HCl and isoproterenol-HCl (Neo-Synephrine and Isuprel; Winthrop Laboratories Inc., New York) were used to monitor reflex and vascular reactivity in sham-operated, denervated and propranolol-treated rats.

Vascular reactivity and the depressor reflex. At the end of the 42-day protocol, representative groups of rats were anesthetized and cannulas were inserted for direct recording of blood pressure and for i.v. injection. Reflex bradycardia during i.v. phenylephrine infusion (2.0 μg/kg/min) was used as a measure of integrity of the baroreceptors and isoproterenol (2.0 μg/kg/min) was used as a measure of net cardiovascular reactivity.

Statistics. Blood pressure and heart rates were recorded at 7-day intervals in animals with at least 14 days prior conditioning to the environment and handler. Recordings were made by the same technician at the same time of day. At least four readings were made at one "sitting," the results were averaged and pooled with the other five of the group. Determinations of significance between groups, either at the 42-day termination point or within each group at different times, were made using the Student's t and analysis of variance or F test (Orkin and Drogin, 1975).

Results

The blood pressure and heart rate data for the young rats are shown in figures 1 and 2, respectively, and for the old rats are shown in figures 3 and 4. The sham-operated or control rats, are represented in Panel C of each figure and the drug, or propranolol controls, are shown in Panel D of each figure. Those rats, subjected only to section of the sympathetic trunk, are shown in Panel E and those having both propranolol and denervation are shown in Panels A and B. Panel A rats had denervation early and Panel B late in the protocol.

Sham-operated controls (Panel C). In the young SHR, both blood pressure and heart rate increased throughout the 42-day protocol. In the older SHR, both remained constant throughout.

Operated controls (Panel E). Bilateral section of the ascending sympathetic trunks, supplying the SCG, had no effects upon blood pressure or heart rate in the young or old groups of rats.

Propranolol controls (Panel D). Propranolol prevented the increase in pressure with time in the young SHR and reduced blood pressure in the old SHR. Propranolol had no effect upon blood pressure in the WKY of either age group. Similarly, heart rates were reduced after 35 days of exposure to propranolol in both the young and old SHR. Heart rates in the WKY after 35 days were subject to scatter leading to statistical rejections of significance.

Propranolol plus denervation of the SCG (Panels A and B). In the young WKY, denervation of the SCG before or midway through the period of exposure to propranolol had no effect upon blood pressure or heart rate.

In the young propranolol-treated SHR, denervation of the SCG at 7 (fig. 1A) or 21 (fig. 1B) days, respectively, prevented or reversed the expression of the antihypertensive effect of the drug. Thus, blood pressures in the denervated, propranolol-treated SHR were 40 to 50 mm Hg higher than in the drug control group (Panel D).

A close relationship between denervation and the pressure rebound was indicated in those rats denervated at 14 days of propranolol treatment in which pressure rose from 150 ± 3.4 to 181.81 mm Hg at 28 days. Although propranolol treatment continued for an additional 21 days, pressure remained at the higher level.

In the old SHR denervation of the SCG, either at the beginning of (Group A) or midway through (Group B), the drug regimen abolished the antihypertensive effect of the drug. The pressure rebound developed over a period of 14 days. Heart rate in the old SHR increased in parallel with the increase in blood pressure.

In the old "normotensive" WKY, devervation produced some perturbations in pressure and heart rate which roughly paralleled in a qualitative way those which occurred in the old SHR.

Challenge with phenylephrine and isoproterenol. Comparisons of the blood pressure and chronotropic responses to phenylephrine and isoproterenol were made in groups of sham-operated controls of young and old SHR and WKY. The results depicted in figure 5 show the pressure responses in young and old rats at the top and the chronotropic responses at the bottom.

Blood pressure. Except for the significantly greater depressor response of the old SHR to isoproterenol, there were no differences among the other groups in response to the two catecholamines.

Heart rate. The chronotropic responses to each agonist were more dependent upon age and hypertensive disposition than the pressor. The response to phenylephrine was a 9 to 12% bradycardia, except in the case of the old WKY in which a 10% tachycardia occurred. On the other hand, the young SHR and old WKY had significantly greater increases in heart rate than the other groups.

Denervation. Although denervation of the SCG produced no change in the blood pressure or heart rates of the SHR and WKY of either age group (figs. 1–4), the response to catecholamine infusion was changed in one respect (fig. 6). Considering only blood pressure, the response to phenylephrine and to isoproterenol was not dissimilar among the two age groups or genetic, *i.e.* SHR/WKY, disposition. However, denervation of the SCG in the WKY of both age groups significantly enhanced the depressor response to isoproterenol. A similar enhancement by denervation was not observed in the SHR of either age group.

Propranolol controls. Isoproterenol was infused into groups of rats previously exposed for 35 days to propranolol and their chronotropic and blood pressure responses were compared with untreated rats. The results are shown in table 1 in which Group C represents the untreated controls and Group D represents the propranolol controls.

The depressor and positive chronotropic responses to isoproterenol were not significantly altered in the WKY exposed to propranolol. When calculated as the percentage of reduction of pressure in the SHR, isoproterenol produced approximately the

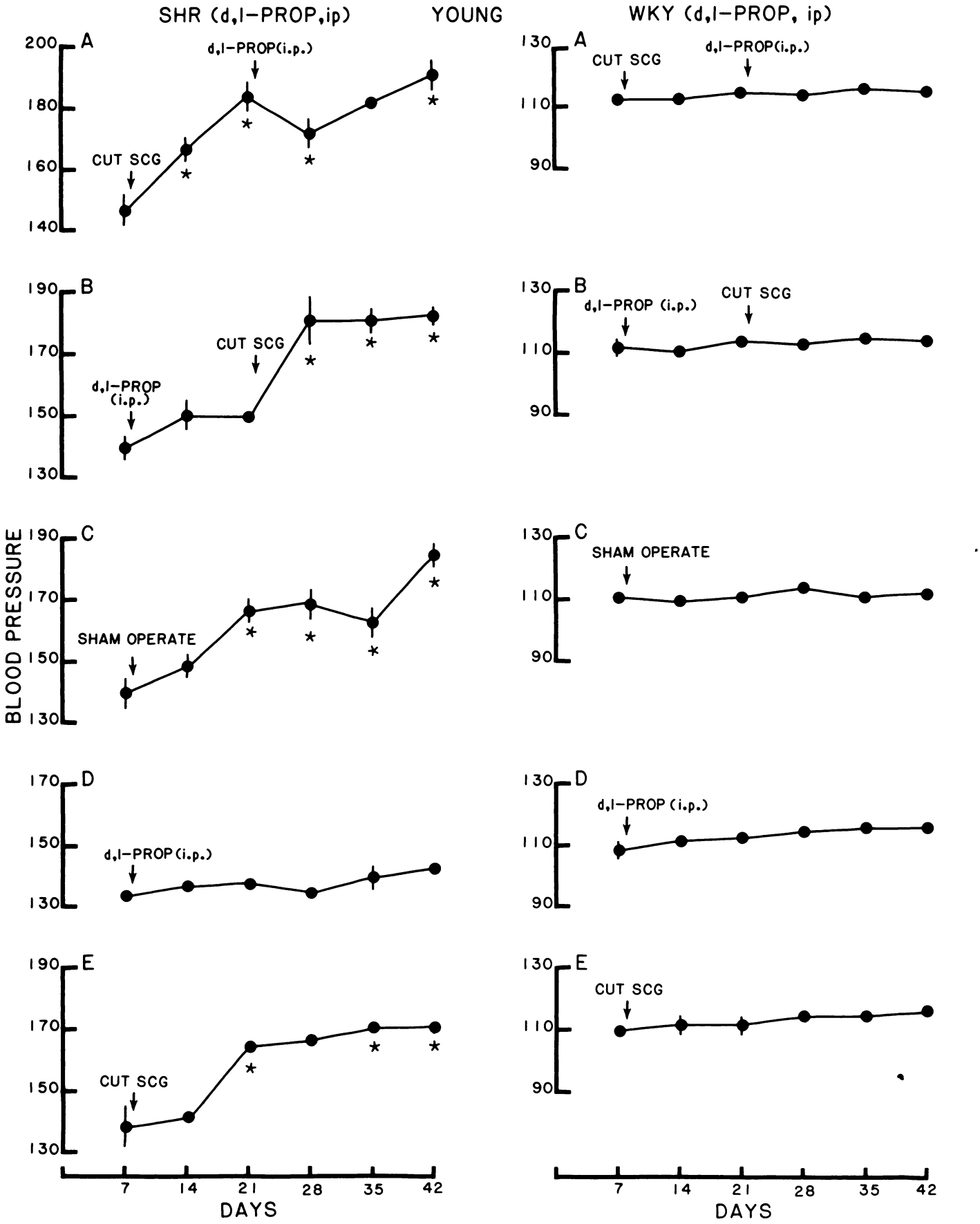

Fig. 1. Effect of *dl*-propranolol (PROP) on blood pressures in young SHR and WKY after (A) and before (B) denervation of the superior cervical ganglia. Respectively, groups C, D and E represent sham-operated untreated controls, drug-treated controls and denervation controls. Each point represents the mean of six rats with four determinations (±S.E.) and the asterisk represents significance ($P < .01$) in relation to the 7-day values.

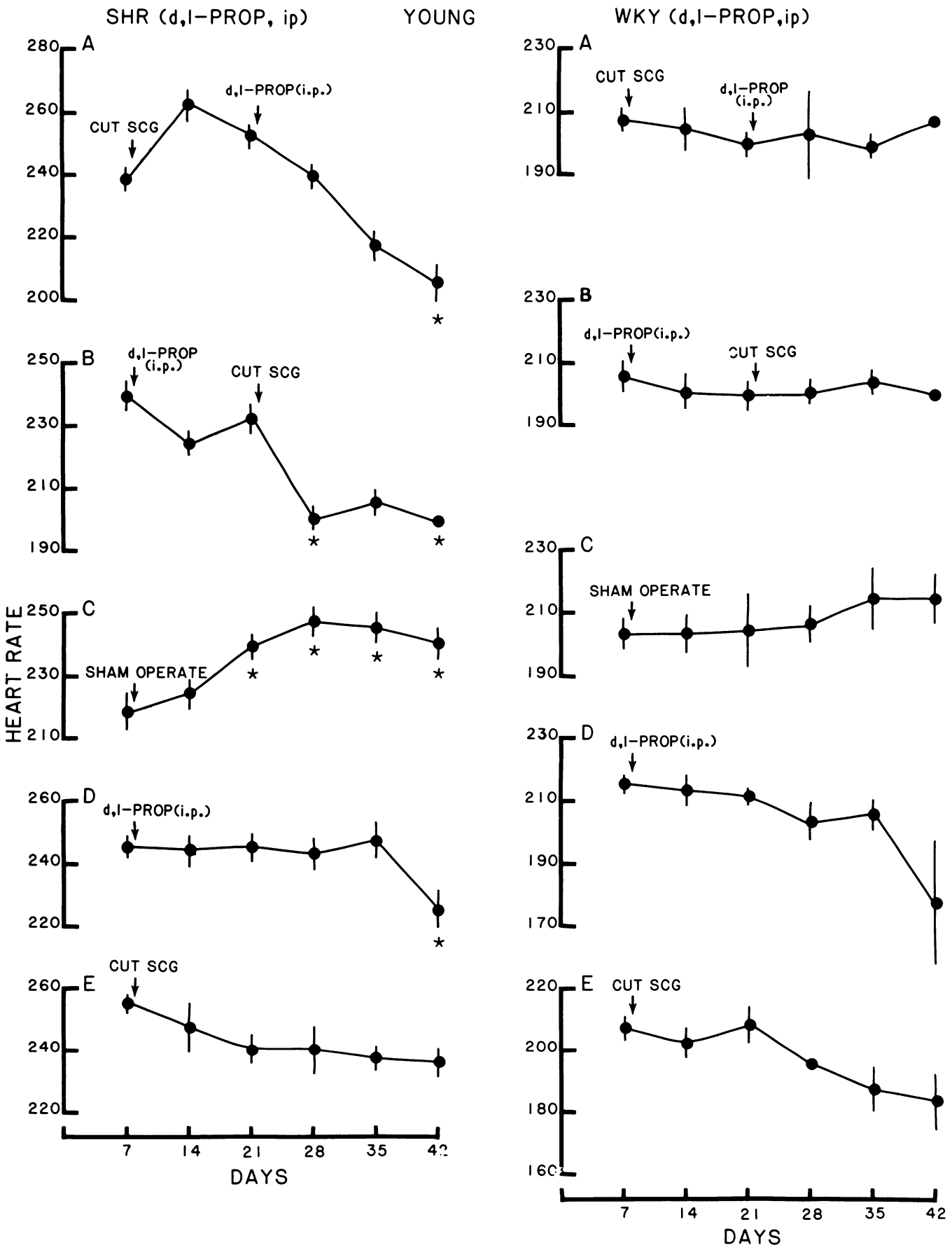

Fig. 2. Effect of *dl*-propranolol (PROP) on heart rates in the same young SHR and WKY shown in figure 1.

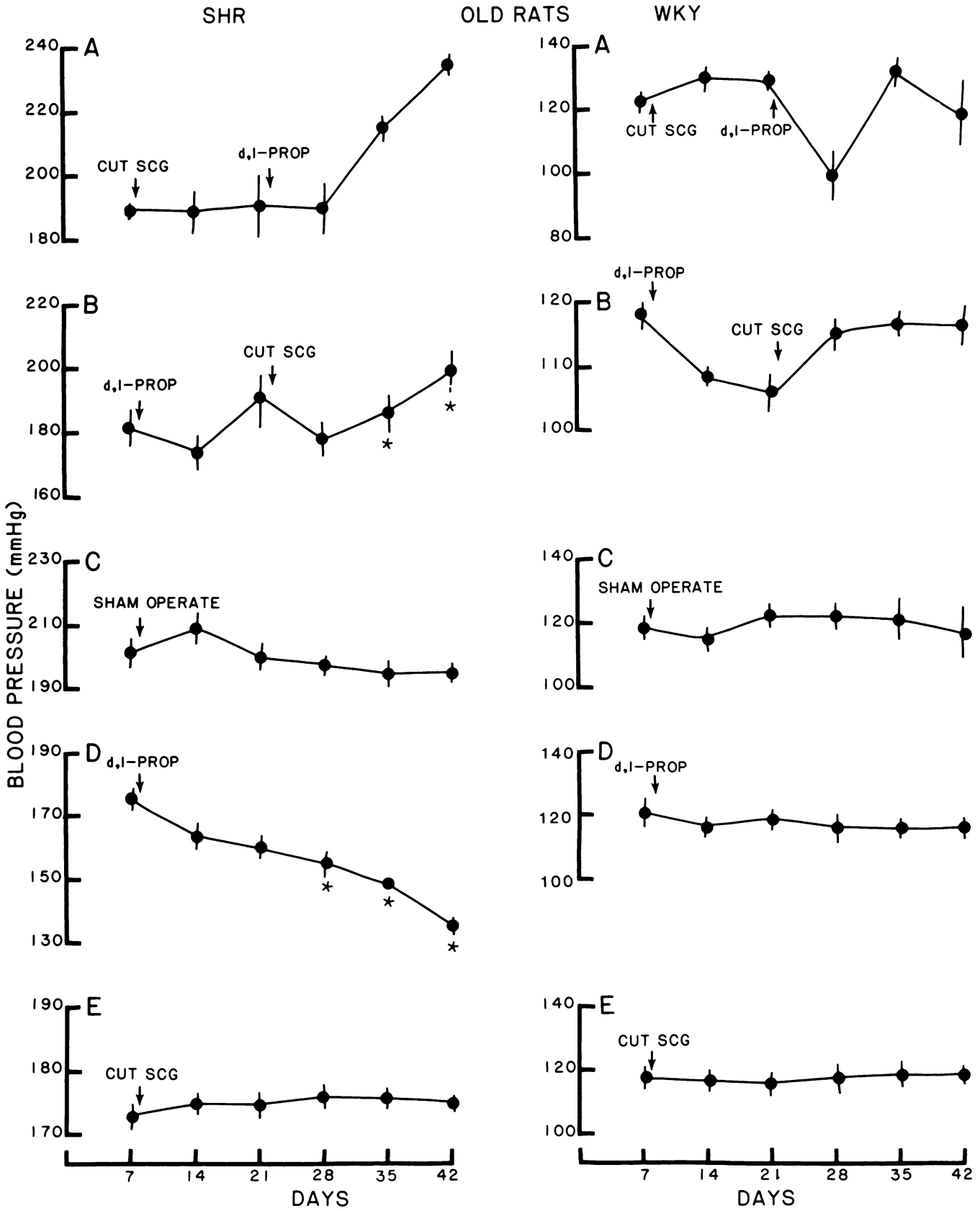

Fig. 3. Effect of *dl*-propranolol (PROP) on blood pressures in old SHR and WKY after (A) and before (B) denervation of the superior cervical ganglia. Respectively, groups C, D and E represent sham-operated untreated controls, drug-treated controls and denervation controls. Each point represents the mean of six rats with four determinations (±S.E.) and the asterisk represents significance ($P < .01$) in relation to the 7-day values.

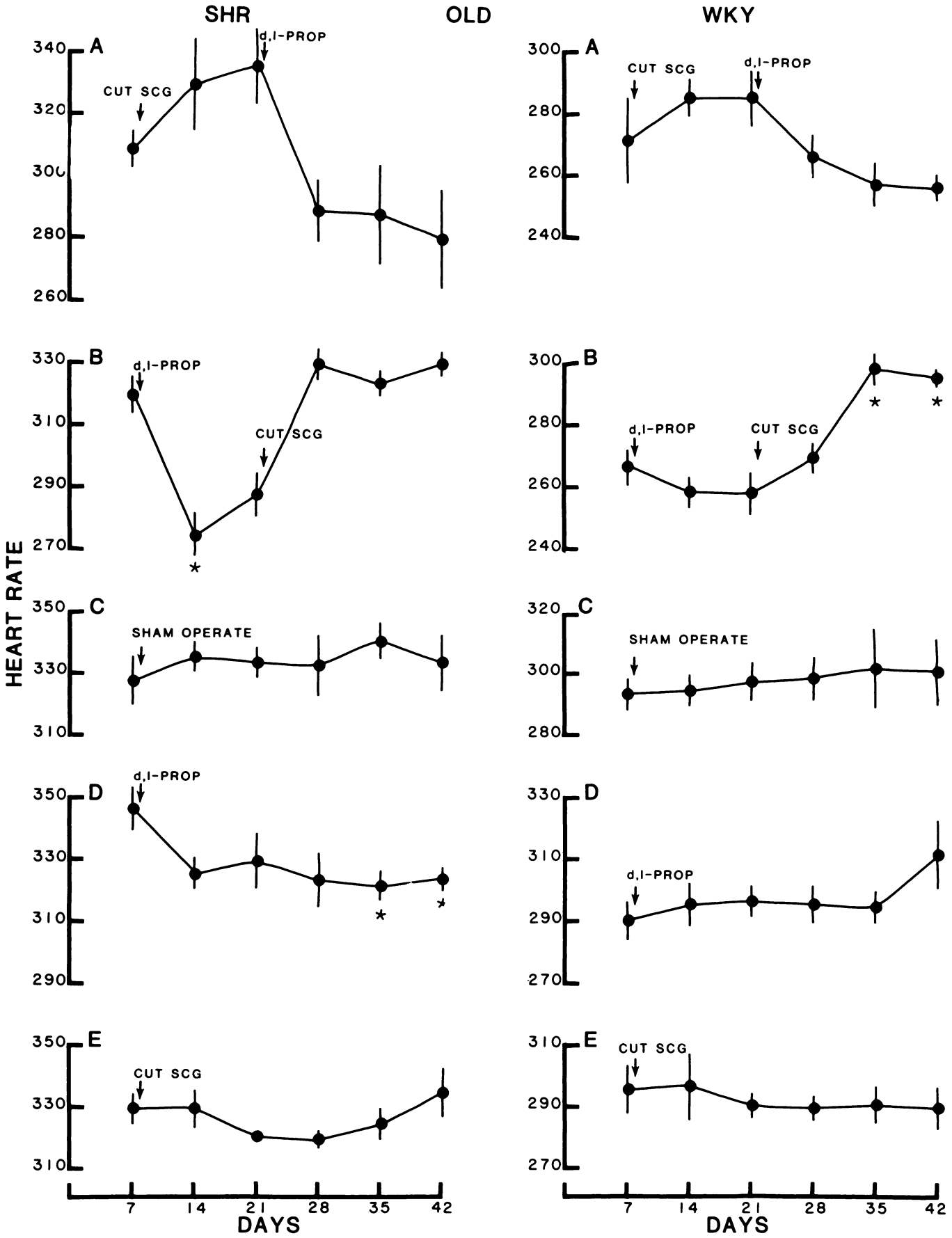

Fig. 4. Effect of *dl*-propranolol (PROP) on heart rates in the same old SHR and WKY shown in figure 3.

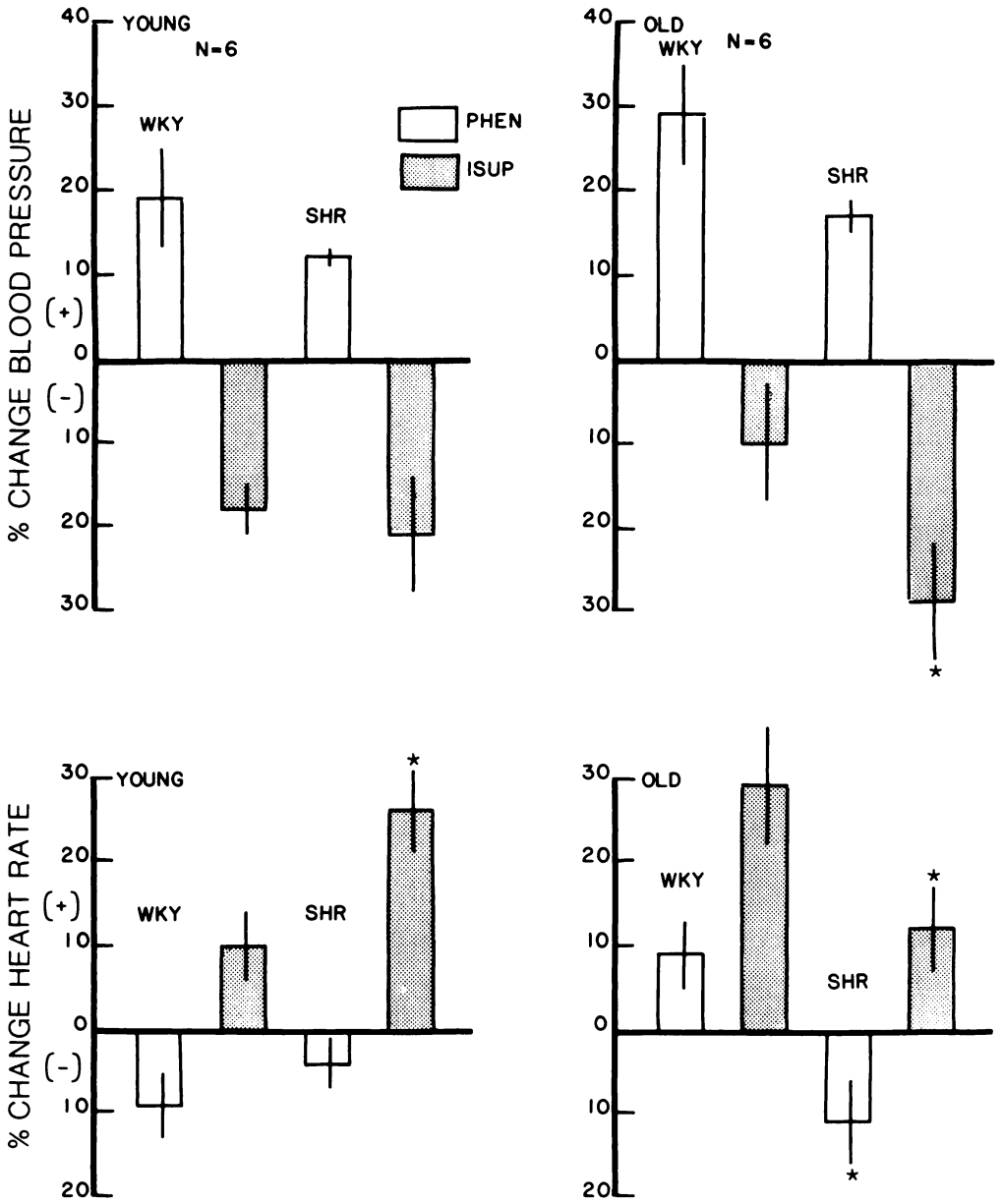

Fig. 5. Response of young and old SHR and WKY to i.v. infusion of phenylephrine (PHEN) and isoproterenol (ISUP; 2 μg/1 kg/min). Percentage of change in blood pressure (±S.E.) at top, heart rates (±S.E.) at bottom, young rats on the left and old rats on the right. Asterisk denotes significant difference ($P < .01$) in percentage of change between the WKY and SHR.

same fall in pressure in rats exposed to propranolol as in those untreated rats (30 *vs.* 24%). However, calculated on the same basis as pressure, the chronotropic response in the treated SHR was reduced, when compared with the untreated controls, from 20 to 8%.

Discussion

The present investigation was designed to determine what role the sympathetic nerves supplying the carotid sinus region play in the long-term antihypertensive effects of *dl*-propranolol. Both young (100–125 day) and old (400–425 day) rats were used in order to establish whether this sympathetic influence was more important in the developing than in the established hypertensive rat.

There is evidence that the older hypertensive rat differs from the young. The vascular architecture in the established hypertensive rat may thicken and lose elasticity. This can increase vascular resistance and ultimately systemic pressure (Folkow *et al.*, 1970). Lowering of blood pressure, through exposure to antihypertensive drugs, has little immediate effect upon these structural changes. However, antihypertensive drugs, by reducing cardiac output and decreasing total peripheral resistance, may permit structural recovery to occur and/or a resetting of the systemic baroreceptors (Wolinsky, 1972; Weiss, 1974; Weiss *et al.*, 1974; Kunze, 1981).

In the young developing SHR, pharmacological intervention may prevent these structural changes from occurring and even provide long-term protection after cessation of drug treatment. Recovery of baroreceptor function may also occur more rapidly in the young than in the old SHR (Weiss *et al.*, 1974).

Histological studies comparing young and old rat vascular muscle were not done in the present study, but the hemodynamic evidence suggests that these rats were suitable models for the young and old SHR (Weiss, 1974; Weiss *et al.*, 1974). The question of whether the genetic hypertensive rat, irregardless of age, represents a model of any form of human hypertension remains the subject of debate but its uniform implication

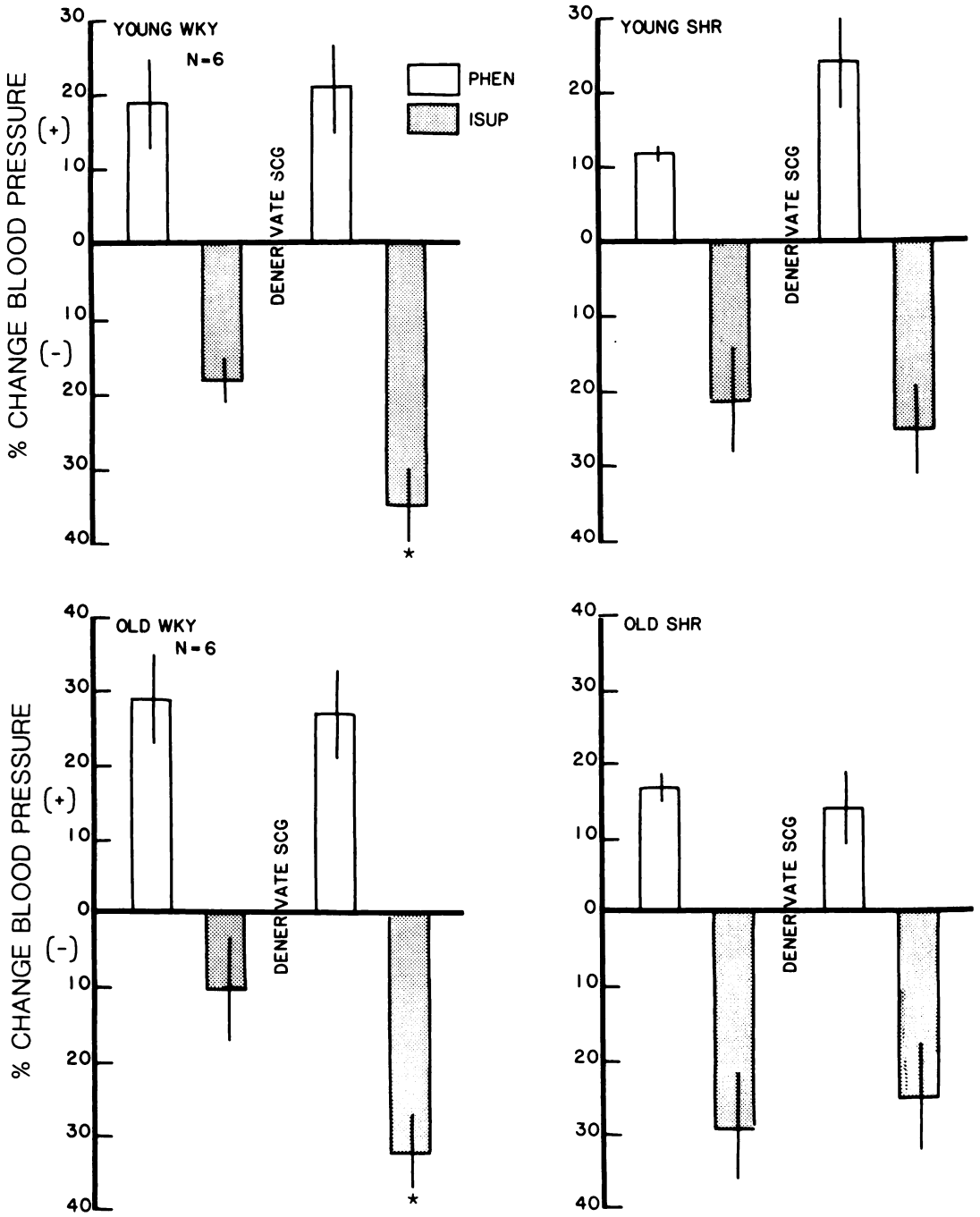

Fig. 6. Effect of sympathetic denervation of the SCG on the blood pressure (top) and heart rate (bottom) response of young and old SHR and WKY to phenylephrine (PHEN) and isoproterenol (ISUP; 2 μg/1 kg/min). Asterisk denotes significant ($P < .01$) difference between response to either drug before and after denervation.

TABLE 1

Comparison of the heart rate of blood pressure responses to isoproterenol in old SHR and WKY before and after propranolol treatment

N = 6	Control		Isoproterenol (2 μg/kg/min)	
	Blood pressure	Heart rate	Blood pressure	Heart rate
$\bar{x} \pm$ S.E.	*mm Hg*	*beats/min*	*mm Hg*	*beats/min*
Group C, WKY	114 ± 3.1	238 ± 10	104 ± 5.0	318 ± 16
Group C, SHR	176 ± 1.6	355 ± 5	123 ± 11.0	398 ± 17
N = 6	Control		Propranolol (1.0 mg/kg/day)	
	Blood pressure	Heart rate	Blood pressure	Heart rate
$\bar{x} \pm$ S.E.	*mm Hg*	*beats/min*	*mm Hg*	*beats/min*
Group D, WKY	125 ± 2.7	290 ± 15.0**	101 ± 3.5	348 ± 8.0
Group D, SHR	135 ± 3.6**	305 ± 15.0**	102 ± 4.5	332 ± 11.0**

** Significant to < .01 level from corresponding valve in columns above.

as such cannot be denied. Blood pressure in the young SHR (at 100–125 days) began at near normotensive levels and increased steadily, approaching that of the older (400–425 day) SHR at 42 days. The latter had a sustained level of elevated pressure.

It is remarkable that there was little difference between the young and old SHR in the response to isoproterenol or phenylephrine. However, there were significant differences between the SHR and WKY in response to isoproterenol. Systemic pressure in the old WKY fell by only one-third as much and heart rate increased by only half as much as in the SHR. Systemic pressure only partly reflects vascular reactivity, but this difference between the SHR and WKY may reflect a higher level of cardiovascular tone in the SHR (Nosaka *et al.*, 1972; Yamaguchi and Kopin, 1980). This may predispose the vascular smooth muscle to a greater influence and range of response to vasodilators such as isoproterenol. Similarly, heart rate, already at higher levels in the SHR, would be less proportionally affected by positive chronotropic agents such as isoproterenol.

Hemodynamic and pharmacologic considerations of the effect of denervation alone on the SCG and its attendant structures are important considering its use in this protocol. Experimentally, neither heart rate nor blood pressure were effected in the short or long term by denervation and only the systemic response to isoproterenol was enhanced in the WKY.

Considering the complexity of the direct and reflex mechanisms controlling cerebral and extracerebral blood flows, numerous investigators report from little or no effect of denervation, or of sympathetic stimulation, to highly transient effects in these regions of the head and brain (reviewed by Purves, 1978). Similarly, denervation sensitivity to catecholamines probably does not occur in cranial structures as it does in other tissues of the body (Araki *et al.*, 1982). Because only the WKY responded to denervation by an enhanced depressor response, it seems more likely that this reflects a difference in reflex sensitivities compared to the SHR. The fall in systemic pressure, with isoproterenol infusion, should increase sympathetic tone at the level of the SCG and cutting this sympathetic supply would interrupt this component of the reflex response. In the WKY, with a lower level of tone than the SHR to begin with (Yamaguchi and Kopin, 1980), and with sinusal walls more sensitive to adrenergic influence than the SHR (Mohring, 1981), interruption of the sympathetic supply could essentially render the WKY as insensitive to reflex influences as the SHR.

Propranolol, as suggested in these studies, apparently reestablishes a more intimate relationship between sinusal pressure, the SCG and the factors predisposing the rat to hypertension in the first place. Thus, in the SHR exposed to propranolol, section of the cervical sympathetics produced a pressure rebound to levels near that of the untreated SHR. The original hypertensive pathology had not been reset by the drug. Because the duration of propranolol treatment in the present study was less than generally recognized as necessary for development of the antihypertensive effect in man, especially that period when *beta* receptor blockade has long since been achieved (Hansson *et al.*, 1974), this rebound effect in the denervated SHR may be a transient phenomenon of propranolol in the hypertensive rat.

The nature of this effect of denervation in the treated SHR remains to be explained. Suggestions have been made by a number of investigators that the SCG may play a functional role in the depressor reflex (Kezdi, 1954; Sampson and Mills, 1970; Bagshaw and Peterson, 1972; Stinnett *et al.*, 1981) and in the antihypertensive action of propranolol (Pickering and Phil, 1971; Endy and Tuttle, 1980). These studies suggest that a change in baroreceptor loading might result from denervation of the SCG and, by reducing the adrenergic input to the sinus, reduce the level of sinus muscle tension. This could raise the sinus pressure threshold, resulting in a resetting of pressure to a higher level (Landgren, 1952).

Recent, unpublished studies have shown that the pressure rebound occurs over the 7- to 14-day period and not abruptly with denervation of the SCG. This might suggest that the relationship between propranolol and the adrenergic innervation of the carotid sinus does not depend upon a tonic sympathetic input to the sinus wall, but rather upon some factor with residual sympathetic influence. There could be changes in ionic, enzymatic or receptor composition and sensitivity which persist with decrement after denervation.

Concepts that explain the antihypertensive action of propranolol by central inhibition of vasomotor outflow (Dollery *et al.*, 1973; Klevans *et al.*, 1976) or by *beta* adrenergic blockade of myocardial rate and force (Hansson *et al.*, 1974) are inappropriate in light of the present study. Neither of these should be effected by cutting the SCG. It seems more likely that some direct mechanism is involved which utilizes the sympathetic inflow to the sinus region and some action of propranolol.

Other explanations are possible. Propranolol has a number of direct actions on isolated and intact vascular smooth muscle which are not related to *beta* adrenergic blockade. In addition to sympathomimetic and membrane stabilizing effects, *dl*-propranolol increases smooth muscle tone and regional vascular resistance (Rajfer, 1981; Powell, 1980). The mechanism for this effect remains the subject of debate inasmuch as *alpha* adrenergic receptors are not involved. However, verapamil does block these effects, suggesting that propranolol may increase free tissue Ca^{++}. Because norepinephrine also mobilizes bound, smooth muscle Ca^{++} (Godfraind, 1976), the combined effect may result in cumulative increase in free Ca^{++} and muscle tone. This could lower the sinus pressure threshold and explain the resetting by antihypertensive drugs.

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