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# Central Hypotensive Activity of *dl*- and *d*-Propranolol

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**Abstract** □ The intraventricular administration of *dl*-propranolol to α-chloralose-anesthetized cats was followed by a decrease in blood pressure and was devoid of an associated tachycardia. *d*-Propranolol in an equivalent dose produced a hypotensive response which was not statistically different from *dl*-propranolol. These data suggest that there is a central component in the hypotensive response to propranolol and that it is independent of the β-adrenergic blocking activity. The intraventricular administration of 500 mcg. of reserpine base produced greater than a 90% depletion of norepinephrine in all brain regions analyzed within 24 hr. This pretreatment with reserpine also reversed the hypotensive response to both *d*- and *dl*-propranolol as well as converted the decrease in heart rate to an increase in heart rate. Thus, at least one of the amines must be required to produce the hypotensive response. Perfusion of the ventricular system with *dl*-propranolol generally produced an increase in epinephrine along with a decrease in norepinephrine in the brain region analyzed. Under the same conditions, *d*-propranolol also increased epinephrine but led to a decrease in norepinephrine in only 50% of the tissues assayed. These changes in amine levels occurred during the perfusion, which also produced a sustained hypotensive effect lasting the duration of the perfusion. The hypotension associated with propranolol therapy may have a central component that is not dependent on the β-adrenergic blocking property of propranolol, which requires one or more of the brain amines, and leads to an increase in the epinephrine level along with a general decrease in the norepinephrine level of the brain.

**Keyphrases** □ *dl*-, *d*-Propranolol—central hypotensive activity □ Hypotensive action, *dl*-, *d*-propranolol—intraventricular injection □ β-Adrenergic blocking activity—propranolol □ Catecholamines, brain—propranolol effect

Propranolol antagonizes the cardiovascular effects of β-adrenergic receptor stimulation produced by either stimulation of effector fibers or by sympathomimetic amines. The intravenous administration of propranolol produces a decrease in the sympathetic component to the heart and blocks the chronotropic effects of isoproterenol and epinephrine and the peripheral vasodilatory effects of isoproterenol (1–3). The acute response to propranolol is a decrease in cardiac output, whereas prolonged administration fails to produce this effect (4). Several reports have shown that the intravenous administration of propranolol to normotensive or hypertensive individuals decreased heart rate and cardiac output along with a concomitant decrease in systemic blood pressure but exhibited no significant effects on systemic peripheral resistance (4–6). Epstein *et al.* (5) and Shinebourne *et al.* (6) reported that the increase in arterial pressure that is associated with exercise was abolished by propranolol *via* reduction in cardiac output.

The central nervous system (CNS) manifestations attributed to propranolol classify it as a sedative and general CNS depressant (7–9). Since both propranolol and pronethalol possess these properties while dichloroisoproterenol (DCI) produces CNS stimulation, these authors have concluded that it is the presence of the naphthyl group rather than the β-adrenergic blockade that is responsible for the CNS effects. The depression or tranquilization in humans associated with propranolol administration is invariably apparent only at dosage levels that are many times greater than those necessary to produce β-adrenergic blockade (10–12). Masuoka and Hansson showed that intravenous administration of $^{14}C$-labeled propranolol is rapidly taken up by the rat brain and concentrated 50 times greater in the brain than in the blood (13).

The hypotensive effect induced by the administration of β-adrenergic blocking agents in man has been well documented (14–22). This response is not exclusive to humans, because other investigators also have noted depressor effects in animals (23–26). The oral administration of propranolol for several weeks has been reported to result in a gradual and significant decrease in systemic arterial pressure in hypertensive patients (10, 16, 22). In all cases, regardless of the time of onset, the dose of the β-adrenergic blocker was many times that required for the blockade of the β-receptors, thus leading to the hypothesis that this response may not be due to antagonism of these receptors. This hypotensive response was unexpected, since the blocking of a neural mechanism that produces vasodilation in the absence of a significant reduction in cardiac output might be expected to result in a rise in systemic blood pressure

(18, 27–29). The mechanism of the hypotensive response to the prolonged oral administration of propranolol has not been elucidated. Several investigators have attempted to explain this hypotensive response on a resetting of the baroreceptor threshold to respond to alterations in systemic blood pressure at a lower level; however, conclusive evidence is currently lacking (30, 31). Frohlich and Page (10) and Waal (21) have suggested that a more fruitful area of research into the mechanism of this hypotensive response would be the elucidation of a possible central component. The purpose of the present study was to investigate the role of the CNS in the hypotensive effects induced by propranolol.

## EXPERIMENTAL

**Perfusion of Left Lateral Ventricle**—Twenty-two adult cats of either sex weighing 2–3 kg. were anesthetized with α-chloralose (65 mg./kg. i.p.) prepared as a 1% solution in warm saline. Systemic blood pressure was recorded from a catheterized femoral artery onto a Grass polygraph, and the ipsilateral femoral vein was catheterized for the administration of drugs. Tracheal intubation was performed, and the animal was ventilated with room air by means of a Harvard respirator. The left lateral ventricle was then prepared for perfusion with artificial cerebrospinal fluid (CSF) (32), following the method described by Bhattacharya and Feldberg (33), by stereotaxically implanting a 22-gauge hypodermic needle which had previously been machined to remove the bevel. The coordinates used were: anterior, 13 mm.; lateral, 2.75 mm.; and horizontal, +7 mm. (34). The successful placement of the cannula was confirmed by the presence of CSF pulsating in the barrel of the cannula. The cannula was then permanently affixed to the skull using dental cement. The perfusate fluid was maintained at 38°, and the lateral ventricle was perfused at a rate of 0.1 ml./min. for 1 hr. prior to drug injection to permit stabilization of the cardiovascular system. After this stabilization period, the perfusion was temporarily interrupted to permit the injection of 0.5 mg. of *d*- or *dl*-propranolol contained in 0.1 ml. of artificial CSF. Perfusion was then resumed.

"Central reserpinization" was performed in 14 cats by implanting a ventricular cannula, following the previously mentioned procedure using an aseptic technique, in cats under pentobarbital anesthesia. Procaine penicillin G (600,000 units i.m.) was administered prior to and on the day following surgery, after which the animal was allowed to recover for 3 days. On the 4th day following surgery, the male cat was removed from the cannula and 500 mcg. of reserpine base[1] in 0.1 ml. of water for injection was then administered into the left lateral ventricle. The cannula then was resealed to effect a functional central sympathectomy (35–38). Twenty-four hours later, the cat was prepared for perfusion of the lateral ventricle as described previously. One-half milligram of *d*- or *dl*-propranolol in 0.1 ml. CSF was administered into the lateral ventricle, and the blood pressure and heart rate were monitored. The brains and hearts from 10 additional adult cats were removed 24 hr. after "central reserpinization" and sectioned into the following regions to delineate the areas adjacent to the ventricular system: medulla, pons, cerebellum, mesencephalon, diencephalon, and telencephalon. These sections were then assayed for norepinephrine content by the method of Brodie *et al.* (39) using a spectrophotofluorometer (Aminco-Bowman).

Eight adult cats weighing 2–3 kg. were prepared for intraventricular perfusion as described and perfused for 1 hr. with either *d*- or *dl*-propranolol (0.5 mg./0.1 ml. CSF, 0.1 ml./min.). The cat then was sacrificed by means of an intravenous injection of air; the brain and heart were rapidly removed, dissected as already described, and frozen. The norepinephrine and epinephrine contents of the various brain sections and myocardia were determined by a modification of the method of Chang (40), in which the fluorescent intensity of the epinephrine in the samples is read within 10 min. following oxidation at an excitation wavelength of 417 mμ (uncorrected) and an emission wavelength of 510 mμ (uncorrected). The samples were then placed in boiling water for 2 min. and cooled to room temperature. The fluorescent intensity of norepinephrine was read at an excitation wavelength of 385 mμ (uncorrected) with an emission wavelength at 485 mμ (uncorrected). The concentrations of epinephrine and norepinephrine were determined using the simultaneous equations described by von Euler and Lishajko (41). All data were analyzed for statistical significance using Student's *t* test unless otherwise indicated.

[1] Serpasil-Ciba.

**Table I**—Effect of *d*- and *dl*-Propranolol on Blood Pressure of Anesthetized Cats[a]

| Compound[b] | Mean Blood Pressure (mm. Hg ± *SE*) Control | After Propranolol | Mean Decrease in Blood Pressure (mm. Hg ± *SE*) | % Decrease |
|---|---|---|---|---|
| *dl*-Propranolol | 100.4 ± 10.3 | 70.5 ± 9.9[c] | 29.9 ± 6.7[d] | 29.8 |
| *d*-Propranolol | 90.3 ± 6.4 | 72.1 ± 3.9[c] | 18.2 ± 3.7 | 20.2 |

[a] $N = 11$. [b] 0.5 mg./0.1 ml. CSF, IVT. [c] $p < 0.05$ compared with controls (paired *t* test). [d] Not significant when compared with *d*-propranolol.

## RESULTS

**Effect of Intraventricular Propranolol on Blood Pressure and Heart Rate of Anesthetized Cats**—The intraventricular (IVT) administration of *d*- or *dl*-propranolol produced significant hypotensive responses which are summarized in Table I. Reflexogenic tachycardia in response to the hypotensive effect of propranolol did not occur, but there was a slight but not statistically significant decrease in heart rate (Table II). Although the degree of the hypotensive response to *dl*-propranolol was greater than that produced by the *d*-isomer, there was no statistically reliable difference between the two hypotensive responses. There was, however, a significant difference between *d*- and *dl*-propranolol in the reduction in heart rate produced. The spinal cord of each animal was transected at the C-2 level to ensure that the observed hypotensive response to IVT-administered propranolol was due to a central component; after the blood pressure had stabilized, the experiment was repeated. Neither compound elicited an effect following spinal transection. These data suggest that a portion of the hypotensive response to propranolol is of central origin and may be independent of β-adrenergic receptor blocking activity.

**Effect of Central Reserpinization on Central Hypotensive Response to Propranolol**—To ascertain the role of endogenous brain amines in the central hypotensive component of propranolol, the compounds were administered IVT to anesthetized cats 24 hr. after administration of reserpine into the lateral ventricle. The data, summarized in Tables III and IV, show that central reserpine pretreatment not only blocked the central hypotensive component previously elicited by both *d*- and *dl*-propranolol but also converted the response to a pressor effect. Whereas propranolol produced a decrease in heart rate in anesthetized nonreserpinized cats, the effect after reserpine was a mild increase in heart rate. These data suggest that the central hypotensive component elicited by both *d*- and *dl*-propranolol is dependent on the presence of central amine stores and a functional sympathetic cardiovascular component. Figure 1 presents a comparison of the effects of IVT propranolol in reserpinized and nonreserpinized anesthetized cats.

**Table II**—Effect of *d*- and *dl*-Propranolol on Heart Rate of Anesthetized Cats[a]

| Compound[b] | Mean Heart Rate/min. ± *SE* Control | After Propranolol | Mean Decrease in Heart Rate/min. ± *SE* | % Decrease |
|---|---|---|---|---|
| *dl*-Propranolol | 175.5 ± 21.5 | 150.9 ± 16.2 | 24.5 ± 7.6[c] | 14.0 |
| *d*-Propranolol | 160.5 ± 15.2 | 158.2 ± 14.7 | 2.3 ± 1.2 | 1.4 |

[a] $N = 11$. [b] 0.5 mg./0.1 ml. CSF, IVT. [c] Significant when compared with *d*-propranolol.

Table III—Effect of Propranolol on Blood Pressure of Anesthetized Cats after "Central Reserpinization"

| Compound[a] | Mean Blood Pressure (mm. Hg ± *SE*) Control | After Propranolol | Mean Increase in Blood Pressure (mm. Hg ± *SE*) | % Increase |
|---|---|---|---|---|
| *dl*-Propranolol ($N = 6$) | 52.2 ± 6.4 | 65.5 ± 3.0 | 13.3 ± 9.2 | 23.8 |
| *d*-Propranolol ($N = 8$) | 47.9 ± 7.2 | 63.0 ± 7.6 | 15.1 ± 7.0 | 24.0 |

[a] 0.5 mg./0.1 ml. CSF, IVT.

**Effect of Central Reserpinization on Brain and Cardiac Norepinephrine Stores**—To ascertain whether a functional central sympathectomy, which previous investigators have shown requires a 90% depletion of brain norepinephrine (35–38), had been achieved, 10 adult cats were pretreated IVT with reserpine 24 hr. before sacrifice. The brain was sectioned and analyzed as previously described, and the results of these assays are summarized in Table V. Every section of the brain analyzed showed at least a 90% depletion in the level of norepinephrine; however, cardiac norepinephrine stores were reduced by only 75%. These results confirm those reported by previous investigators for the IVT administration of 500 mcg. of reserpine 24 hr. prior to sacrifice (42–44).

**Effect of IVT Perfusion with Propranolol on Regional Distribution of Brain Epinephrine and Norepinephrine**—Since *dl*-propranolol has been reported to cause a decrease in brain norepinephrine with a simultaneous increase in cardiac norepinephrine, the effect was investigated in light of the central propranolol component described previously, possibly to correlate it with the hypotensive response. Data on the regional distribution of brain epinephrine and norepinephrine following 1 hr. IVT perfusion with either *d*- or *dl*-propranolol are summarized in Tables VI and VII. These data show that both the *d*- and *dl*-propranolol produced an increase in the level of epinephrine in the various brain regions with one exception. *dl*-Propranolol produced an 11% decrease in the epinephrine level of the diencephalon along with a slight decrease in the level of norepinephrine, although neither amounted to a significant depletion. In all other areas, *dl*-propranolol increased epinephrine content in varying degrees up to 125% in the medulla; however, only in the medulla ($p < 0.0005$), pons ($p < 0.005$), and telencephalon ($p < 0.025$) were these increases statistically significant. The level of norepinephrine was consistently reduced after *dl*-propranolol perfusion, with the effect being greatest in the medulla (32%); however, there was a 22% increase in norepinephrine ($p < 0.01$) in the telencephalon. The reduction in norepinephrine level in the pons ($p < 0.05$) and medulla ($p < 0.05$) proved to be statistically significant.

The epinephrine level was increased in each region of the brain following perfusion with *d*-propranolol, with a maximum of 167% in the medulla. The increase in epinephrine proved to be statistically reliable in the medulla ($p < 0.005$), pons ($p < 0.005$), mesencephalon ($p < 0.05$), and telencephalon ($p < 0.025$). The level of norepinephrine increased in the mesencephalon, diencephalon, and telencephalon but decreased in the medulla, pons, and cerebellum; however, the changes noted in any one region fell short of statistical reliability. The results of perfusing with either *d*- or *dl*-propranolol were parallel in both direction and magnitude of change, with the exception of the mesencephalon and diencephalon.

Table IV—Effect of Propranolol on Heart Rate of Anesthetized Cats after "Central Reserpinization"

| Compound[a] | Mean Heart Rate/min. ± *SE* Control | After Propranolol | Mean Increase in Heart Rate/min. ± *SE* | % Increase |
|---|---|---|---|---|
| *dl*-Propranolol ($N = 6$) | 115.0 ± 6.2 | 119.2 ± 10.8 | 4.2 ± 3.0 | 3.5 |
| *d*-Propranolol ($N = 8$) | 123.7 ± 5.9 | 132.5 ± 8.3 | 8.8 ± 2.1 | 6.7 |

[a] 0.5 mg./0.1 ml. CSF, IVT.

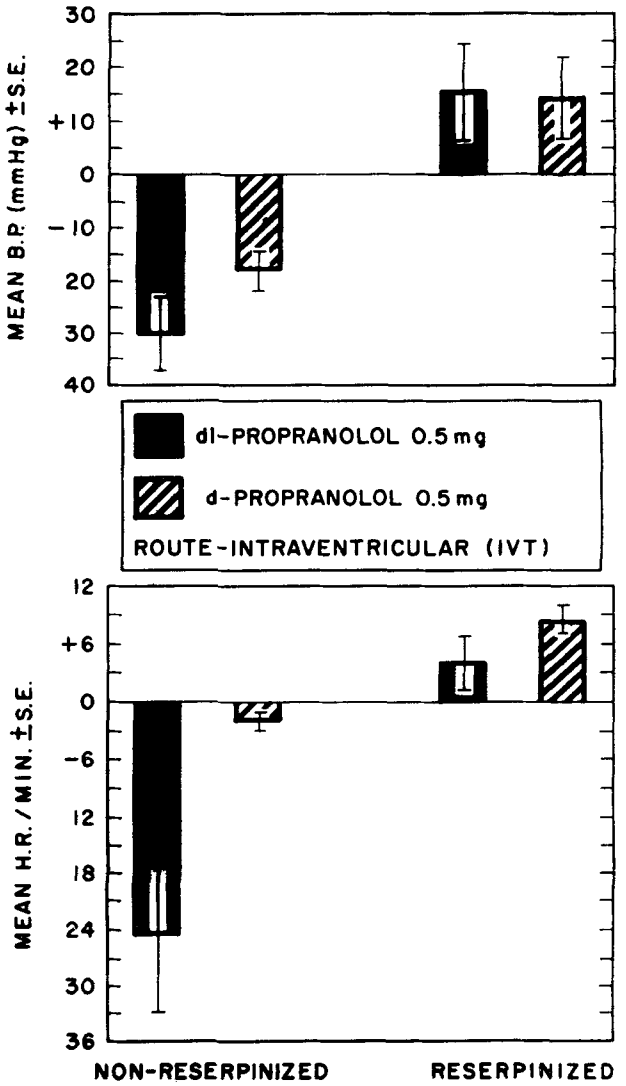


**Figure 1**—*Effect of "central reserpinization" (500 mcg. reserpine, IVT, 24 hr. prior to experiment) on the blood pressure and heart rate response to propranolol.*

Masuoka and Hansson (13) have studied the CNS distribution of $^{14}C$-labeled propranolol in rats and have found that propranolol is highly concentrated in those areas corresponding to the regions where the greatest changes in catecholamine levels have been found: telencephalon, mesencephalon, pons, and medulla. These areas showed the highest and most prolonged concentration of the labeled propranolol. There have been no reports to date on the uptake and distribution of $^{14}C$-labeled propranolol in the cat.

The IVT perfusion with either *d*- or *dl*-propranolol resulted in a significant hypotensive response. This response was of a similar

Table V—Effect of "Central Reserpinization" on Regional Distribution of Brain Norepinephrine[a]

| Region | Control[b] | Reserpinized[b] | % of Control |
|---|---|---|---|
| Telencephalon | 0.248 ± 0.01 | 0.0240 | 9.7 |
| Diencephalon | 0.416 ± 0.05 | 0.0217 | 5.2 |
| Mesencephalon | 0.359 ± 0.04 | 0.0180 | 5.0 |
| Cerebellum | 0.147 ± 0.01 | 0.0136 | 9.3 |
| Pons | 0.449 ± 0.02 | 0.0449 | 10.0 |
| Medulla | 0.299 ± 0.03 | 0.0102 | 3.4 |

[a] Expressed as mcg./g. tissue, wet weight; mean ± *SE*. [b] $N = 10$.

**Table VI**—Effect of IVT Perfusion with *d*-Propranolol[a] on Regional Distribution of Brain Epinephrine[b] and Norepinephrine[b]

| Region | Control[c] | | Perfused[c] | | % Change | |
|---|---|---|---|---|---|---|
| | Epinephrine | Norepinephrine | Epinephrine | Norepinephrine | Epinephrine | Norepinephrine |
| Medulla | 0.012 ± 0.001 | 0.372 ± 0.051 | 0.032 ± 0.001 | 0.280 ± 0.021 | +167 | −25 |
| Pons | 0.009 ± 0.001 | 0.431 ± 0.023 | 0.017 ± 0.001 | 0.394 ± 0.008 | +89 | −9 |
| Cerebellum | 0.024 ± 0.001 | 0.201 ± 0.011 | 0.026 ± 0.002 | 0.189 ± 0.010 | +8 | −6 |
| Mesencephalon | 0.012 ± 0.001 | 0.308 ± 0.024 | 0.016 ± 0.001 | 0.316 ± 0.032 | +33 | +3 |
| Diencephalon | 0.028 ± 0.005 | 0.358 ± 0.043 | 0.030 ± 0.001 | 0.398 ± 0.009 | +7 | +11 |
| Telencephalon | 0.011 ± 0.001 | 0.162 ± 0.006 | 0.013 ± 0.001 | 0.182 ± 0.007 | +18 | +12 |

[a] 0.5 mg./0.1 ml. at 0.1 ml./min. for 60 min. [b] Expressed as mcg./g. tissue, wet weight; mean ± *SE*. [c] $N = 4$.

**Table VII**—Effect of IVT Perfusion with *dl*-Propranolol[a] on Regional Distribution of Brain Epinephrine[b] and Norepinephrine[b]

| Region | Control[c] | | Perfused[c] | | % Change | |
|---|---|---|---|---|---|---|
| | Epinephrine | Norepinephrine | Epinephrine | Norepinephrine | Epinephrine | Norepinephrine |
| Medulla | 0.012 ± 0.001 | 0.372 ± 0.051 | 0.027 ± 0.001 | 0.255 ± 0.011 | +125 | −32 |
| Pons | 0.009 ± 0.001 | 0.431 ± 0.023 | 0.016 ± 0.001 | 0.363 ± 0.014 | +78 | −16 |
| Cerebellum | 0.024 ± 0.001 | 0.201 ± 0.011 | 0.025 ± 0.005 | 0.199 ± 0.010 | +4 | −1 |
| Mesencephalon | 0.012 ± 0.001 | 0.308 ± 0.024 | 0.013 ± 0.001 | 0.268 ± 0.017 | +8 | −13 |
| Diencephalon | 0.028 ± 0.005 | 0.358 ± 0.043 | 0.025 ± 0.002 | 0.356 ± 0.011 | −11 | −1 |
| Telencephalon | 0.011 ± 0.001 | 0.162 ± 0.006 | 0.013 ± 0.001 | 0.198 ± 0.010 | +18 | +22 |

[a] 0.5 mg./1.0 ml. CSF at 0.1 ml./min. for 60 min. [b] Expressed as mcg./g. tissue, wet weight; mean ± *SE*. [c] $N = 4$.

magnitude to that seen previously with single IVT injections and persisted through the entire perfusion period. This hypotensive response also was devoid of a concomitant tachycardia. A comparison of the hypotensive response from *d*- and *dl*-propranolol perfusion is summarized in Fig. 2.

## DISCUSSION

Many reports have noted a hypotensive effect of propranolol. This response may occur during the acute administration of the compound in which the fall in blood pressure is usually mediated by a decrease in cardiac output (4–6). The acute hemodynamic response to parenterally administered propranolol has been shown to differ from that observed during prolonged administration, because the decrease in cardiac output observed upon acute administration is absent during chronic administration (4, 45). The results of the present studies utilizing the IVT administration of *dl*-propranolol have shown that propranolol can produce a hypotensive response *via* central mechanisms. The hypotensive response produced was statistically significant and was devoid of a concomitant tachycardia, which may suggest the involvement of vasomotor regulatory centers. The results, however, do not rule out the possibility of a vagal action producing the decrease in heart rate and the absence of a concomitant reflexogenic tachycardia.

Several investigators have presented evidence to suggest that many of the effects noted with propranolol, including those on the CNS, are independent of the β-adrenergic blocking activity of the compound (7–9). This also has been shown to be true with the hypotensive response associated with prolonged oral administration of propranolol (4, 31). The present study involved the use of *d*-propranolol, which has been reported to have only 1–2% of the β-blocking activity of the racemic mixture, to differentiate between the hypotensive and β-blocking activity of propranolol (2, 46, 47). The findings suggest that the central hypotensive response induced by *dl*-propranolol is not dependent on β-adrenergic blocking activity, since the *d*-isomer also produces a centrally mediated hypotensive response which was not statistically different from that produced by the racemic mixture. Although Gagnon and Melville (48) have shown that the response to isoproterenol is similar after intravenous or IVT administration (consisting of myocardial augmentation and hypotension), there remains speculation regarding the nature of the adrenergic receptors involved in mediating these responses. Thus, although the *d*-isomer of propranolol has been demonstrated to exhibit only 1–2% of the β-adrenergic receptor blocking activity of *d*-propranolol peripherally, this relationship may not hold true centrally. The β-receptorlike property exhibited centrally may not necessarily demonstrate an equivalent sensitivity to β-adrenergic agonists or antagonists as shown peripherally and thus could give a false indication in the differentiation between central and peripheral β-adrenergic functions. Based on present knowledge, however, the evidence suggests that this central hypotensive response is independent of β-adrenergic blocking activity.

The depletion of brain and cardiac norepinephrine produced by IVT reserpine was similar to that previously reported from this laboratory (44). The depletion of brain amines by reserpine was utilized to study the role played by endogenous brain amines in the centrally mediated hypotensive response demonstrated by both *d*- and *dl*-propranolol. These data suggest that either a level of endogenous brain amine exceeding 10% of normal or a functional central sympathetic component is required for the central hypotensive response to propranolol. These data must be evaluated with the knowledge that reserpine does not selectively deplete norepinephrine but rather produces a gross depletion of other biogenic amines as well.

Propranolol has been reported to produce a decrease in brain catecholamines when 10 mg. i.p./kg./day was administered to mice for 4 days. Other investigators, however, have failed to reproduce these effects with propranolol, using the same dose and time schedule (50, 51). The present studies were also undertaken to determine if perfusion of the brain with propranolol would result in an alteration of the catecholamine content of the brain and to investigate the possibility that there may be a change in the epinephrine–norepinephrine balance. Epinephrine has been reported to repre-

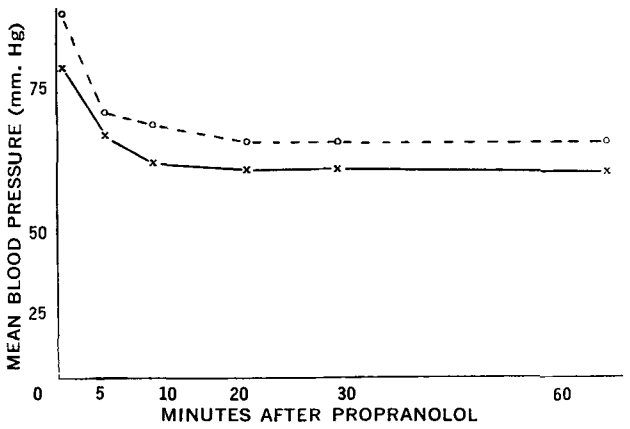


**Figure 2**—*A comparison of the hypotensive response to IVT perfusion of propranolol, 0.5 mg./0.1 ml. CSF, 0.1 ml./min., in anesthetized cats. Key:* ×—×, dl-*propranolol* (N = 4); *and* o--o, d-*propranolol* (N = 4).

sent 4–17% of the total concentration of catecholamines in the brain (52–54). The rapid metabolism and enzymatic synthesis of epinephrine in the brain suggest that this potent amine may function as a neuroregulatory agent (55–60); some investigators have reported epinephrine to be an inhibitor of synaptic transmission within the CNS (61–63). The data presented here show that there is an alteration in the brain levels of both epinephrine and norepinephrine caused by perfusion with propranolol; however, these alterations are not uniform. The great increase in epinephrine within the pons and medulla strongly suggests that amine alterations associated with vasomotor regulatory centers may play a role in the central hypotensive response of prolonged therapy with propranolol. Furthermore, these data reinforce the idea that determining the whole brain concentration of a particular compound is less desirable than assaying individual brain regions, since an increase in one region may compromise a concurrent decrease in another region when assayed as a whole. This apparently led to the aforementioned reports noting both a decrease or no change in the brain level of norepinephrine following propranolol (45, 50, 51).

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