CHAPTER-V

R E S U L T S

I. Experiments in vivo

(1) Antihypertensive action of indapamide

(i) Effect of indapamide on blood pressure of normotensive and hypertensive rats

The blood pressure of normotensive rats was not modified by indapamide but that of hypertensive rats was reduced ($P < 0.01$) (Fig.1).

(ii) Effect of chronic treatment with indomethacin on the blood pressure of indapamide treated normotensive and hypertensive rats

(a) Indomethacin treatment had no effect on the blood pressure of normotensive and indapamide treated normotensive rats (Fig.1).

(b) Indomethacin treatment did not modify the blood pressure of hypertensive rats; it also did not reverse or potentiate the hypotensive effect of indapamide (Fig.1).

(iii) Effect of chronic treatment with verapamil on the blood pressure of indapamide treated normotensive and hypertensive rats

(a) Verapamil treatment had no effect on the blood pressure of normotensive rats but reduced ($P < 0.05$) that of hypertensive rats (Fig.2).

Fig. 1

Effect of oral treatment with indapamide and indomethacin on the blood pressure of normotensive (left hand panel) and hypertensive rats (right hand panel). Open bars (☐) represent blood pressure in untreated rats, stippled bars (▦) in indomethacin treated rats, black bars (■) in indapamide treated rats and hatched bars (▨) in indomethacin + indapamide treated rats. Vertical lines denote S.E.M. (n = 5 for each observation). The level of significance is indicated by asterisks. ** ($P < 0.01$) in relation to hypertensive control and * ($P < 0.05$) in relation to indomethacin treated hypertensive rats.

FIG: 1

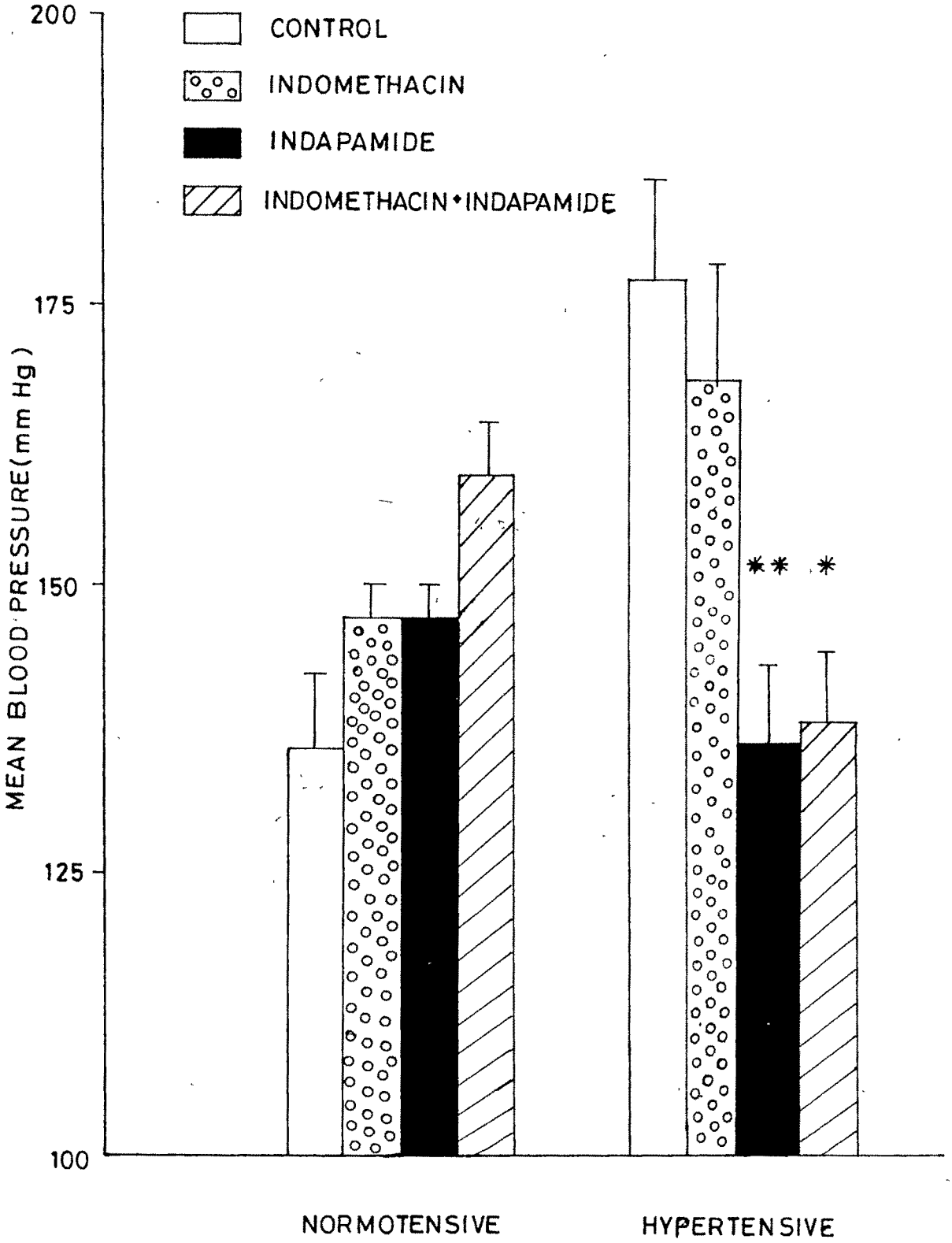
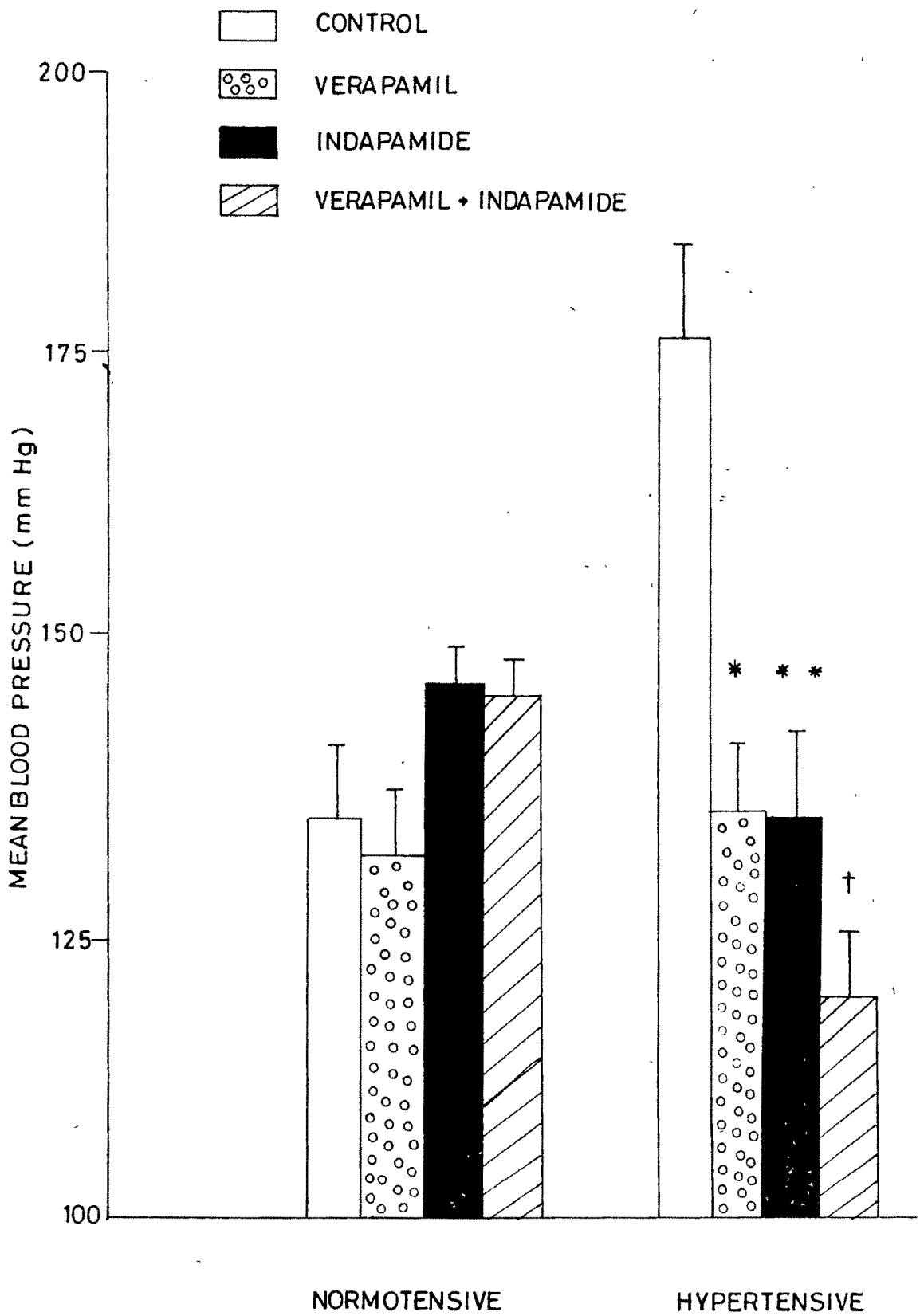

200
175
150
125
100
MEAN BLOOD PRESSURE (mm Hg)
CONTROL
INDOMETHACIN
INDAPAMIDE
INDOMETHACIN + INDAPAMIDE
**
*
NORMOTENSIVE
HYPERTENSIVE

Fig. 2

Effect of verapamil on the blood pressure of indapamide treated normotensive (left hand panel) and hypertensive rats (right hand panel). Open bars (☐) represent blood pressure in untreated rats, stippled bars (▫) in verapamil treated rats, black bars (■) in indapamide treated rats and hatched bars (▨) in verapamil + indapamide treated rats. Vertical lines denote S.E.M. ($n = 6$ to 7 for each observation). The level of significance is indicated by asterisks ($*P < 0.05$ and $** P < 0.01$) in relation to hypertensive control and by † in relation to verapamil treated hypertensive rats.

FIG: 2


CONTROL
VERAPAMIL
INDAPAMIDE
VERAPAMIL + INDAPAMIDE
200
175
150
125
100
MEAN BLOOD PRESSURE (mm Hg)
*
*
*
†
NORMOTENSIVE
HYPERTENSIVE

(b) Verapamil did not modify the blood pressure of indapamide treated normotensive rats while it further reduced ($P < 0.05$) that of indapamide treated hypertensive rats (Fig.2).

(iv) Comparison of the antihypertensive effect of hydrallazine and indapamide

(a) Hydrallazine treatment reduced ($P < 0.01$) the blood pressure of hypertensive rats; there was no further lowering of blood pressure when hydrallazine and indapamide treatment were given together in hypertensive rats (Fig.3).

(2) Action of indapamide on heart rate

(i) Effect of indapamide on the heart rate of normotensive and hypertensive rats

Indapamide had no effect on the heart rate of normotensive rats but increased ($P < 0.05$) the heart rate of hypertensive rats (Fig.4).

(ii) Effect of indomethacin on the heart rate of indapamide treated normotensive and hypertensive rats

Indomethacin did not modify the heart rate of normotensive and indapamide treated normotensive rats (Fig.4) and also had no effect on heart rate of hypertensive rats. However, indomethacin prevented

Fig.3

Effect of indapamide on the blood pressure of chronic hydrallazine treated hypertensive rats. Open bars (☐) represent the blood pressure in untreated hypertensive rats, stippled bars (▫) in hydrallazine treated rats, black bars (■) in indapamide treated rats and hatched bars (▨) in hydrallazine + indapamide treated rats. Vertical lines denote S.E.M. (n = 5 to 6 for each observation). The level of significance ($P < 0.01$) is indicated by asterisks.

FIG: 3

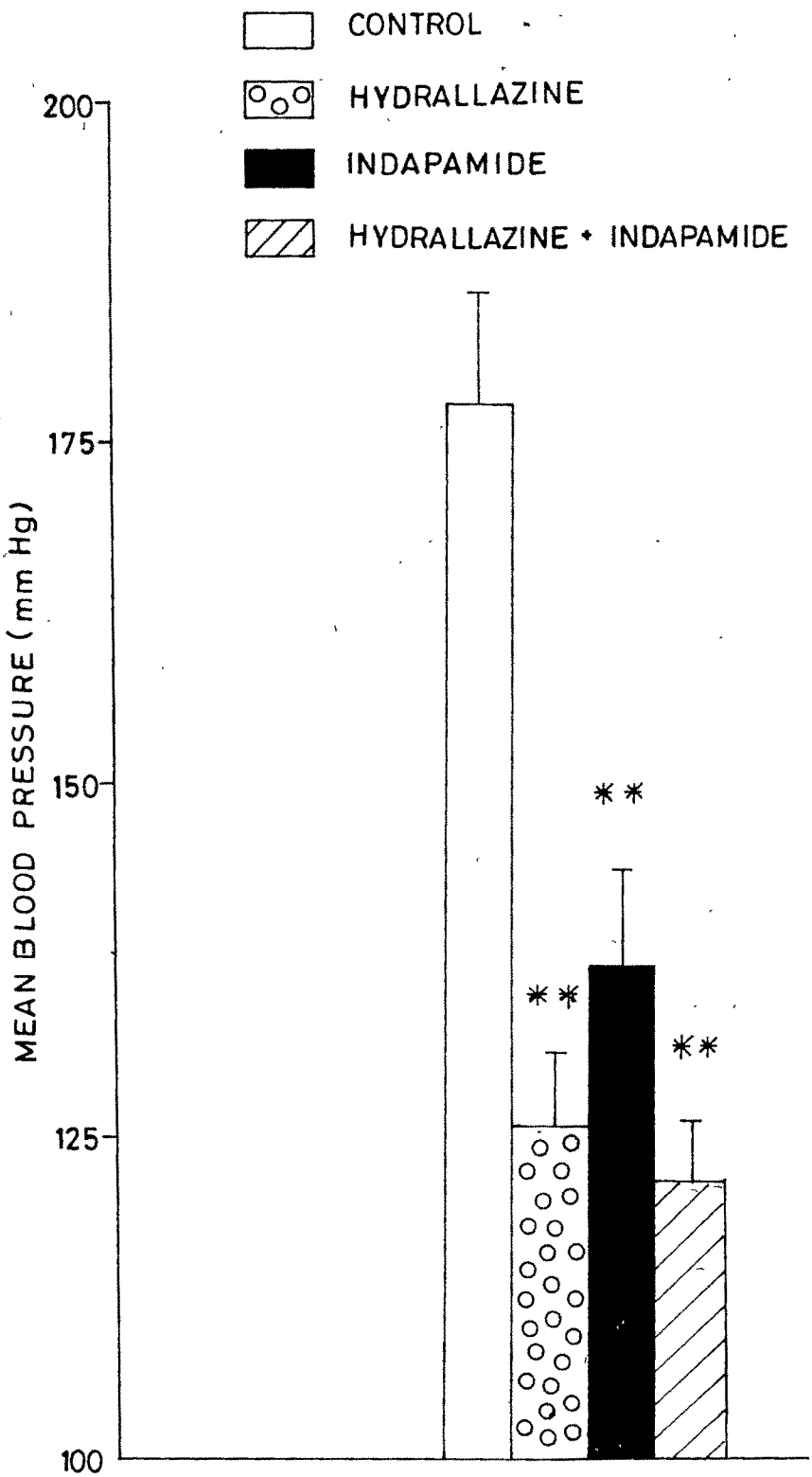
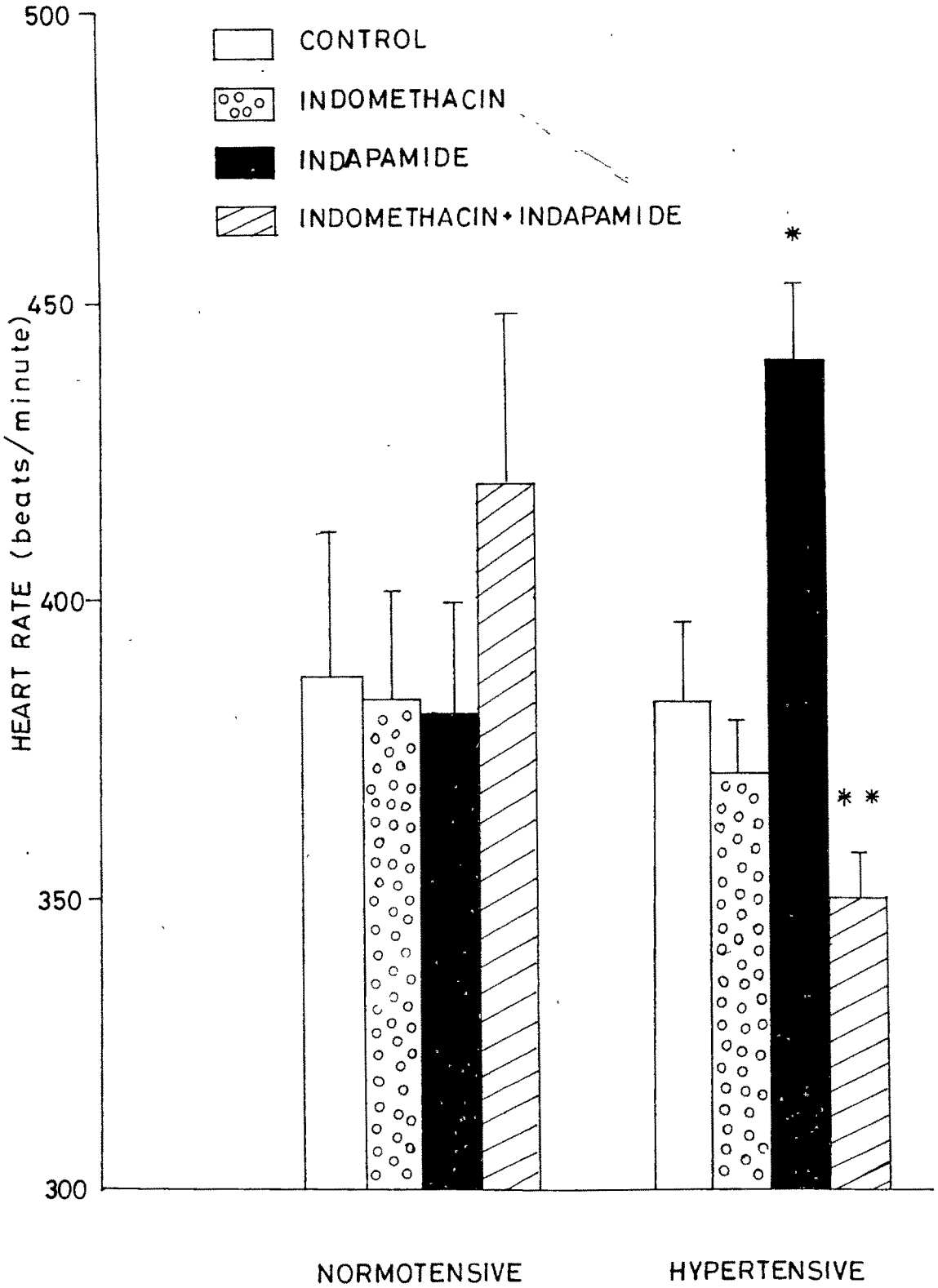

CONTROL
HYDRALLAZINE
INDAPAMIDE
HYDRALLAZINE + INDAPAMIDE
MEAN BLOOD PRESSURE (mm Hg)
200
175
150
125
100
**
**
**

Fig. 4

Effect of indapamide and indomethacin on the heart rate of indapamide treated normotensive (left hand panel) and hypertensive rats (right hand panel). Open bars (☐) represent heart rate in untreated rats, stippled bars (▫) in indomethacin treated rats, black bars (■) in indapamide treated rats and hatched bars (▨) in indomethacin + indapamide treated rats. Vertical lines denote S.E.M. (n = 5 to 6 for each observation). The level of significance ($P < 0.05$) is indicated by asterisks * in relation to hypertensive control and ** in relation to indapamide treated hypertensive rats.

FIG: 4


500
450
400
350
300
HEART RATE (beats/minute)
CONTROL
INDOMETHACIN
INDAPAMIDE
INDOMETHACIN + INDAPAMIDE
*
* *
NORMOTENSIVE
HYPERTENSIVE

($P < 0.05$) the increase in heart rate observed after indapamide treatment in hypertensive rats (Fig.4).

(iii) Effect of verapamil on the heart rate of indapamide treated normotensive and hypertensive rats

(a) Verapamil did not modify the heart rate in normotensive rats but increased ($P < 0.05$) it in indapamide treated normotensive rats (Fig.5).

(b) Verapamil did not modify the heart rate in hypertensive rats but prevented ($P < 0.05$) the increase in heart rate observed after indapamide treatment (Fig.5).

(3) Cardiovascular reactivity to intravenous pressor agents in normotensive and hypertensive rats

(i) Pressor responses to intravenous agonists in indapamide treated normotensive and hypertensive rats

(a) NA, ADR and PE (0.5, 1, 2 ug/kg) produced dose related pressor responses in normotensive, indapamide treated normotensive, hypertensive and indapamide treated hypertensive rats. There was no difference in the reactivity to NA in any of the four groups studied (Fig.6 a,b,c).

Fig.5

Effect of verapamil on the heart rate of indapamide treated normotensive (left hand panel) and hypertensive rats (right hand panel). Open bars () represent the heart rate in untreated rats, stippled bars () in verapamil treated rats, black bars () in indapamide treated rats and hatched bars () in verapamil + indapamide treated rats. Vertical lines denote S.E.M.(n = 6 to 7 for each observation). The level of significance ($P < 0.05$) is indicated by asterisks * in relation to control and ** in relation to indapamide treated hypertensive rats.

FIG:5

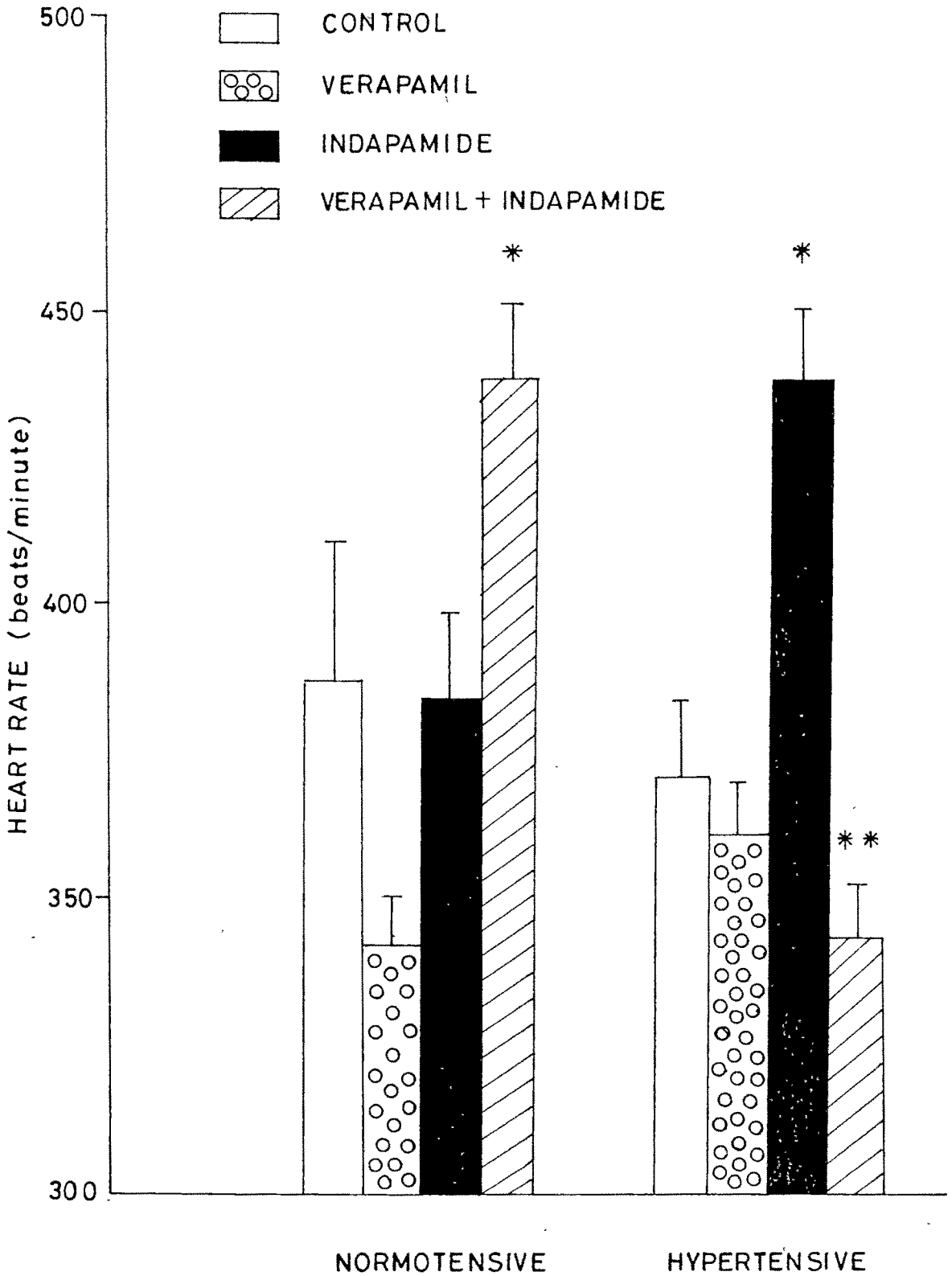
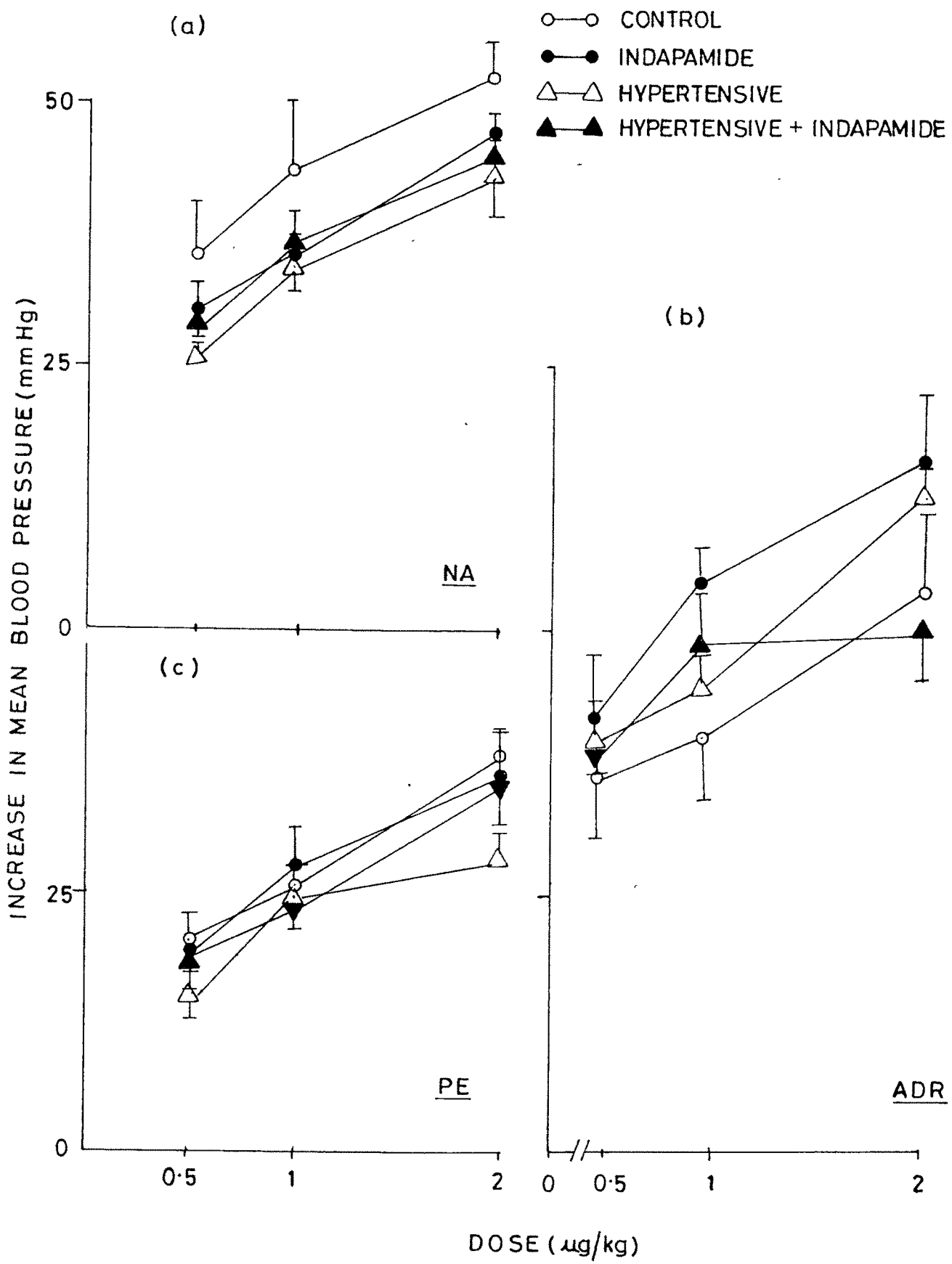

500
450
400
350
300
HEART RATE (beats/minute)
CONTROL
VERAPAMIL
INDAPAMIDE
VERAPAMIL + INDAPAMIDE
*
*
* *
NORMOTENSIVE
HYPERTENSIVE

Fig.6

Effect of indapamide on the pressor responses to i.v. NA (a), ADR (b) and PE (c) in normotensive and hypertensive rats. The abscissa depicts the dose of NA and the ordinate increase in mean blood pressure. Open circles (o—o) represent pressor responses in normotensive rats and closed circles (●—●) in indapamide treated normotensive rats, open triangles (△—△) in hypertensive rats and closed triangles (▲—▲) in indapamide treated hypertensive rats. Vertical lines denote S.E.M. (n = 5 to 6 for each observation).

FIG:6


(a)
CONTROL
INDAPAMIDE
HYPERTENSIVE
HYPERTENSIVE + INDAPAMIDE
50
25
0
INCREASE IN MEAN BLOOD PRESSURE (mm Hg)
NA
(b)
(c)
PE
ADR
25
0
0·5
1
2
0
0·5
1
2
DOSE (µg/kg)

(b) TYR (100, 200 ug/kg) produced pressor responses in normotensive, indapamide treated normotensive, hypertensive and indapamide treated hypertensive rats. There was no difference in the reactivity to TYR in any of the four groups studied (Fig.7).

(c) ANG (25, 50, 100 ng/kg) produced dose related pressor responses in normotensive, indapamide treated normotensive, hypertensive and indapamide treated hypertensive rats. There was no difference in the reactivity to ANG in any of the four groups studied (Fig.8).

(ii) Effect of indomethacin on the reactivity to various pressor agents in indapamide treated normotensive and hypertensive rats

(a) Reactivity to NA: Indapamide alone did not modify reactivity to NA in normotensive and hypertensive rats (Fig.9a,b). Indomethacin did not modify pressor responses to NA in normotensive rats but potentiated them in indapamide treated normotensive rats (Fig.9a). Indomethacin also potentiated the pressor responses to NA in hypertensive rats. The potentiating effect of indomethacin was blocked after indapamide treatment (Fig.9b).

Fig.7

Effect of indapamide on the pressor responses to i.v. TYR in normotensive (left hand panel) and hypertensive rats (right hand panel). Ordinate depicts the increase in mean blood pressure and figures below the histograms indicate the dose of TYR. Open bars (☐) represent pressor responses in untreated rats and black bars (■) in indapamide treated rats. Vertical lines denote S.E.M. (n = 4).

FIG:7

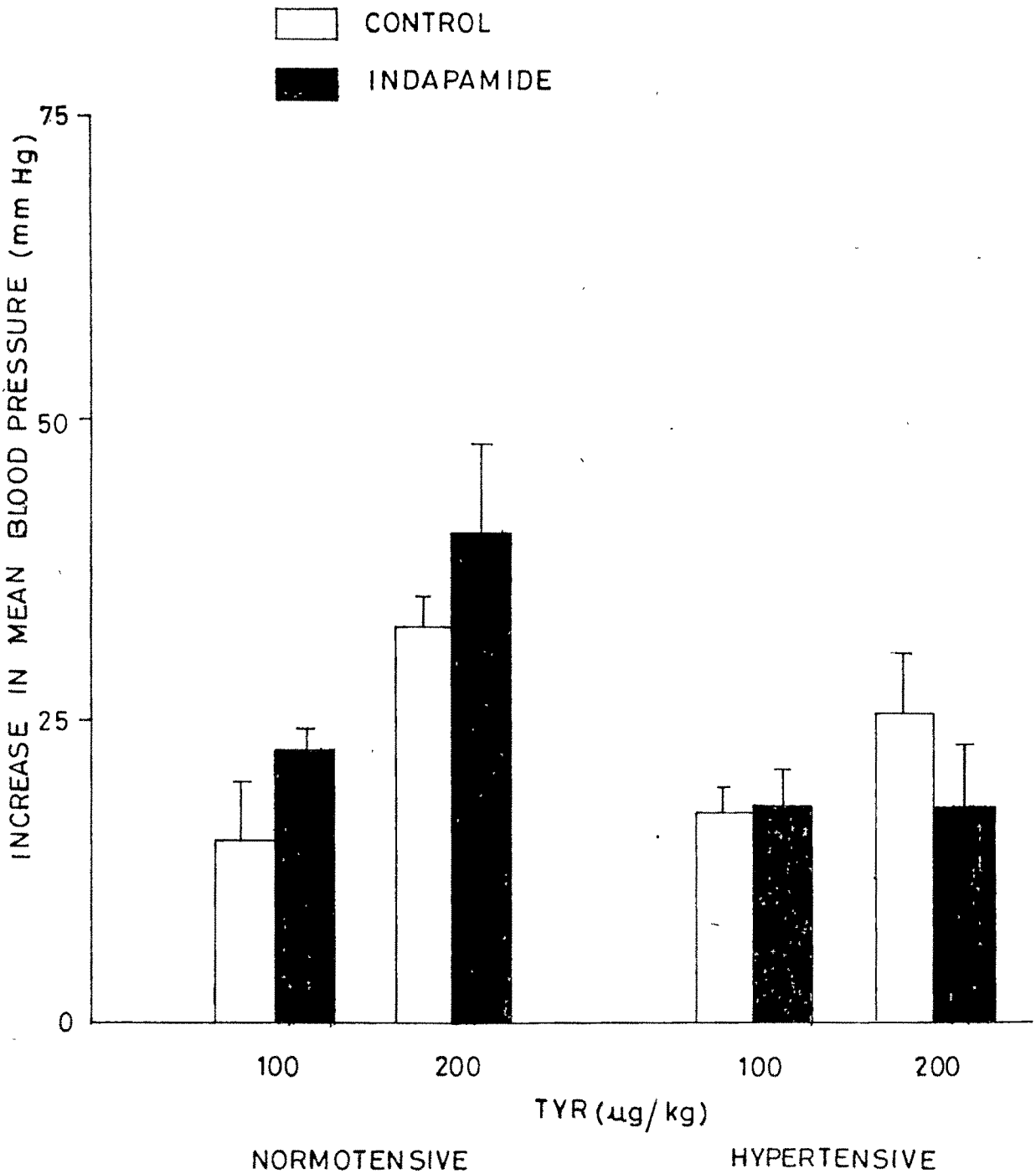

CONTROL
INDAPAMIDE
INCREASE IN MEAN BLOOD PRESSURE (mm Hg)
75
50
25
0
100
200
100
200
TYR (µg/kg)
NORMOTENSIVE
HYPERTENSIVE

Fig. 8

Effect of indapamide on the pressor responses to i.v. ANG in normotensive and hypertensive rats. The abscissa depicts dose of ANG and the ordinate the increase in mean blood pressure. Open circles (o—o) represent pressor responses in normotensive rats, closed circles (●—●) in indapamide treated normotensive rats, open triangles (△—△) in hypertensive rats and closed triangles (▲—▲) in indapamide treated hypertensive rats. Vertical lines denote S.E.M. (n = 3).

FIG: 8

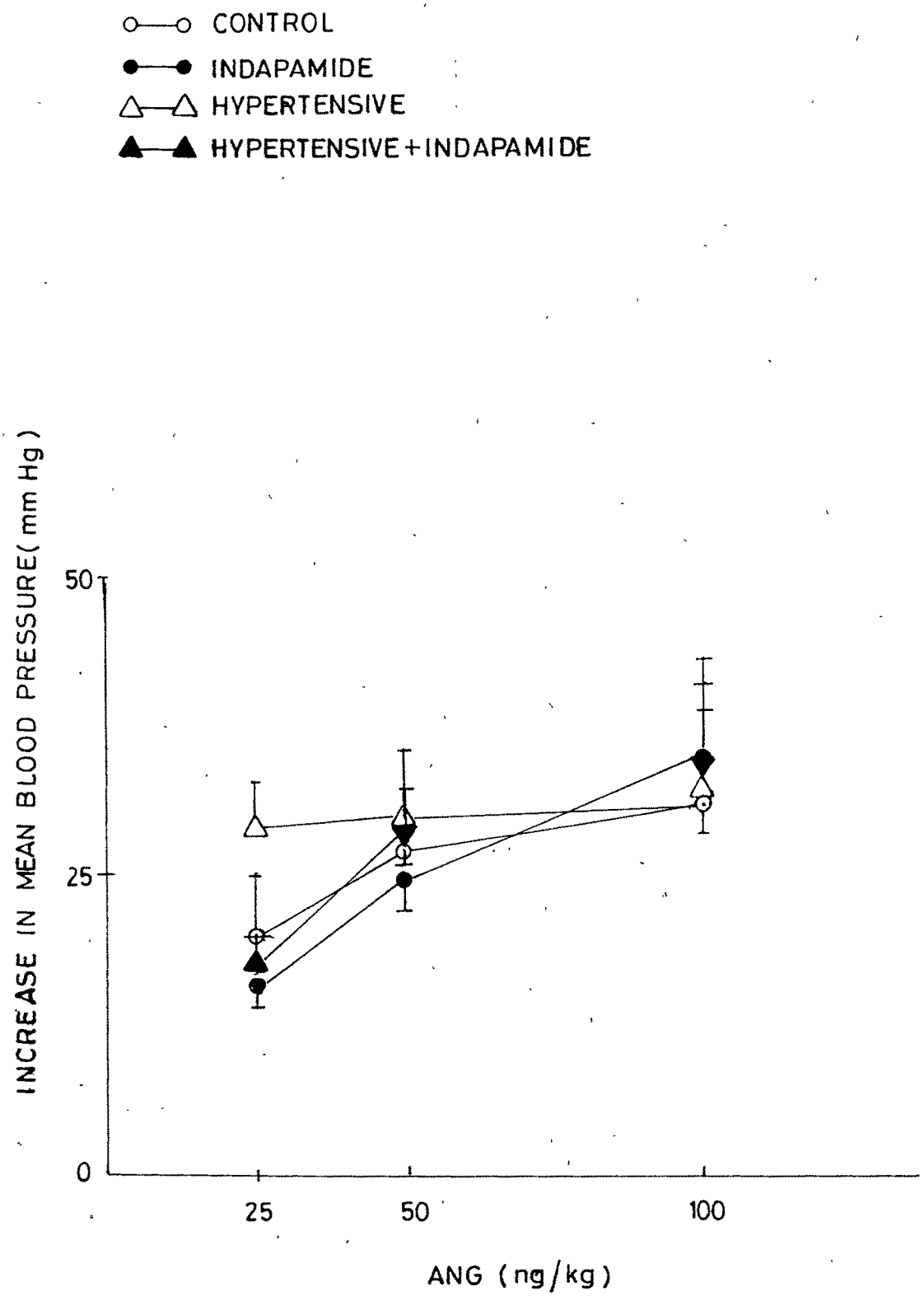
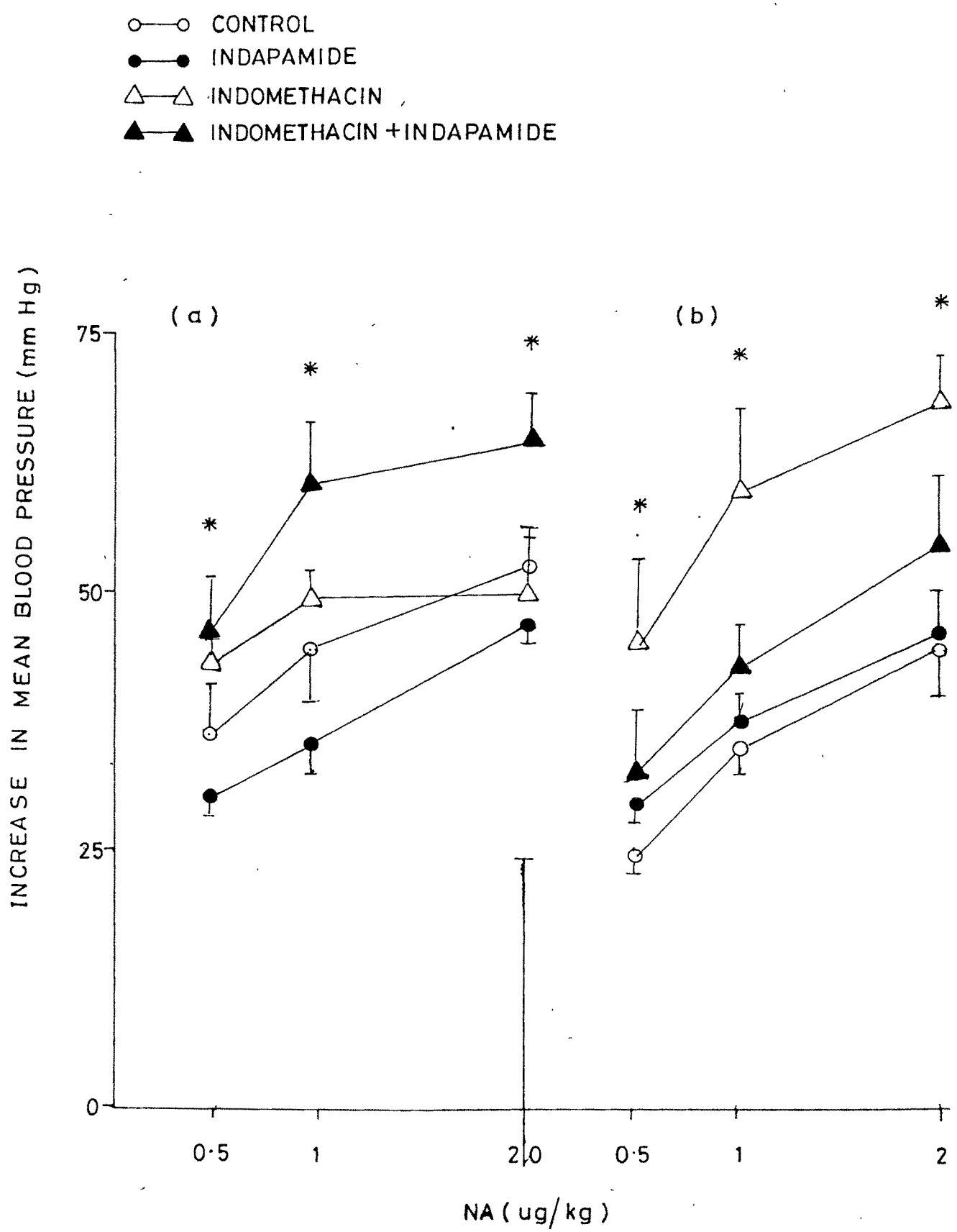

CONTROL
INDAPAMIDE
HYPERTENSIVE
HYPERTENSIVE+INDAPAMIDE
INCREASE IN MEAN BLOOD PRESSURE(mm Hg)
50
25
0
25
50
100
ANG (ng/kg)

Fig.9

Effect of indapamide on the pressor responses to NA in indomethacin treated normotensive rats (a) and hypertensive rats (b). The abscissa depicts dose of NA and ordinate the increase in mean blood pressure. Open circles (o—o) represent responses in control rats, closed circles (●—●) in indapamide treated rats, open triangles(△—△) in indomethacin treated rats and closed triangles (▲—▲) in indomethacin + indapamide treated rats. Vertical lines denote S.E.M. (n = 4 to 6 for each observation). The level of significance ($P < 0.05$) is indicated by asterisk (*).

FIG: 9


CONTROL
INDAPAMIDE
INDOMETHACIN
INDOMETHACIN + INDAPAMIDE
INCREASE IN MEAN BLOOD PRESSURE (mm Hg)
(a)
(b)
75
50
25
0
0·5
1
2·0
0·5
1
2
NA (ug/kg)

(b) Reactivity to ADR: Indomethacin potentiated pressor responses to ADR (2 ug) in normotensive rats but did not modify them in indapamide treated normotensive rats (Fig.10a). Indomethacin potentiated ($P < 0.05$) pressor responses to ADR in hypertensive and indapamide treated hypertensive rats (Fig.10b).

(c) Reactivity to ANG: Indomethacin did not modify pressor responses to ANG in normotensive and indapamide treated normotensive rats (Fig.11a).

Indomethacin potentiated pressor responses to ANG in hypertensive rats, this potentiating effect of indomethacin was blocked after indapamide treatment (Fig.11b).

(iii) Effect of verapamil on the reactivity to various pressor agents in indapamide treated normotensive and hypertensive rats

(a) Reactivity to NA: Pressor responses to NA were not modified by verapamil treatment in normotensive rats but were potentiated in verapamil and indapamide treated normotensive rats (Fig.12a).

Verapamil potentiated pressor responses to NA in hypertensive and indapamide treated

Fig. 10

Effect of indapamide on the pressor responses to i.v. ADR in indomethacin treated normotensive rats (a) and hypertensive rats (b). The abscissa depicts dose of ADR and ordinate increase in mean blood pressure. Open circles (○——○) represent responses in control rats, closed circles (●——●) in indapamide treated rats, open triangles (△——△) in indomethacin treated rats and closed triangles (▲——▲) in indomethacin + indapamide treated rats. Vertical lines denote S.E.M. (n = 4 to 5 for each observation). The level of significance ($P < 0.05$) is indicated by asterisk (*).

FIG: 10

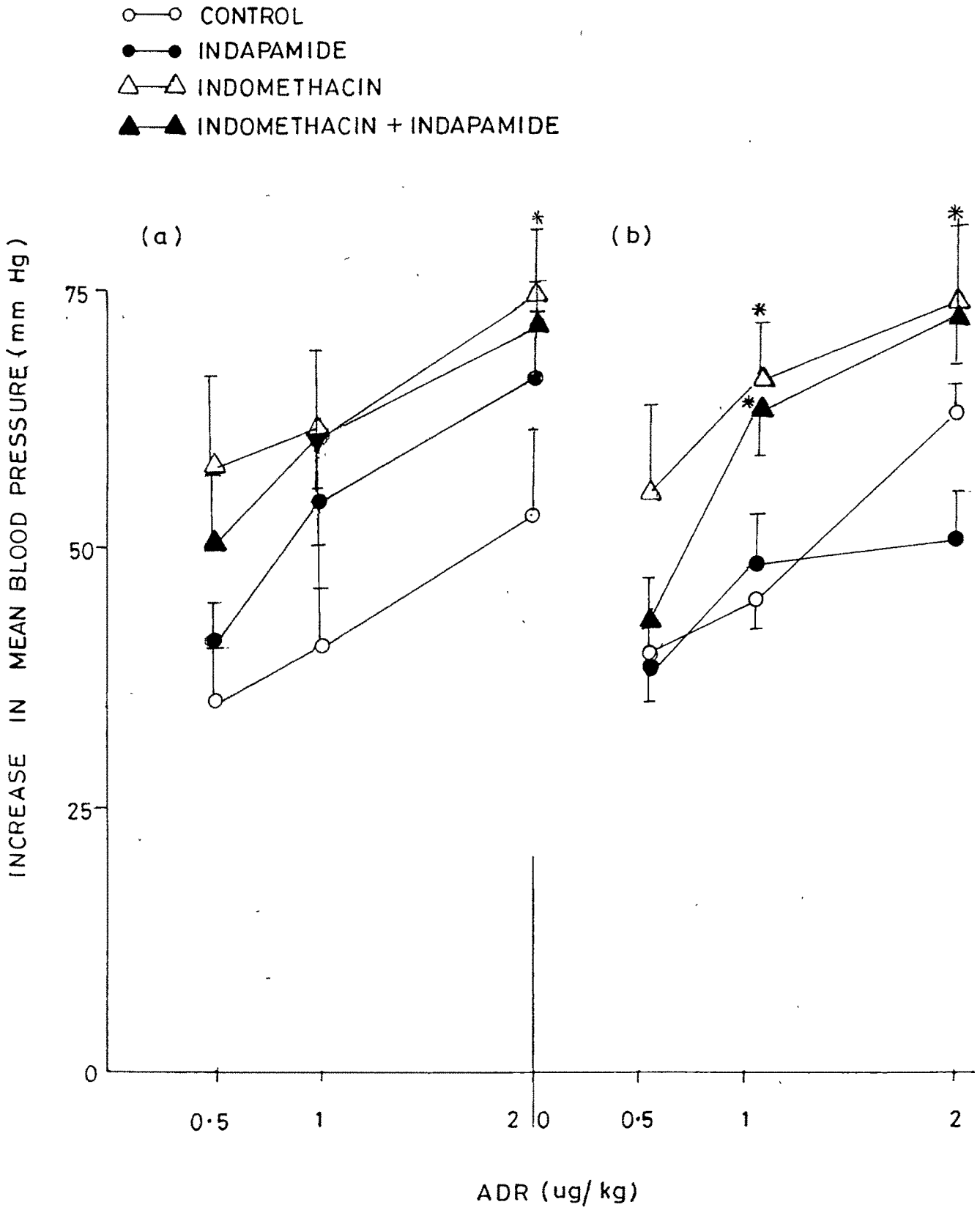

CONTROL
INDAPAMIDE
INDOMETHACIN
INDOMETHACIN + INDAPAMIDE
(a)
(b)
INCREASE IN MEAN BLOOD PRESSURE (mm Hg)
75
50
25
0
0·5
1
2
0
0·5
1
2
ADR (ug/ kg)

Fig. 11

Effect of indapamide on the pressor responses to i.v. ANG in indomethacin treated normotensive rats (a) and hypertensive rats (b). The abscissa depicts doses of ANG and ordinate increase in mean blood pressure. Open circles (○—○) represent responses in control rats, closed circles (●—●) in indapamide treated rats, open triangles (△—△) in indomethacin treated rats and closed triangles (▲—▲) in indomethacin + indapamide treated rats. Vertical lines denote S.E.M. (n = 4 to 6 for each observation). The level of significance ($P < 0.05$) is indicated by asterisk (*).

FIG : 11

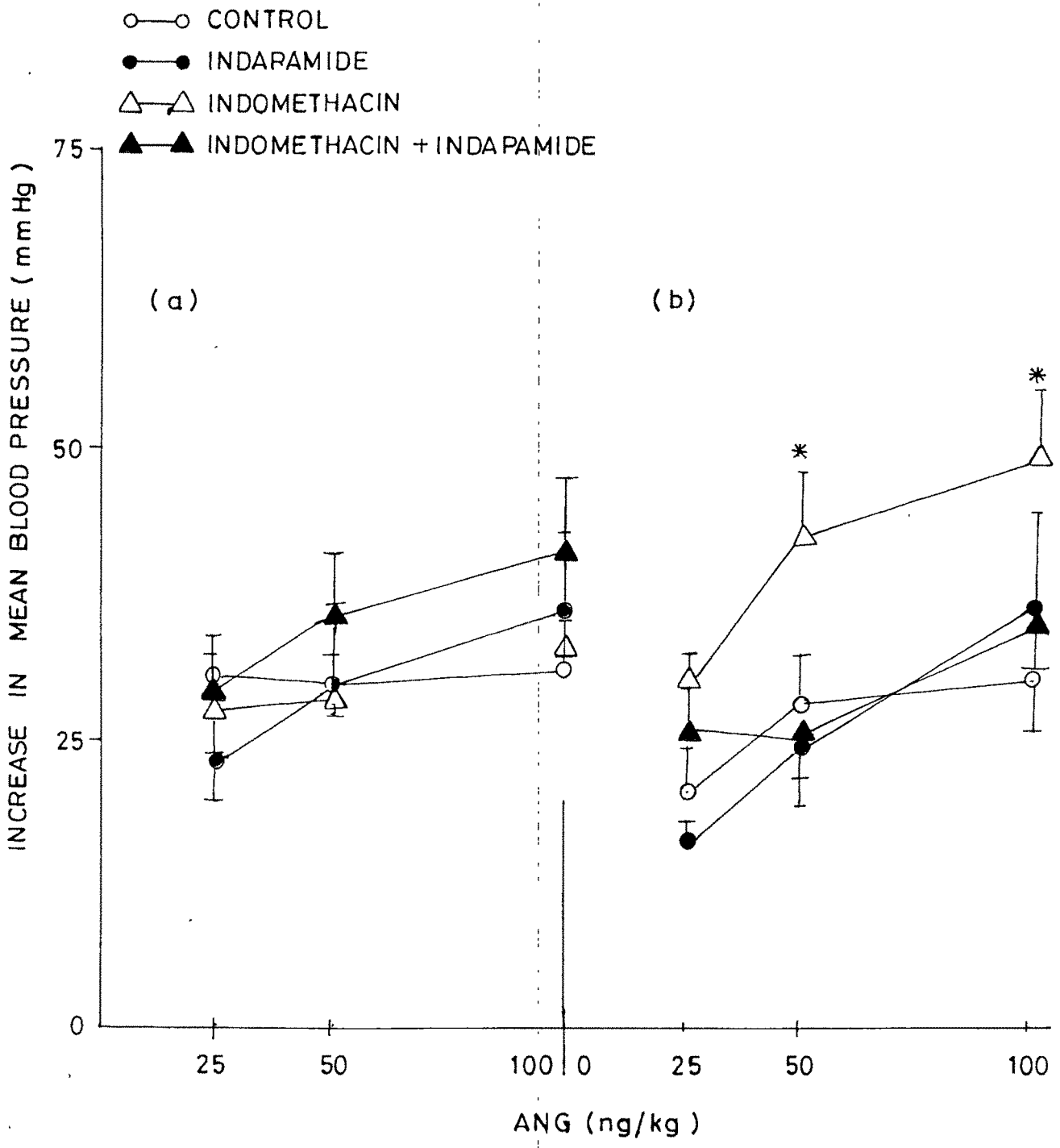
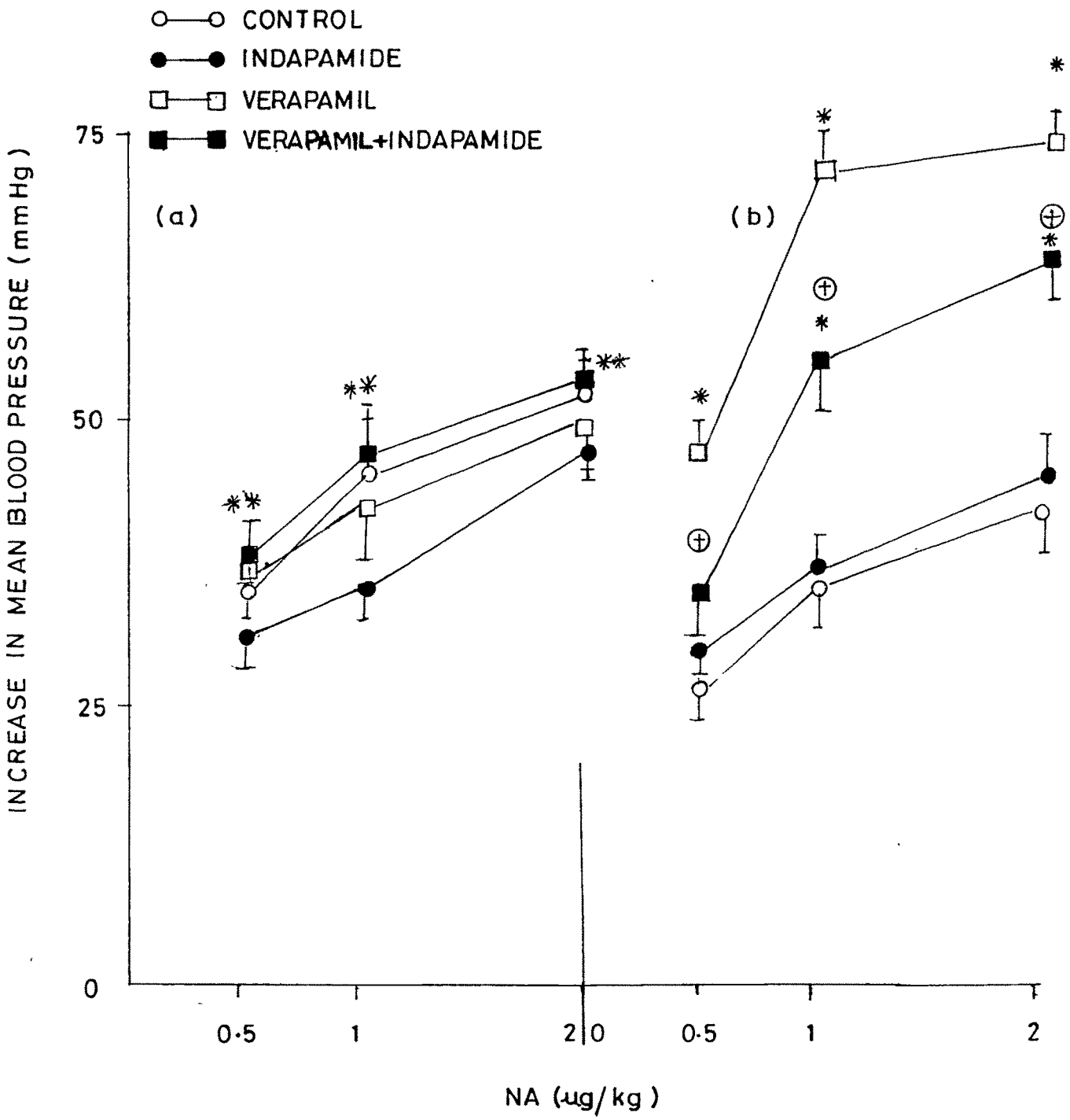

CONTROL
INDAPAMIDE
INDOMETHACIN
INDOMETHACIN + INDAPAMIDE
INCREASE IN MEAN BLOOD PRESSURE (mm Hg)
75
50
25
0
(a)
(b)
*
*
25
50
100
0
25
50
100
ANG (ng/kg)

Fig. 12

Effect of indapamide on the pressor responses to NA in verapamil treated normotensive rats (a) and hypertensive rats (b). The abscissa depicts dose of NA and ordinate increase in mean blood pressure. Open circles (○—○) represent responses in control rats, closed circles (●—●) in indapamide treated rats, open squares (□—□) in verapamil treated rats and closed squares (■—■) in verapamil + indapamide treated rats. Vertical lines denote S.E.M. (n = 4 to 6 for each observation). The level of significance ($P < 0.05$) is indicated by asterisks (*) in relation to control ** ($P < 0.05$) in relation to indapamide treated normotensive rats and by in relation to verapamil treated hypertensive rats.

FIG:12


CONTROL
INDAPAMIDE
VERAPAMIL
VERAPAMIL+INDAPAMIDE
(a)
(b)
INCREASE IN MEAN BLOOD PRESSURE (mmHg)
75
50
25
0
0·5
1
2
0
0·5
1
2
NA (ug/kg)

hypertensive rats; however potentiation was significantly ($P < 0.05$) less in indapamide and verapamil treated hypertensive rats than in those treated with verapamil alone (Fig.12b).

(b) Reactivity to ADR: Pressor responses to ADR were not affected by verapamil treatment in normotensive and indapamide treated normotensive rats (Fig.13a). Verapamil treatment potentiated ($P < 0.05$) pressor response to ADR in hypertensive and indapamide treated hypertensive rats (Fig.13b).

(c) Reactivity to PE: Verapamil potentiated pressor response (1 ug) to PE in normotensive rats which was blocked by indapamide treatment (Fig.14a). Verapamil also potentiated pressor responses to PE in hypertensive rats and this potentiation was not observed in indapamide treated hypertensive rats (Fig.14b).

(d) Reactivity to TYR: Verapamil did not modify pressor responses to tyramine in normotensive and indapamide treated normotensive rats (Fig.15a). The drug potentiated pressor responses to TYR in hypertensive and indapamide treated hypertensive rats (Fig.15b).

Fig. 13

Effect of indapamide on the pressor responses to ADR in chronic verapamil treated normotensive rats (a) and hypertensive rats (b). The abscissa depicts the dose of ADR and ordinate increase in mean blood pressure. Open circles (○—○) represent responses in control rats, closed circles (●—●) in indapamide treated rats, open squares (□—□) in verapamil treated rats and closed squares (■—■) in verapamil + indapamide treated rats. Vertical lines denote S.E.M. (n = 5 to 6 for each observation). The level of significance ($P < 0.05$) is indicated by asterisk (*).

FIG:13

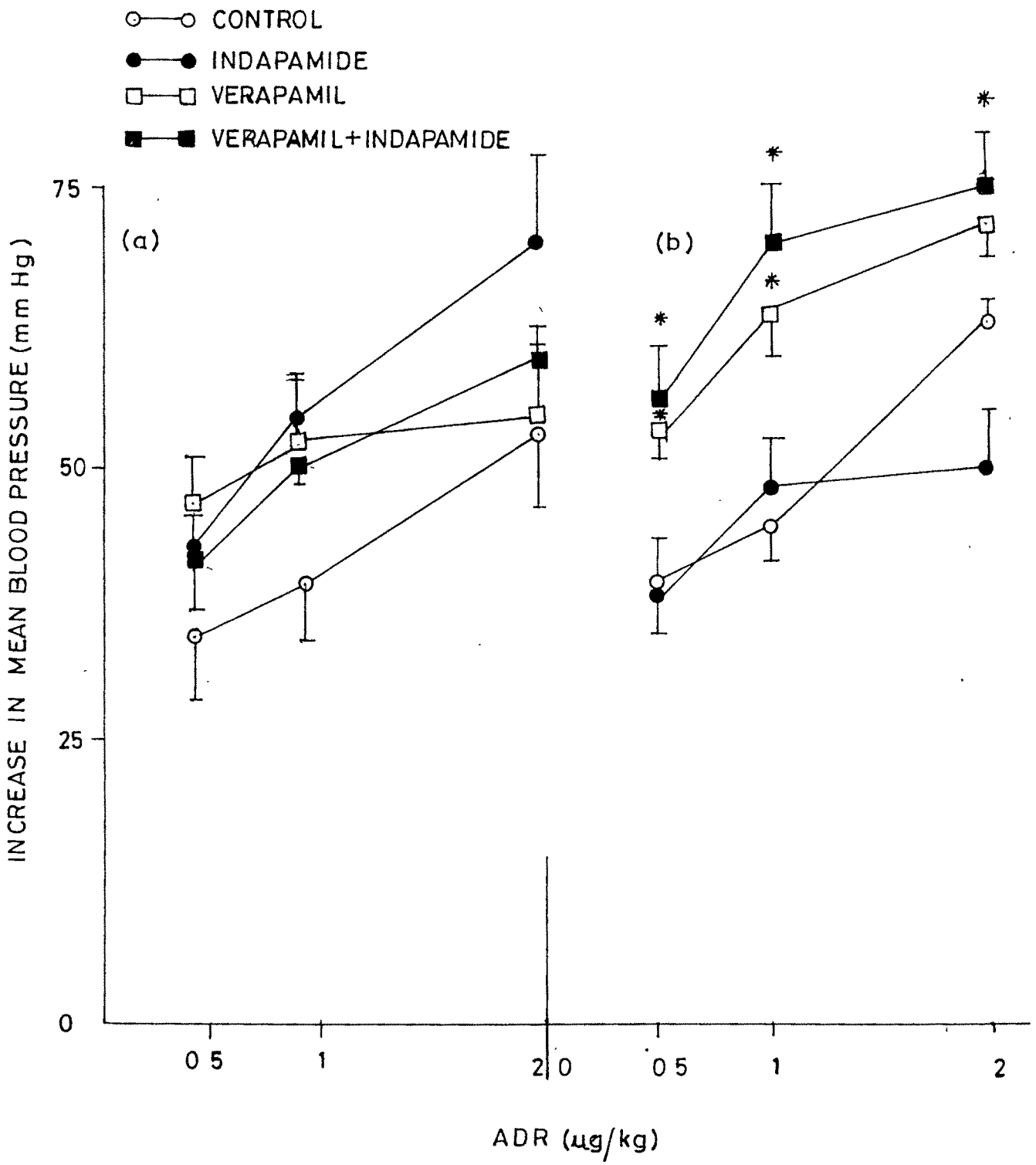

CONTROL
INDAPAMIDE
VERAPAMIL
VERAPAMIL+INDAPAMIDE
(a)
(b)
75
50
25
0
INCREASE IN MEAN BLOOD PRESSURE (mm Hg)
0 5
1
2
0 5
1
2
ADR (µg/kg)

Fig.14

Effect of indapamide on the pressor responses to PE in chronic verapamil treated normotensive rats(a) and hypertensive rats (b). The abscissa depicts the dose of PE and ordinate the increase in mean blood pressure. Open circles (o—o) represent responses in control rats, closed circles (●—●) in indapamide treated rats, open squares (□—□) in verapamil treated and closed squares (■—■) in verapamil + indapamide treated rats. Vertical lines denote S.E.M.(n = 4 to 5 for each observation). The level of significance ($P < 0.05$) is indicated by asterisk (*), in relation to verapamil treated normotensive and by ⊕ in relation to control rats.

FIG: 14

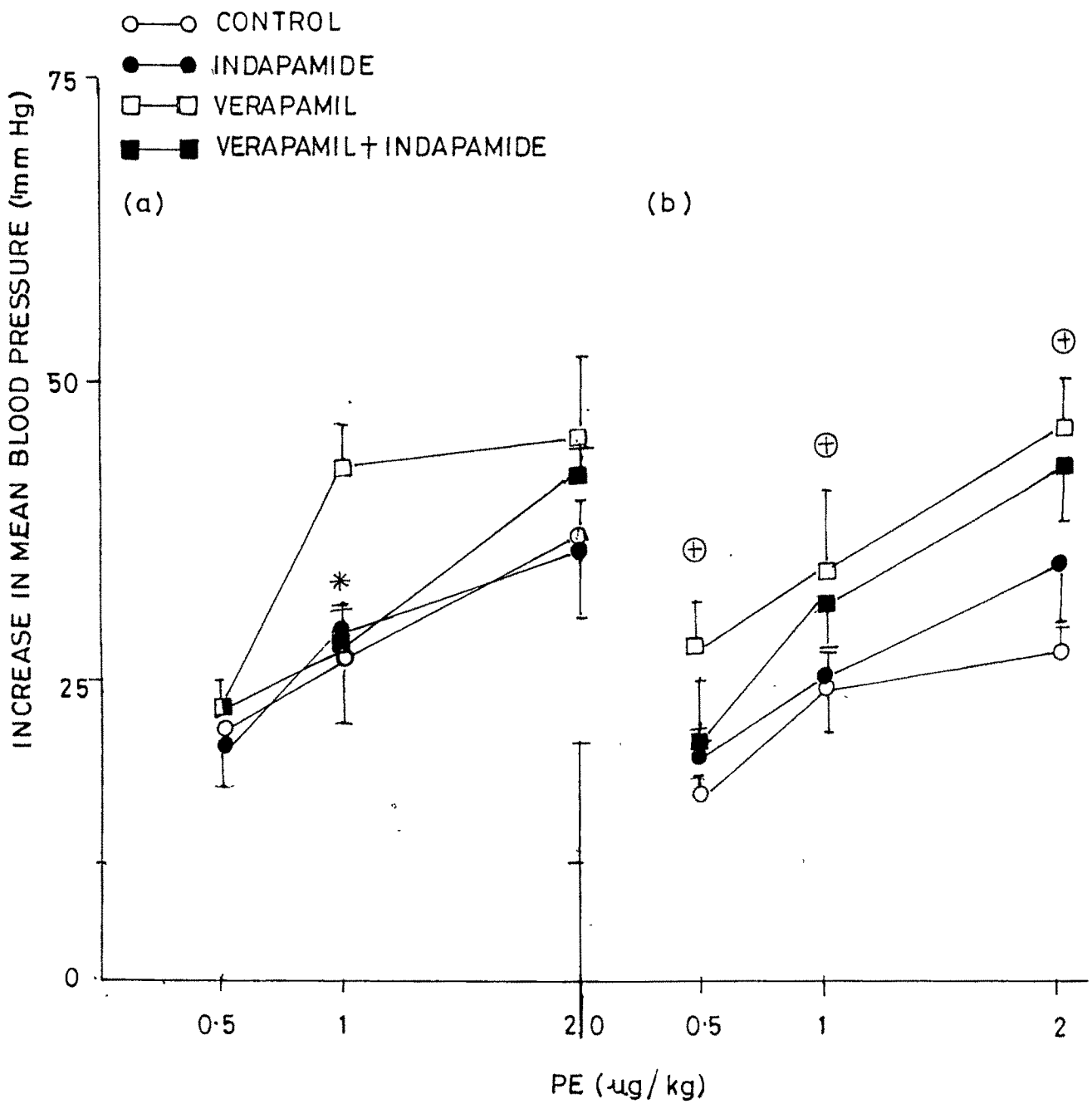
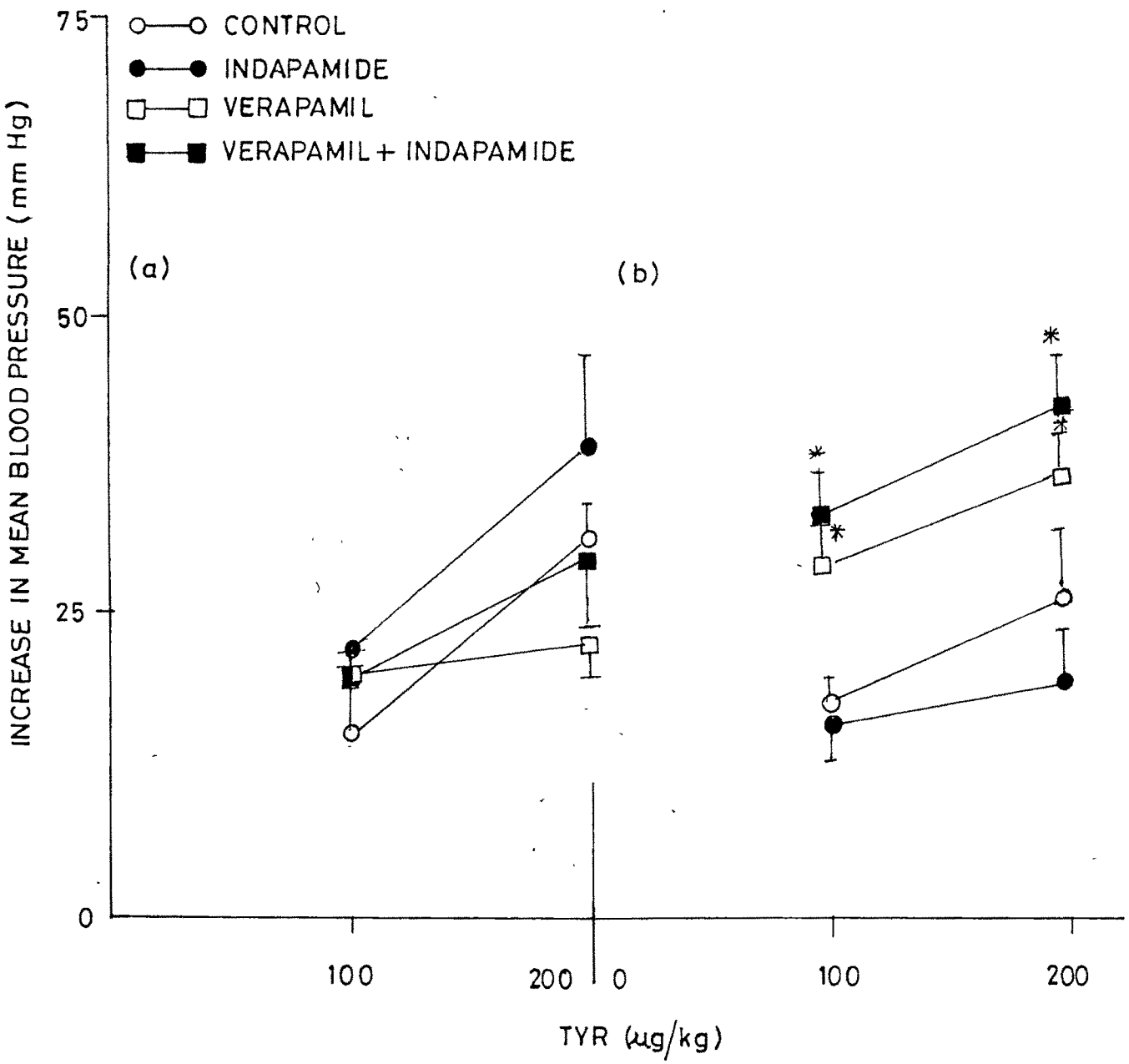

CONTROL
INDAPAMIDE
VERAPAMIL
VERAPAMIL + INDAPAMIDE
(a)
(b)
INCREASE IN MEAN BLOOD PRESSURE (mm Hg)
75
50
25
0
0·5
1
2
0
0·5
1
2
PE (µg/kg)

Fig. 15

Effect of indapamide on the pressor responses to TYR in chronic verapamil treated normotensive rats (a) and hypertensive rats (b). The abscissa depicts the dose of TYR and ordinate the increase in mean blood pressure. Open circles (o—o) represent responses in control rats, closed circles (●—●) in indapamide treated rats, open squares (□—□) in verapamil treated rats and closed squares (■—■) in verapamil + indapamide treated rats. Vertical lines denote S.E.M. (n = 5 to 6 for each observation). The level of significance ($P < 0.05$) is indicated by asterisk (*).

FIG: 15


CONTROL
INDAPAMIDE
VERAPAMIL
VERAPAMIL + INDAPAMIDE
(a)
(b)
INCREASE IN MEAN BLOOD PRESSURE (mm Hg)
75
50
25
0
100
200
0
100
200
TYR (µg/kg)

(e) Reactivity to ANG: Verapamil did not modify pressor responses to ANG in normotensive, indapamide treated normotensive, hypertensive and indapamide treated hypertensive rats (Fig.16 a,b).

(iv) Effect of chronic treatment with hydrallazine on reactivity to NA in hypertensive and indapamide treated hypertensive rats

(a) Hydrallazine inhibited pressor responses to 0.5 and 1 ug/kg of NA in hypertensive rats while responses to higher dose (2 ug/kg) were unaffected. Indapamide treatment further inhibited pressor response to even higher dose of NA (Fig.17).

(v) Heart rate with different i.v. agonists in indapamide treated normotensive and hypertensive rats

(a) The heart rates with different doses of NA, PE and TYR were not different in normotensive, indapamide treated normotensive and hypertensive rats. However, there was significant bradycardia ($P < 0.05$) with NA, PE and TYR (200 ug/kg) in indapamide treated hypertensive rats (Fig.18 a,c; 20).

Fig. 16

Effect of indapamide on the pressor responses to ANG in verapamil treated normotensive rats (a) and hypertensive rats (b). The abscissa depicts dose of ANG and ordinate the increase in mean blood pressure. Open circles (○—○) represent responses in control rats, closed circles (●—●) in indapamide treated rats, open squares (□—□) in verapamil treated rats and closed squares (■—■) in verapamil + indapamide treated rats. Vertical lines denote S.E.M. (n = 5 to 6 for each observation).

FIG: 16

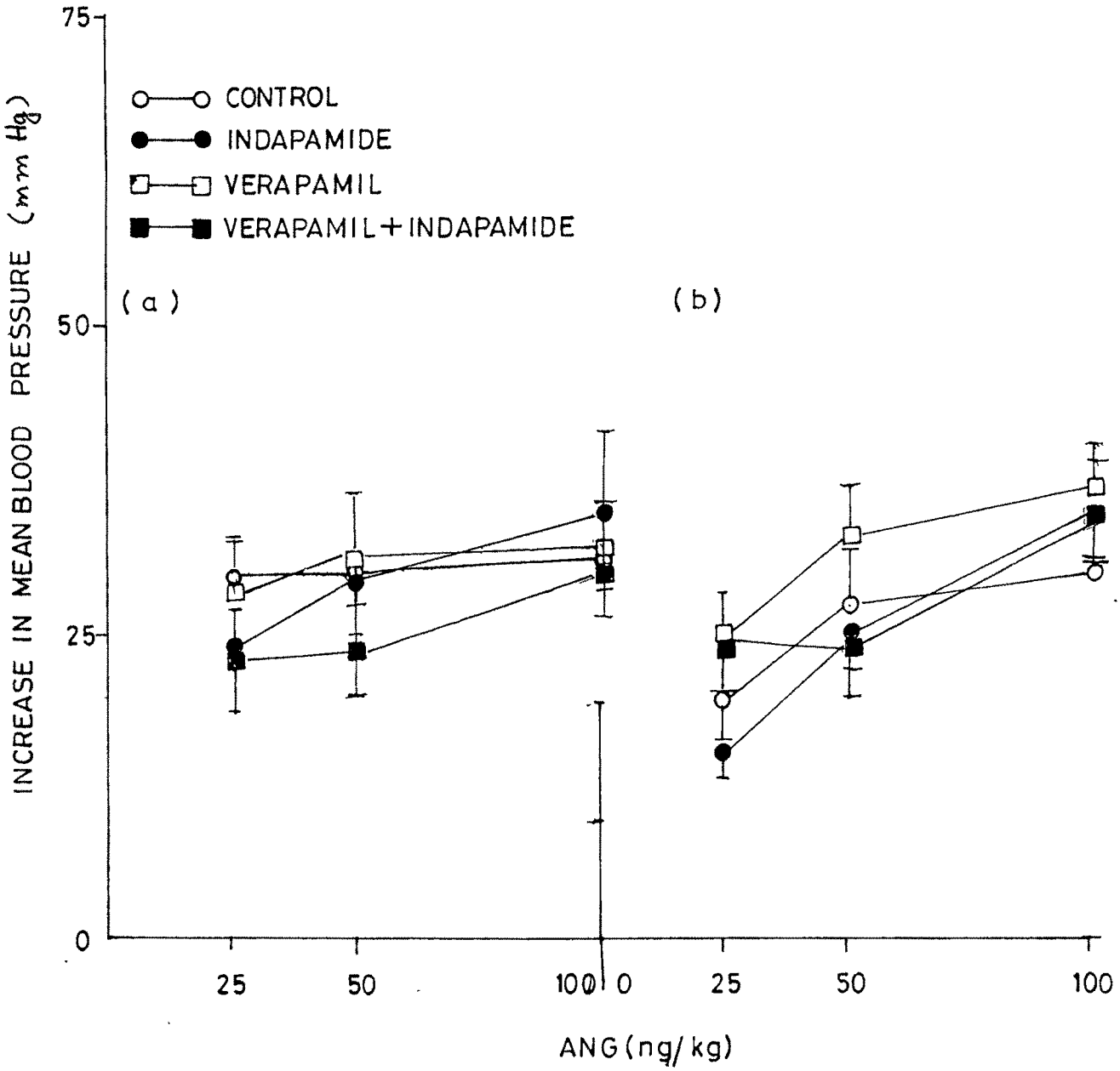

75
50
25
0
INCREASE IN MEAN BLOOD PRESSURE (mm Hg)
CONTROL
INDAPAMIDE
VERAPAMIL
VERAPAMIL + INDAPAMIDE
(a)
(b)
25
50
100
0
25
50
100
ANG (ng/kg)

Fig.17

Effect of indapamide on the pressor responses to NA in chronic hydrallazine treated hypertensive rats. The abscissa depicts dose of NA and ordinate the increase in mean blood pressure. Open circles (O—Ó) represent responses in control rats, closed circles (●—●) in indapamide treated rats, open triangles (△—△) in hydrallazine treated rats and closed triangles (▲—▲) in hydrallazine + indapamide treated rats. Vertical lines denote S.E.M. (n = 5 to 6 for each observation). The level of significance ($P < 0.05$) is indicated by asterisks (*) in relation to control and by ⊕ in relation to hydrallazine treated rats.

FIG: 17

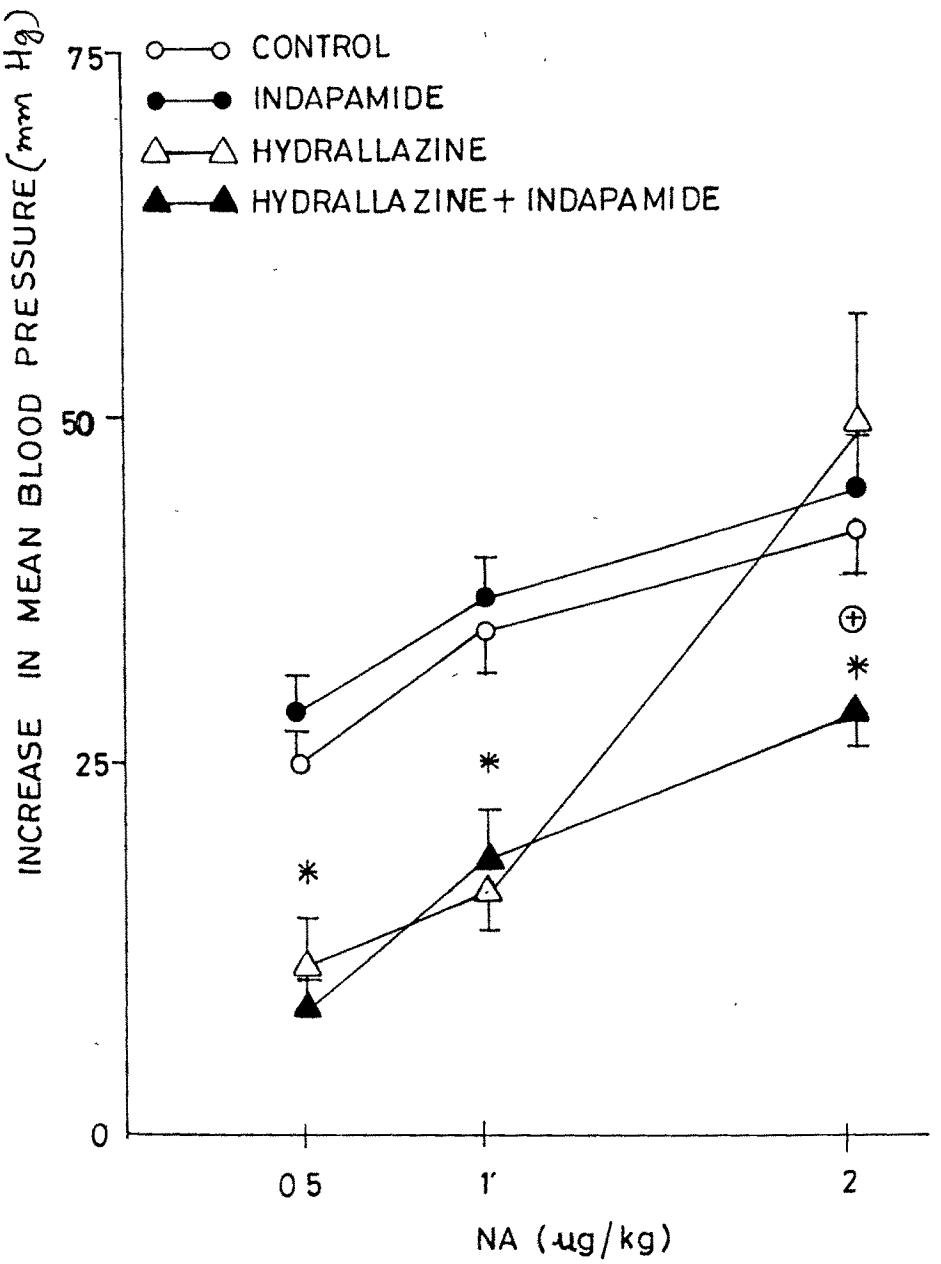
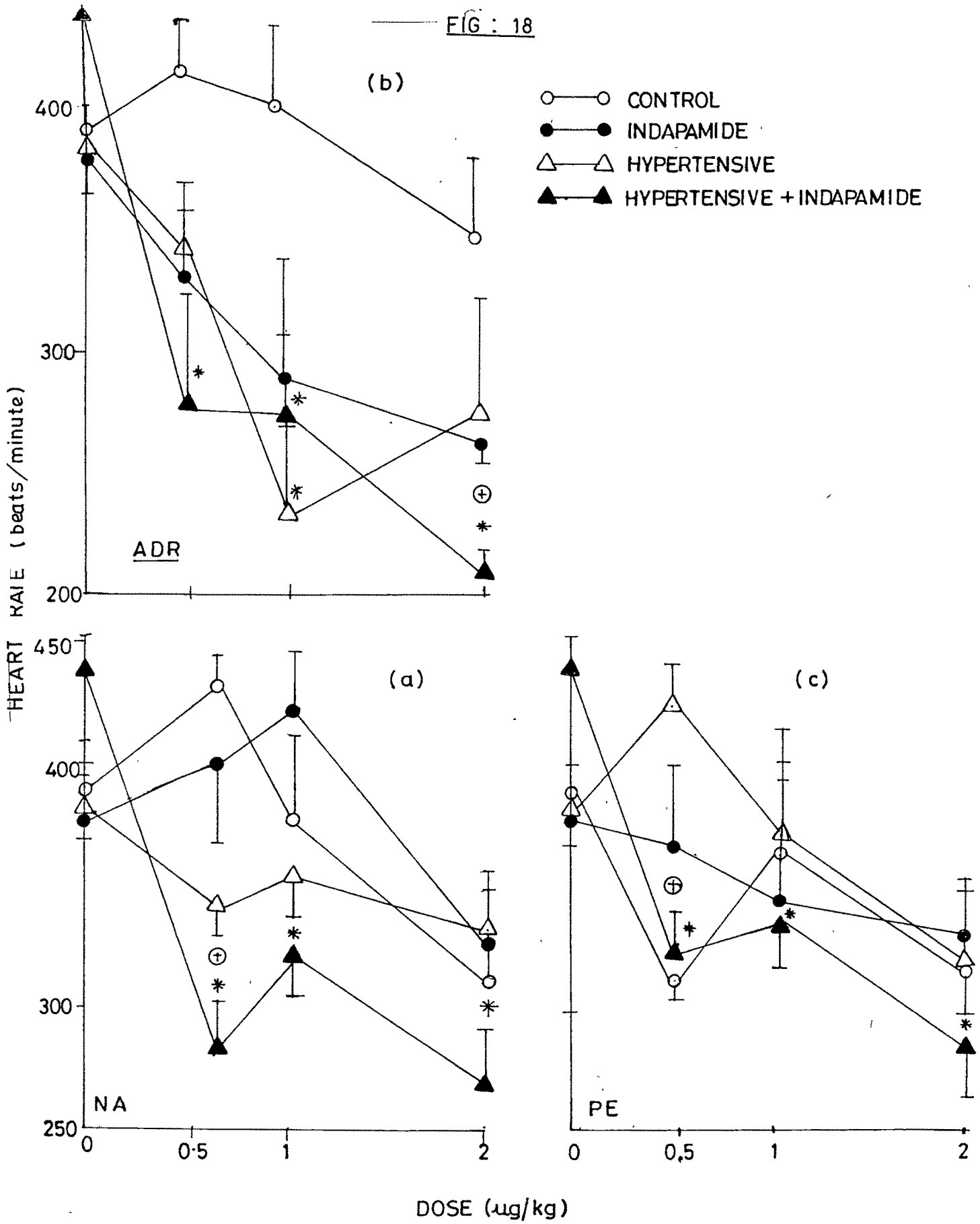

INCREASE IN MEAN BLOOD PRESSURE (mm Hg)
75
50
25
0
CONTROL
INDAPAMIDE
HYDRALLAZINE
HYDRALLAZINE + INDAPAMIDE
0 5
1'
2
NA (ug/kg)

Fig. 18

Effect of indapamide on the heart rate with i.v. NA (a), ADR (b) and PE (c) in normotensive and hypertensive rats. The abscissa depicts dose of the amine and ordinate the heart rate beats/min. Points on the ordinate show basal heart rate. Open circles (O—O) represent the heart rate in control normotensive rats, closed circles (●—●) in indapamide treated normotensive rats, open triangles (△—△) in hypertensive rats and closed triangles (▲—▲) in indapamide treated hypertensive rats. Vertical lines denote S.E.M. (n = 5 to 6 for each observation). The level of significance ($P < 0.05$) is indicated by asterisk (*) in relation to basal heart rate and by ⊕ in relation to heart rate with the amine in hypertensive rats.

FIG : 18


(b)
CONTROL
INDAPAMIDE
HYPERTENSIVE
HYPERTENSIVE + INDAPAMIDE
400
300
200
ADR
HEART RATE (beats/minute)
(a)
450
400
300
250
NA
0
0·5
1
2
(c)
PE
0
0,5
1
2
DOSE (µg/kg)

(b) The heart rate with different doses of ADR was not different in normotensive and indapamide treated notmotensive rats (Fig.18b). ADR produced dose related bradycardia in hypertensive and indapamide treated hypertensive rats however, there was greater bradycardia with higher dose of ADR (2 ug) compared to untreated hypertensive rats (Fig.18b).

(c) The heart rate with different doses of ANG was not different in normotensive, indapamide treated normotensive and hypertensive rats. However, there was significant bradycardia ($P < 0.05$) with 25 ng/kg of ANG in indapamide treated hypertensive rats (Fig.19).

(vi) Effect of indomethacin on heart rate with different i.v. pressor agents in indapamide treated normotensive and hypertensive rats

(a) NA, ADR produced dose related bradycardia in indomethacin treated normotensive and hypertensive rats. This effect was not observed after indapamide treatment (Fig.21a,b).

(b) Heart rate with different doses,of ANG was not different in indomethacin treated, indomethacin and indapamide treated normotensive, indomethacin treated, or indomethacin and indapamide treated hypertensive rats (Fig.22).

Fig.19

Effect of indapamide on the heart rate with i.v. ANG in normotensive and hypertensive rats. The abscissa depicts dose of ANG and the ordinate the heart rate beats/min. Points on the ordinate show basal heart rate. Open circles (O—O) represent heart rate in control normotensive rats, closed circles (●—●) in indapamide treated normotensive rats, open triangles (△—△) in control hypertensive rats and closed triangles (▲—▲) in indapamide treated hypertensive rats. Vertical lines denote S.E.M.(n = 3). The level of significance ($P < 0.05$) is indicated by asterisk (*).

FIG: 19

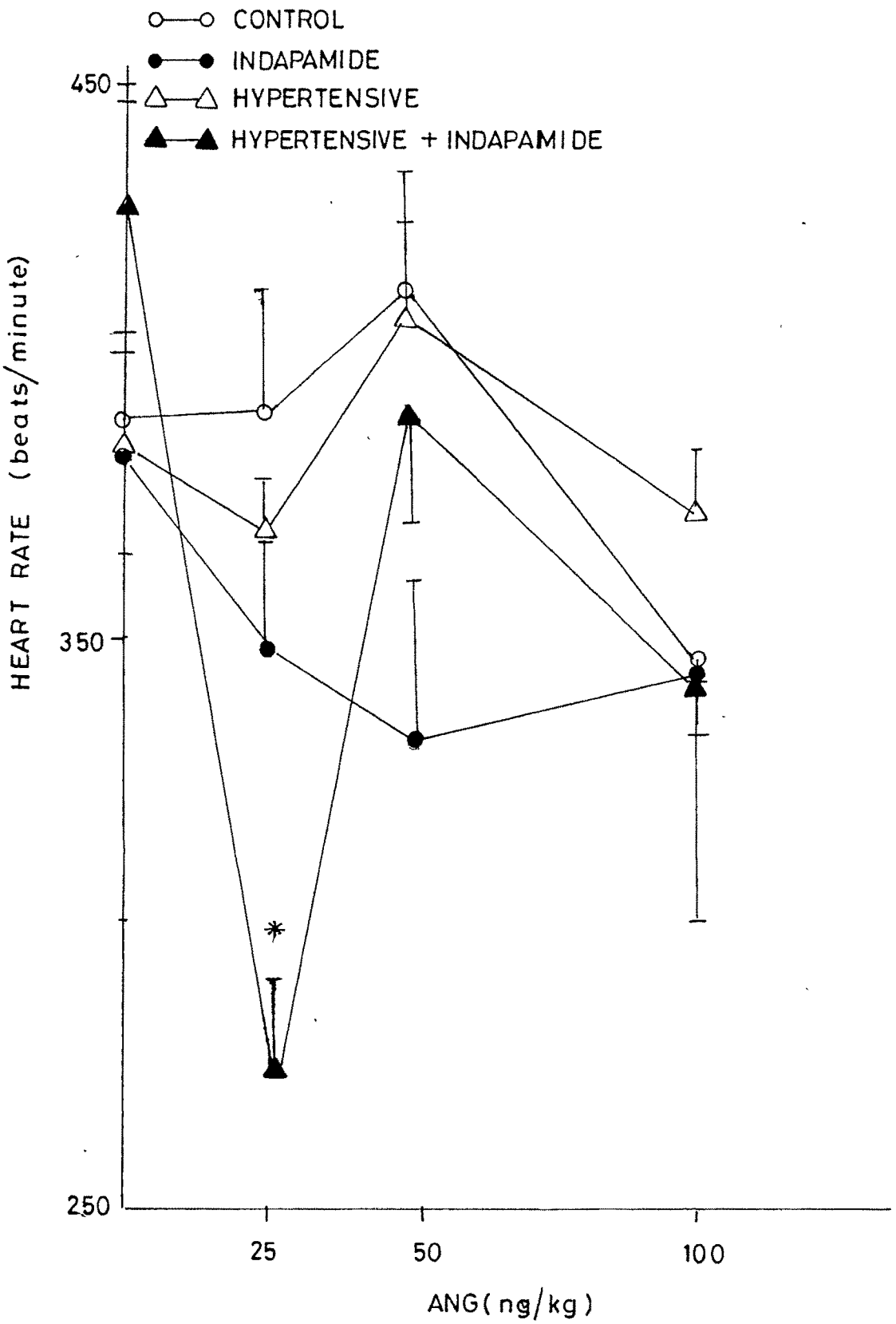

CONTROL
INDAPAMIDE
HYPERTENSIVE
HYPERTENSIVE + INDAPAMIDE
450
350
250
HEART RATE (beats/minute)
25
50
100
ANG(ng/kg)

Fig. 20

Effect of indapamide on the heart rate with i.v. TYR in normotensive (left hand panel) and hypertensive rats (right hand panel). Ordinate depicts the heart rate (beats/min) and squares below the histograms indicate the dose of TYR. Open bars (☐) represent pressor responses in untreated rats and black bars (■) in indapamide treated rats. Vertical lines denote S.E.M. (n = 4). The level of significance ($P < 0.05$) is indicated by asterisk (*).

FIG: 20

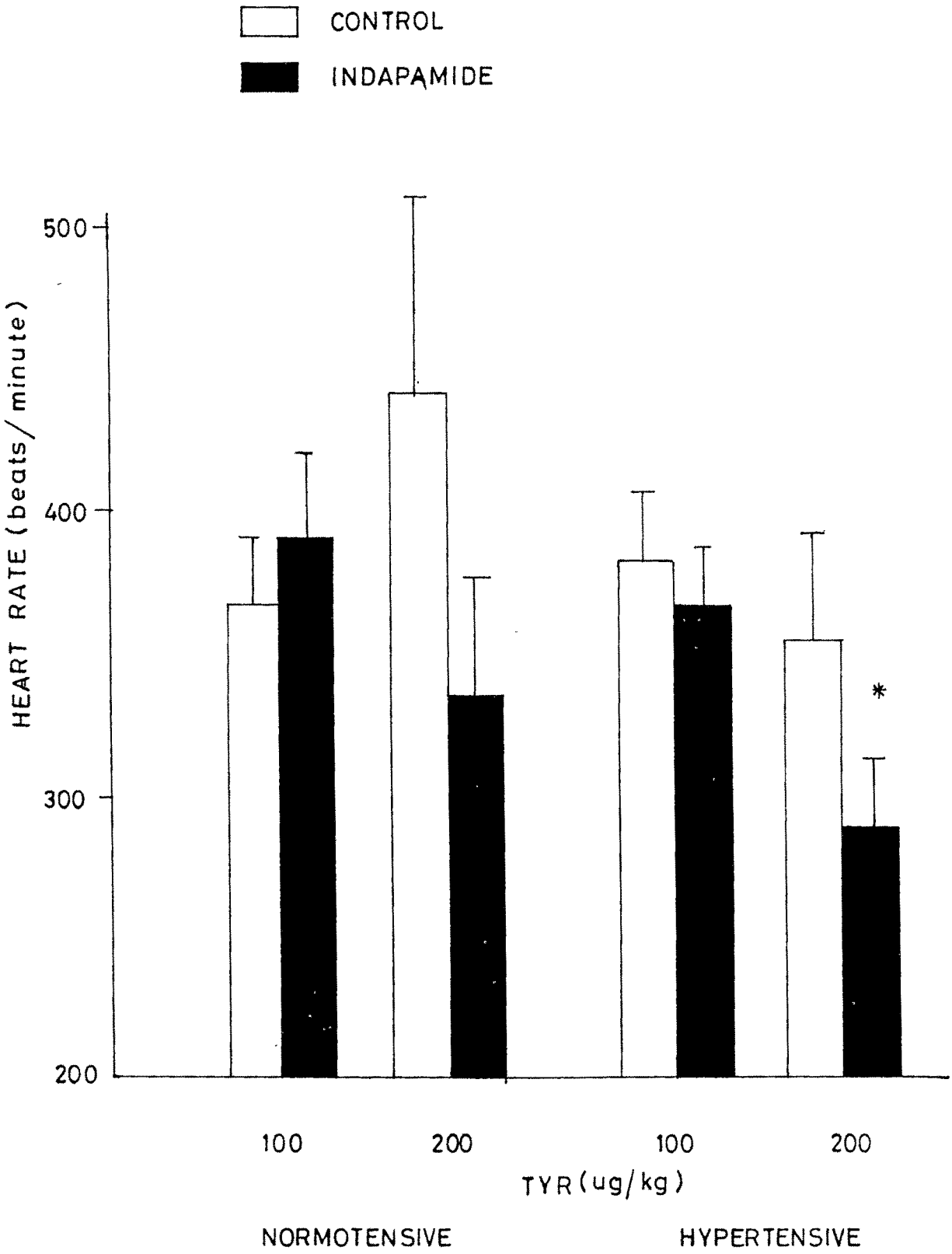

CONTROL
INDAPAMIDE
HEART RATE (beats/minute)
500
400
300
200
*
100
200
100
200
TYR (ug/kg)
NORMOTENSIVE
HYPERTENSIVE

Fig.21

Effect of indomethacin on heart rate with i.v. NA (a) and ADR (b) in indapamide treated normotensive and hypertensive rats. The abscissa depicts the dose of amine and ordinate the heart rate in beats/min. Points on the ordinate show basal heart rate. Open circles (○—○) represent the heart rate in indomethacin treated normotensive rats, closed circles (●—●) in indomethacin + indapamide treated normotensive rats, open triangles (△—△) in indomethacin treated hypertensive rats and closed triangles (▲—▲) in indomethacin + indapamide treated hypertensive rats. Vertical lines denote S.E.M. (n = 4 to 6 for each observation). The level of significance ($P < 0.05$) is indicated by asterisk (*).

FIG: 21

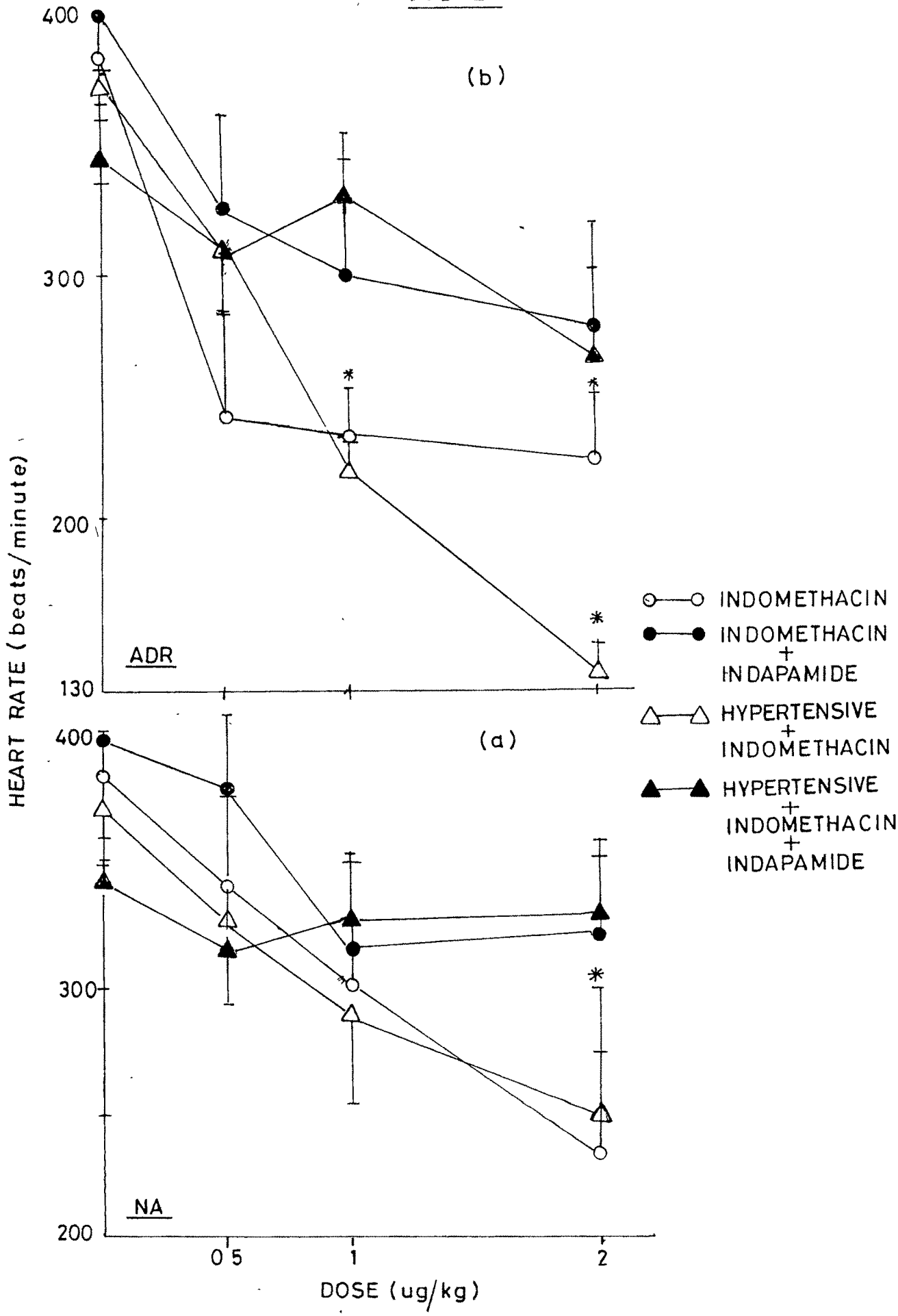
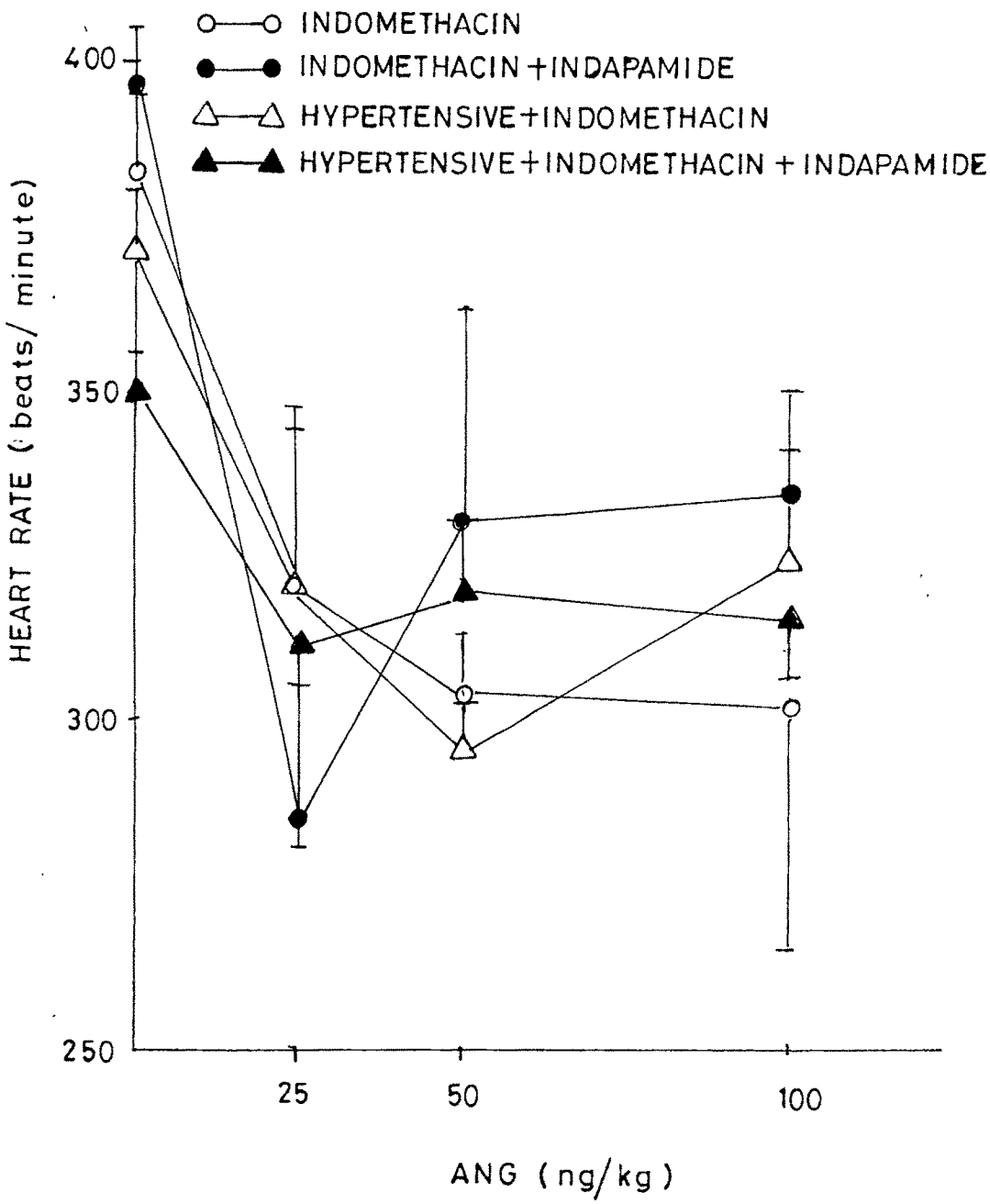

400
300
200
130
(b)
ADR
400
300
200
(a)
NA
HEART RATE (beats/minute)
0 5
1
2
DOSE (ug/kg)
INDOMETHACIN
INDOMETHACIN + INDAPAMIDE
HYPERTENSIVE + INDOMETHACIN
HYPERTENSIVE + INDOMETHACIN + INDAPAMIDE

Fig. 22

Effect of indomethacin treatment on the heart rate with i.v. ANG in indapamide treated normotensive and hypertensive rats. The abscissa depicts the dose of ANG and ordinate the heart rate in beats/min. Points on the ordinate show basal heart rate. Open circles (o—o) represent the heart rate in indomethacin treated normotensive rats, closed circles (●—●) in indomethacin + indapamide treated normotensive rats, open triangles (△—△) in indomethacin treated hypertensive rats and closed triangles (▲—▲) in indomethacin + indapamide treated hypertensive rats. Vertical lines denote S.E.M. (n = 4 to 6 for each observation).

FIG:22


INDOMETHACIN
INDOMETHACIN + INDAPAMIDE
HYPERTENSIVE + INDOMETHACIN
HYPERTENSIVE + INDOMETHACIN + INDAPAMIDE
HEART RATE (beats/ minute)
400
350
300
250
25
50
100
ANG (ng/kg)

(vii) Effect of verapamil on the heart rate with different i.v. pressor agents in indapamide treated normotensive and hypertensive rats

(a) NA and ADR produced dose related bradycardia in verapamil treated normotensive rats which was blocked by indapamide plus verapamil treatment (Fig.23a,b). Heart rates with NA and ADR were not different in verapamil treated and verapamil plus indapamide treated hypertensive rats (Fig.23a,b).

(b) Heart rates with different doses of PE and TYR were not different in verapamil treated, verapamil plus indapamide treated normotensive, verapamil treated and verapamil plus indapamide treated hypertensive rats (Fig.23c, 24).

(c) Heart rates with different doses of ANG were not different in verapamil treated, verapamil plus indapamide treated normotensive, verapamil treated or verapamil plus indapamide treated hypertensive rats (Fig.25).

Fig.23

Effect of indapamide on the heart rate with different doses of NA (a), ADR (b) and PE (c) in chronic verapamil treated normotensive and hypertensive rats. The abscissa depicts the dose of the amine and ordinate the heart rate (beats/min). Points on the ordinate show basal heart rate. Open circles (o—o) represent heart rate in control verapamil treated rats, closed circles (●—●) in verapamil + indapamide treated normotensive rats, open squares (□—□) in verapamil treated hypertensive rats and closed squares (■—■) in indapamide + verapamil treated hypertensive rats. Vertical lines denote S.E.M.(n = 5 to 7nfor each observation). The level of significance ($P < 0.05$) is depicted by asterisk (*).

FIG: 23

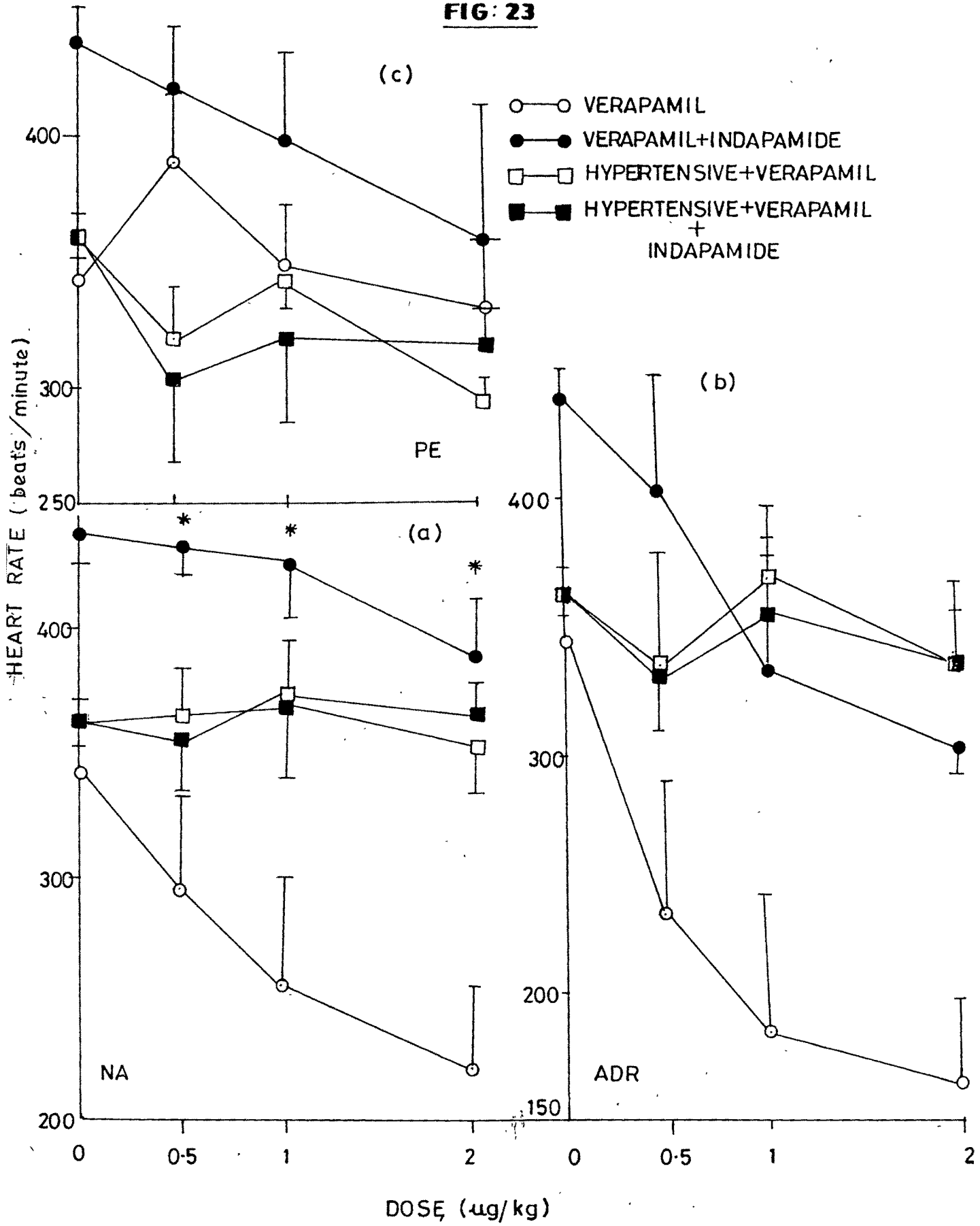

(c)
VERAPAMIL
VERAPAMIL+INDAPAMIDE
HYPERTENSIVE+VERAPAMIL
HYPERTENSIVE+VERAPAMIL + INDAPAMIDE
400
300
250
PE
(a)
400
300
200
NA
(b)
400
300
200
150
ADR
HEART RATE (beats/minute)
0
0·5
1
2
DOSE (µg/kg)

Fig. 24

Effect of indapamide on the heart rate with i.v. TYR in chronic verapamil treated normotensive and hypertensive rats. The abscissa depicts dose of TYR and the ordinate the heart rate (beats/min). Points on the ordinate show basal heart rate. Open circles (O—O) represent heart rate in verapamil treated normotensive rats, closed circles (●—●) in verapamil + indapamide treated normotensive rats, open squares (□—□) in verapamil treated hypertensive rats and closed squares (■—■) in verapamil + indapamide treated hypertensive rats. Vertical lines denote S.E.M. (n = 4 to 6 for each observation).

FIG: 24

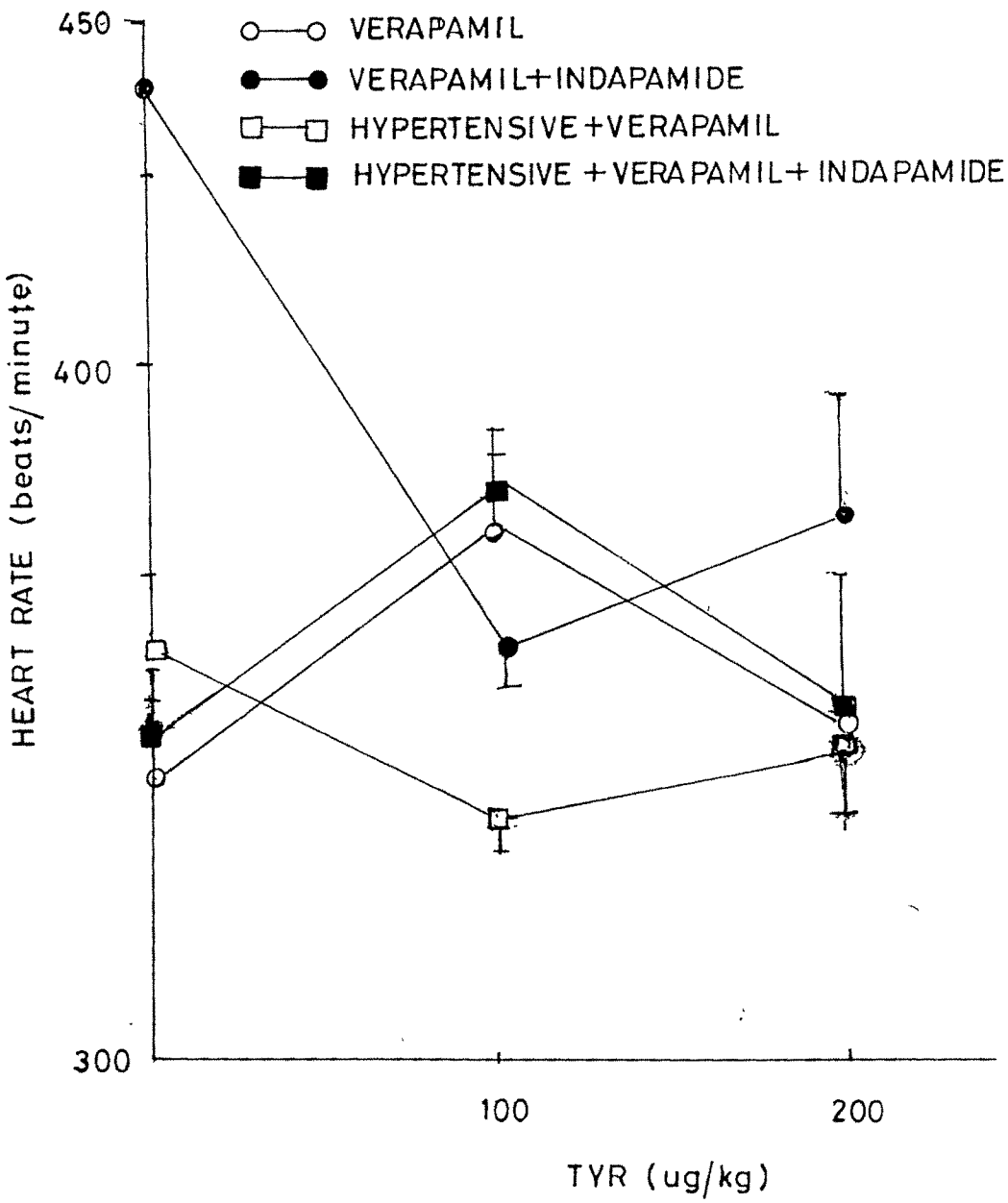
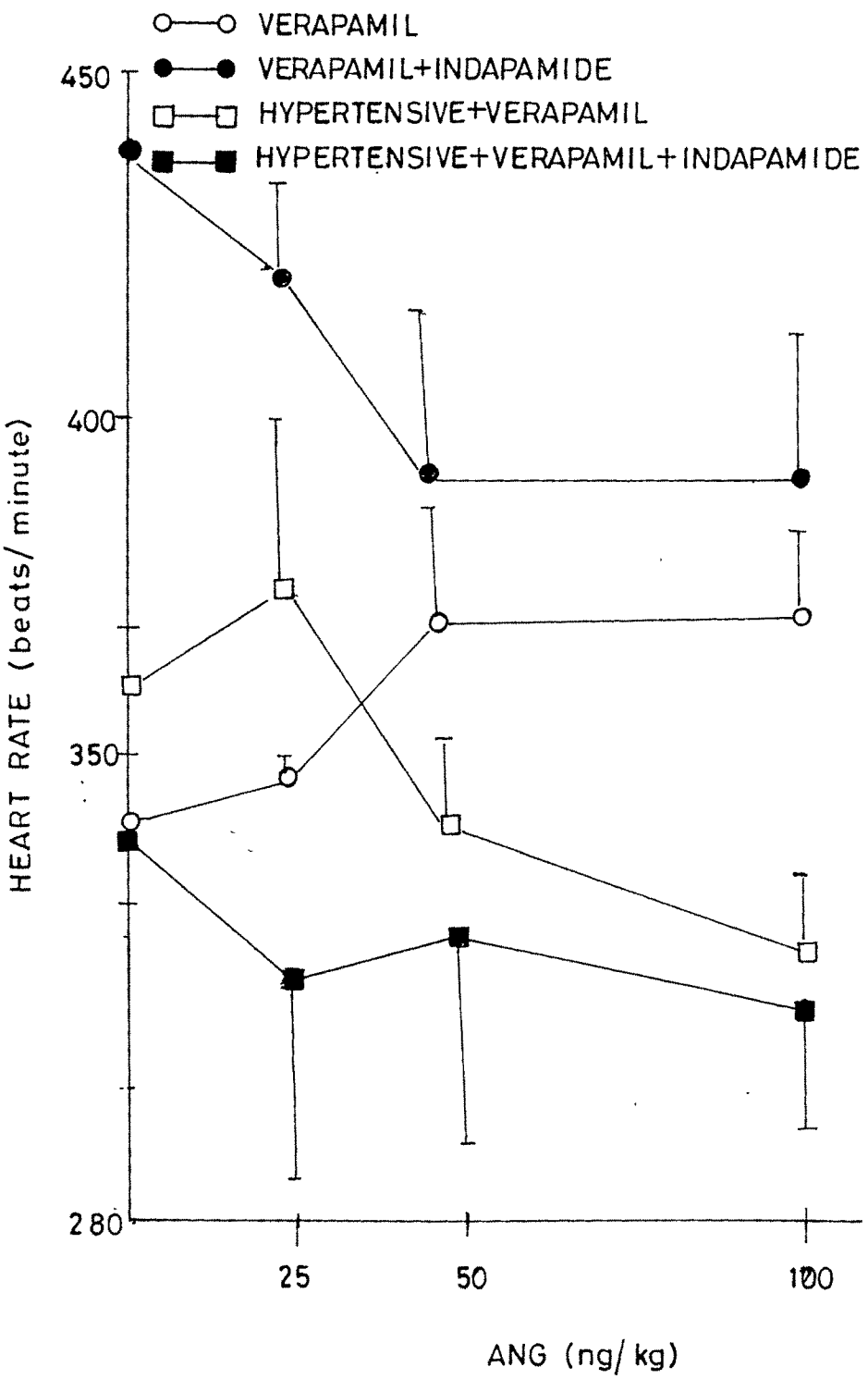

VERAPAMIL
VERAPAMIL+INDAPAMIDE
HYPERTENSIVE+VERAPAMIL
HYPERTENSIVE +VERAPAMIL+ INDAPAMIDE
450
400
300
HEART RATE (beats/minute)
100
200
TYR (ug/kg)

Fig. 25

Effect of indapamide on the heart rate with i.v. ANG in verapamil treated normotensive and hypertensive rats. The abscissa depicts the dose of ANG and the ordinate the heart rate in beats/min. Open circles (○—○) represent heart rate in verapamil treated normotensive rats, closed circles (●—●) in indapamide + verapamil treated normotensive rats, open squares (□—□) in verapamil treated hypertensive rats and closed squares (■—■) in verapamil + indapamide treated hypertensive rats. Vertical lines denote S.E.M. (n = 5 to 6 for each observation).

FIG:25


VERAPAMIL
VERAPAMIL+INDAPAMIDE
HYPERTENSIVE+VERAPAMIL
HYPERTENSIVE+VERAPAMIL+INDAPAMIDE
450
400
350
280
HEART RATE (beats/minute)
25
50
100
ANG (ng/kg)

II. Experiments in vitro

(1) Aortic strip of rat

(i) Contractile responses to NA: NA produced dose related contractile responses. Indapamide (3.0×10^{-5}M and 3.0×10^{-4}M) shifted the DRC of NA towards the right with depression of the maxima (Fig.26a,b).

(ii) Contractile responses to KCl: KCl produced dose related contractile responses. Indapamide (3.0×10^{-5}M) inhibited the responses with depression of the maxima (Fig.27).

(iii) Contractile responses to $CaCl_2$ in depolarized medium: $CaCl_2$ produced dose related contractile responses. Indapamide (3.0×10^{-5}M) inhibited the responses with depression of the maxima (Fig.28).

(iv) Contractile responses to TYR: TYR produced dose related contractile responses. Indapamide (3.0×10^{-5}M) inhibited the responses with depression of the maxima (Fig.29).

(v) Contractile responses to ANG: ANG produced dose related contractile responses. Indapamide (3.0×10^{-5}M) inhibited the responses with depression of the maxima (Fig.30).

Fig.26

Effect of indapamide on the concentration-response curve of NA in the rat isolated aorta. The abscissa depicts the concentration of NA and the ordinate the responses as percentage of control maximum response. Open circles (O—O) represent control concentration response curve, closed triangles (▲—▲) in the presence of vehicle and closed circles (●—●) in the presence of indapamide (3.0×10^{-4}M in a and 3.0×10^{-5}M in b). Vertical lines denote S.E.M. (n = 4 to 6 for each observation). The level of significance is indicated by asterisks. * $P < 0.05$ and ** $P < 0.01$.

FIG : 26

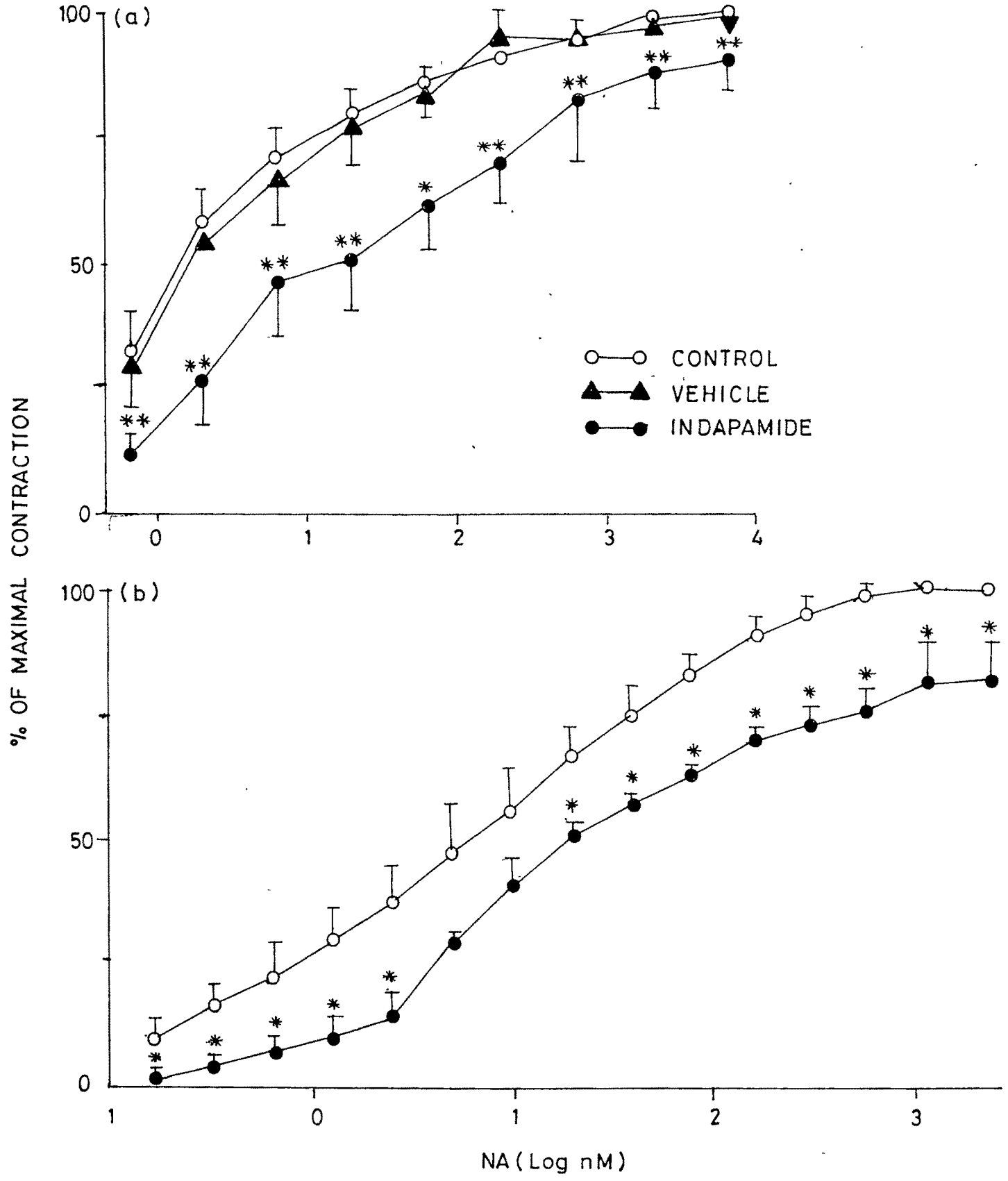

(a)
100
50
0
0
1
2
3
4
CONTROL
VEHICLE
INDAPAMIDE
(b)
100
50
0
1
0
1
2
3
% OF MAXIMAL CONTRACTION
NA (Log nM)

Fig.27

Effect of indapamide on the concentration-response curve of KCl in the rat isolated aorta. The abscissa depicts the concentration of KCl and the ordinate the response as percentage of control maximum response. Open circles (O—O) represent control concentration curve, closed triangles (▲—▲) in the presence of vehicle, and closed circles (●—●) in the presence of indapamide (3.0×10^{-5}M). Vertical lines denote S.E.M. (n = 7). The level of significance ($P < 0.05$) is indicated by asterisk (*).

FIG:27

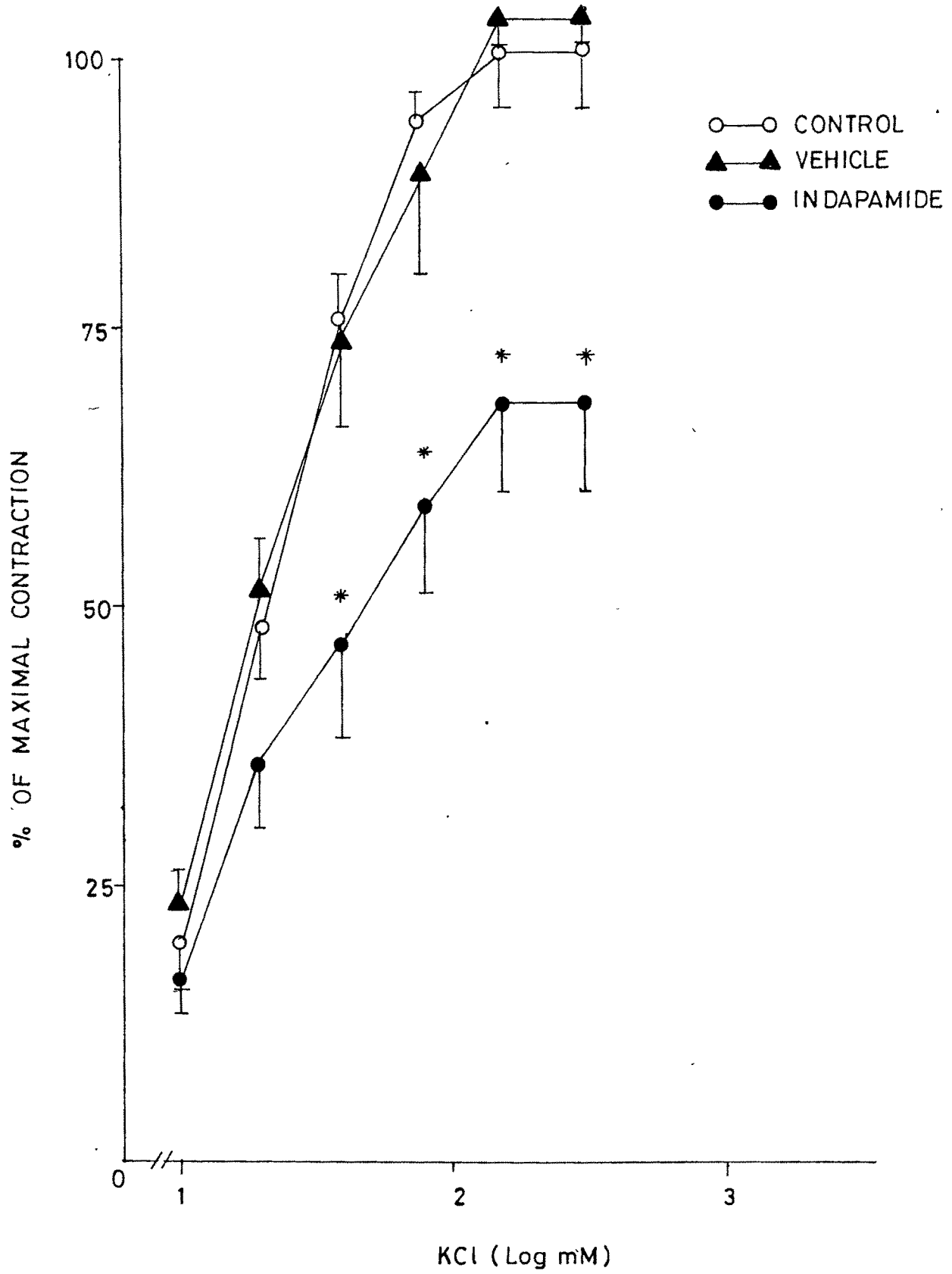

100
75
50
25
0
1
2
3
% OF MAXIMAL CONTRACTION
KCl (Log mM)
CONTROL
VEHICLE
INDAPAMIDE
*
*
*
*

Fig. 28

Effect of indapamide on the concentration-response curve of $CaCl_2$ in the rat isolated aorta. The abscissa depicts the concentration of $CaCl_2$ and the ordinate the responses as percentage of control maximum response. Open circles (○—○) represent control concentration response curve and closed circles (●—●) in the presence of indapamide (3.0×10^{-5}M). Vertical lines denote S.E.M. (n = 6). The level of significance is indicated by asterisks. *$P < 0.05$ and **$P < 0.01$.

FIG: 28

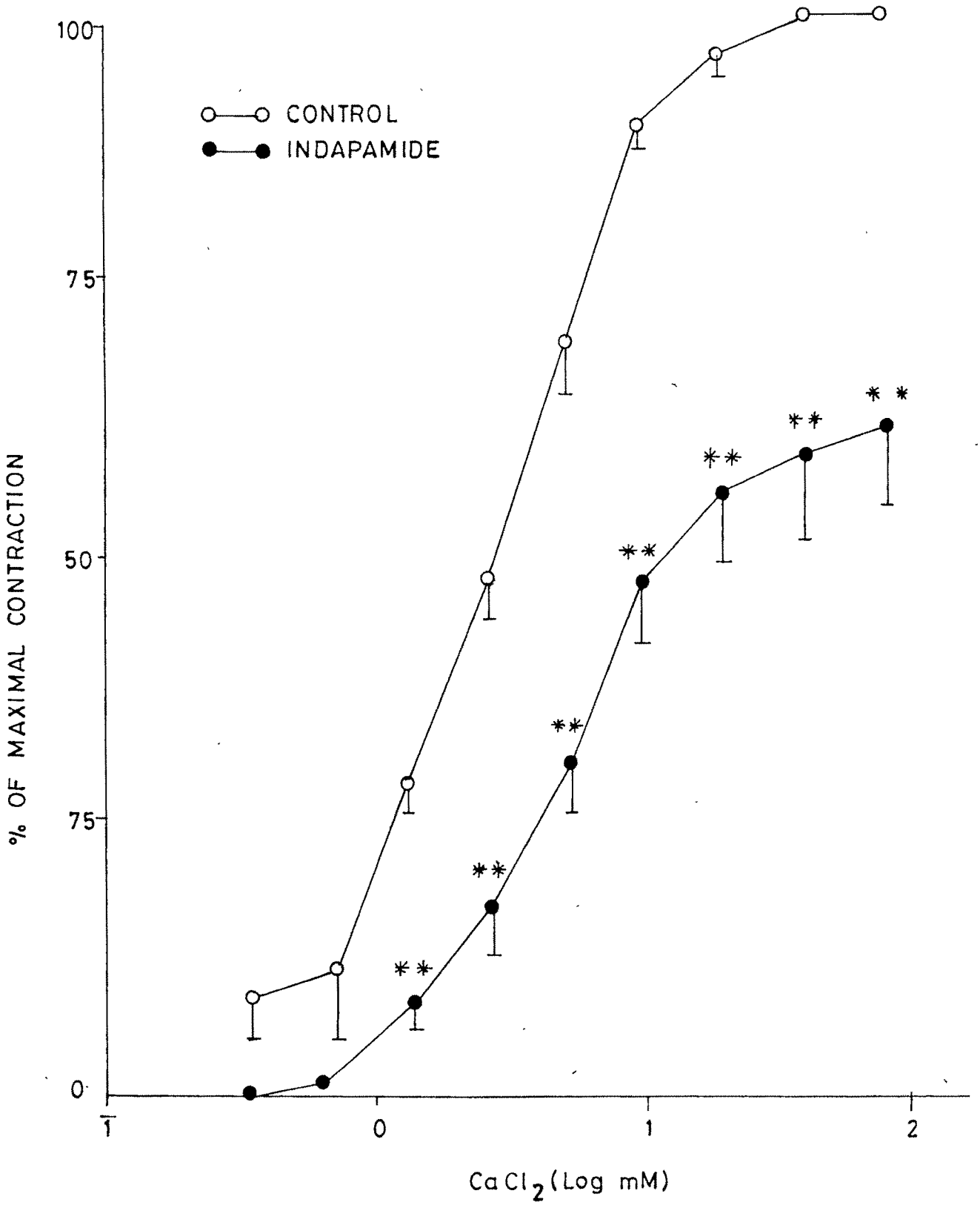

100
75
50
75
0
CONTROL
INDAPAMIDE
% OF MAXIMAL CONTRACTION
1
0
1
2
CaCl2 (Log mM)

Fig.29

Effect of indapamide on the concentration-response curve of TYR in the rat isolated aorta. The abscissa depicts concentration of TYR and the ordinate the responses as percentage of control maximum response. Open circles (O—O) represent control concentration response curve and closed circles (●—●) in the presence of indapamide (3.0×10^{-5}M). Vertical lines denote S.E.M. (n = 6). The level of significance is indicated by asterisks. *$P < 0.05$ and ** $P < 0.01$.

FIG:29

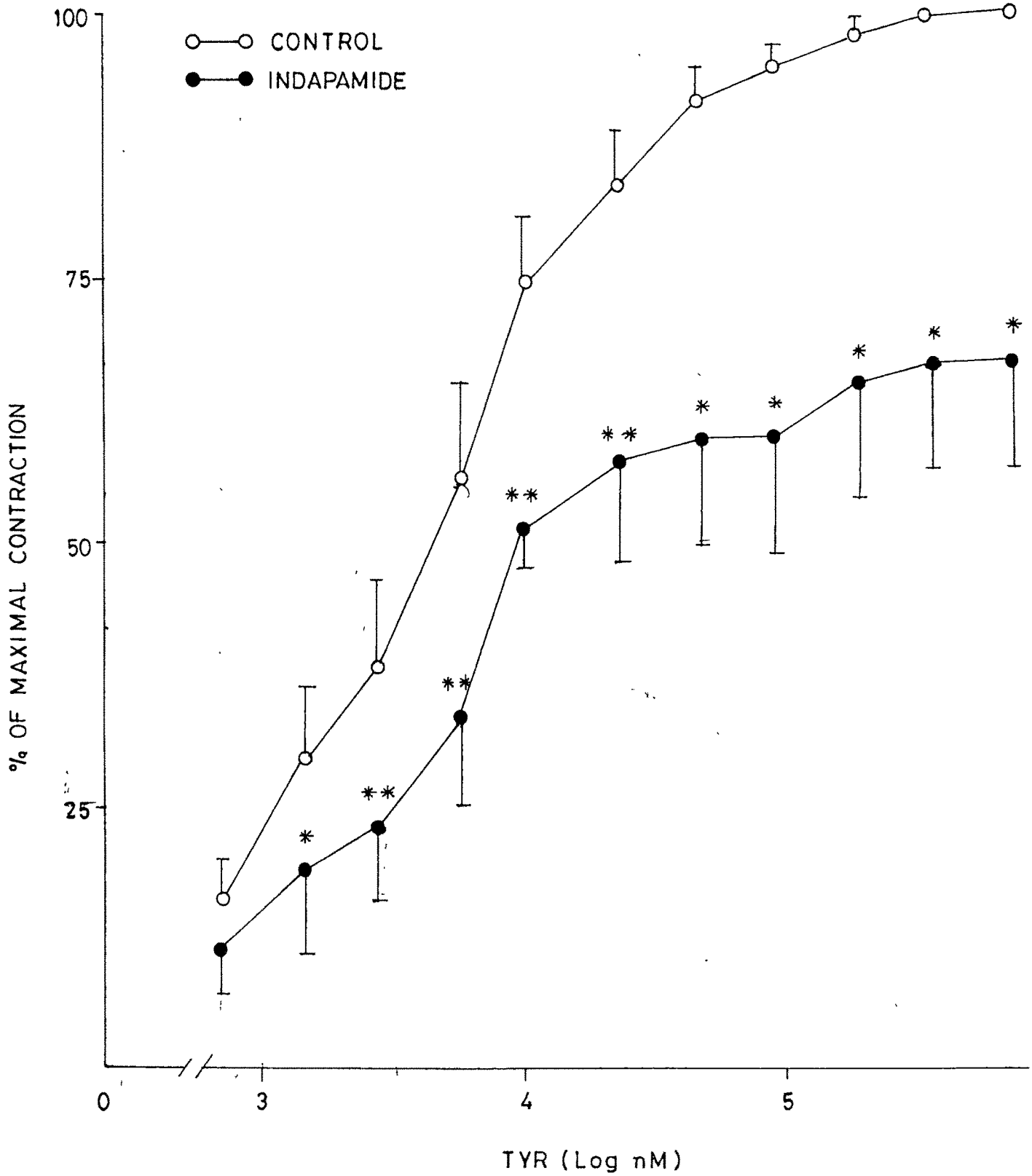
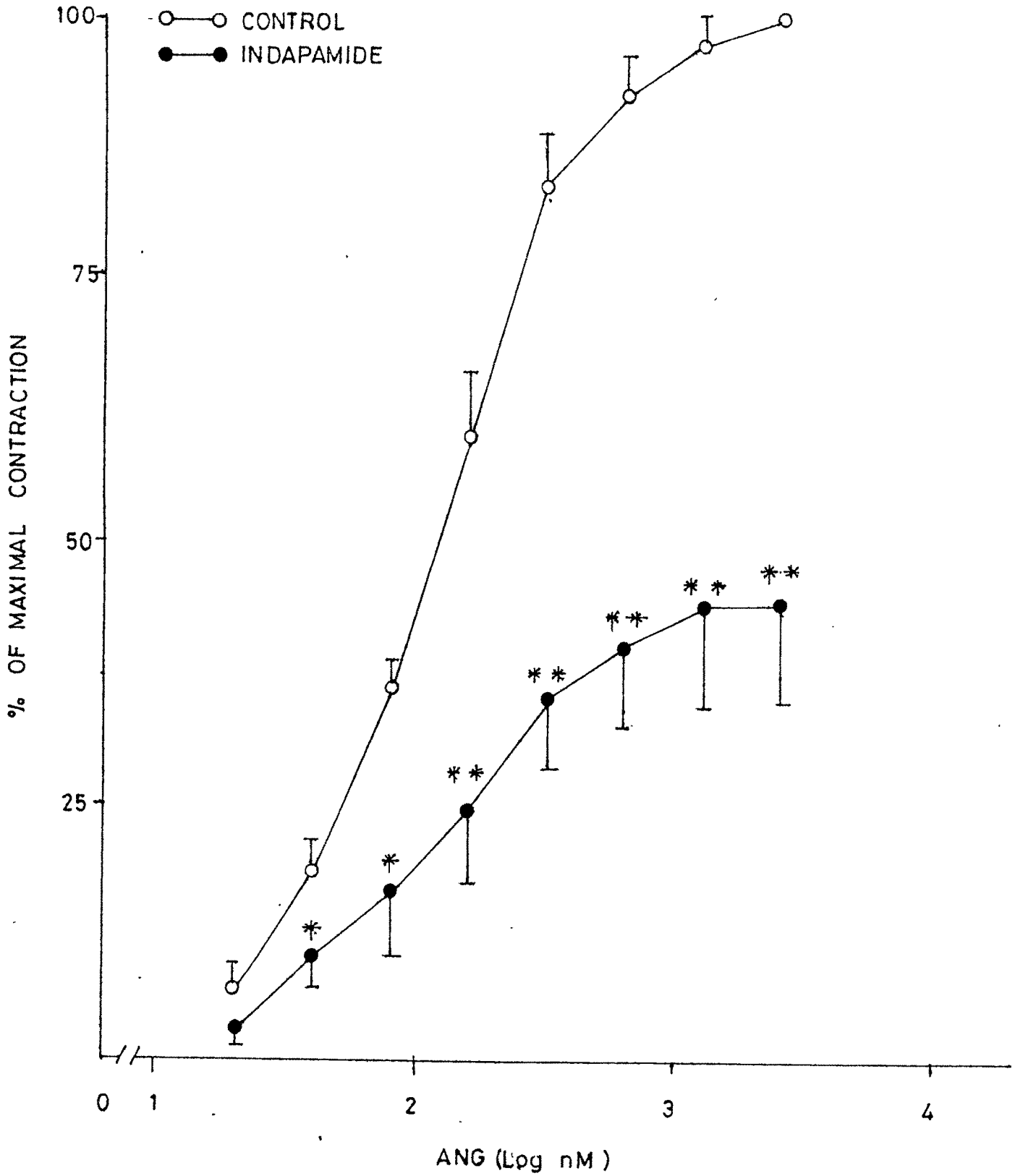

100
75
50
25
0
3
4
5
CONTROL
INDAPAMIDE
% OF MAXIMAL CONTRACTION
TYR (Log nM)
*
**
**
**
*
*
*
*
*

Fig.30

Effect of indapamide on the concentration-response curve of ANG in rat isolated aorta. The abscissa depicts the concentration of ANG and the ordinate the responses as percentage of control maximum response. Open circles (O——O) represent control concentration response curve and closed circles (●——●) in the presence of indapamide (3.0×10^{-5}M). Vertical lines denote S.E.M.(n = 6). The level of significance is indicated by asterisks. *P $<$ 0.05 and **P $<$ 0.01.

FIG: 30


CONTROL
INDAPAMIDE
100
75
50
25
% OF MAXIMAL CONTRACTION
0
1
2
3
4
ANG (Log nM)

(iv) Contractile responses to 5-HT: 5-HT produced dose related contractile responses. Indapamide (3.0×10^{-5}M) inhibited the responses with depression of the maxima (Fig.31).

(vii) Effect of indapamide on responses to K^+ in the presence of verapamil: K^+ produced dose related contractile responses. Verapamil (1.1×10^{-6}M) inhibited the responses. Indapamide (3.0×10^{-5}M) further inhibited responses to K^+ in the presence of verapamil (Fig.32).

(viii) Effect of indapamide on contractile responses to NA in the presence of indomethacin: NA produced dose related contractile responses. Indomethacin (2.8×10^{-5}M) modified the middle portion of the DRC of NA. Indapamide (3.0×10^{-4}M) further inhibited responses to NA in the presence of indomethacin (Fig.33).

(2) Portal vein of rat

In all experiments, the spontaneous rhythmic movements of the preparations were inhibited after incubation with indapamide.

(i) Contractile responses to NA: NA produced dose related contractile responses. Indapamide (3.0×10^{-5}M) inhibited the responses with depression of the maxima (Fig.34).

Fig.31

Effect of indapamide on the concentration-response curve of 5-HT in the rat isolated aorta. The abscissa depicts the concentration of 5-HT and the ordinate the responses as percentage of the control maximum response. Open circles (o—o) represent the control concentration response curve and closed circles (●—●) in the presence of indapamide (3.0×10^{-5}M). Vertical lines denote S.E.M.(n = 6). The level of significance is indicated by asterisks. *$P < 0.05$ and **$P < 0.01$.

FIG:31

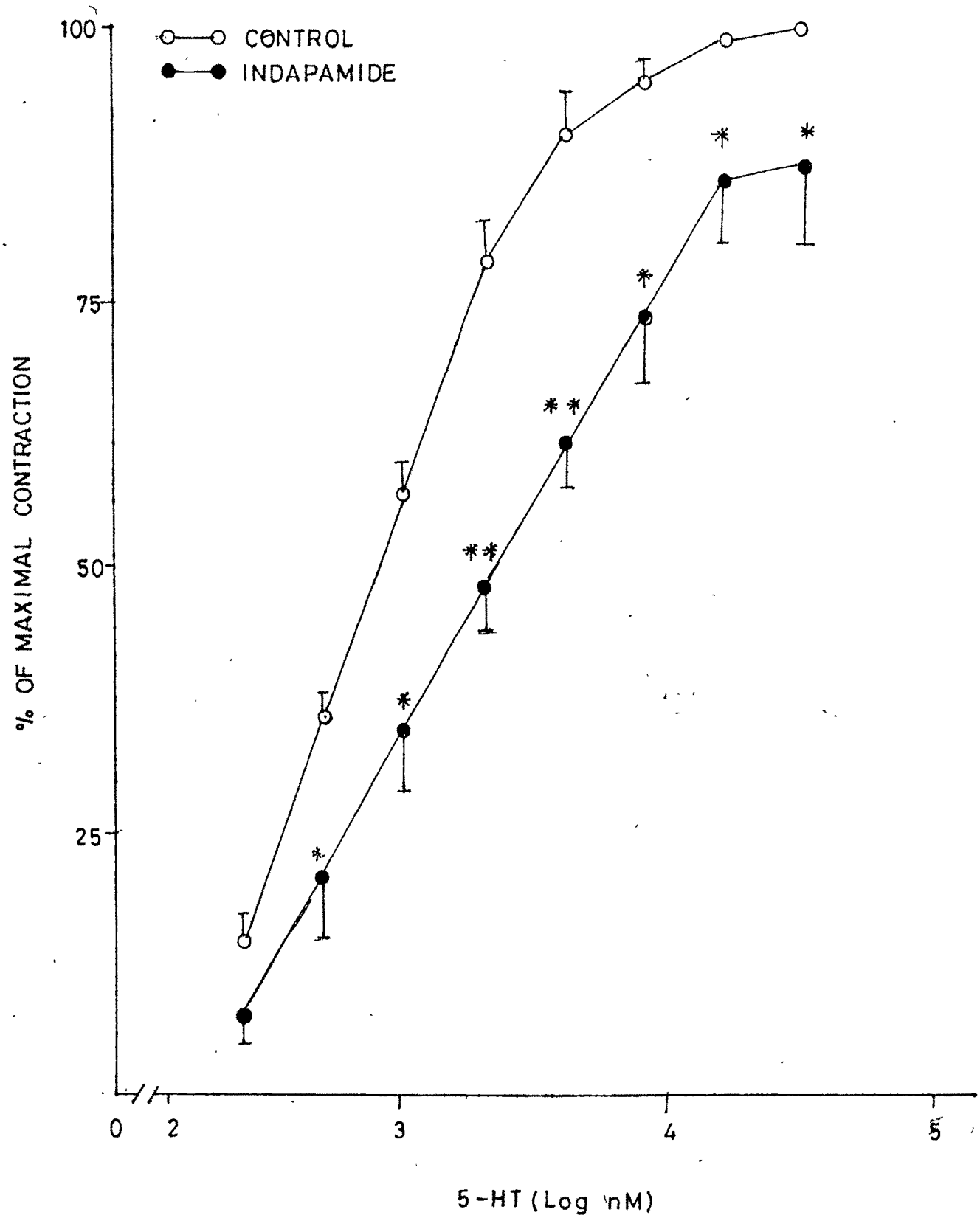

CONTROL
INDAPAMIDE
100
75
50
25
% OF MAXIMAL CONTRACTION
0
2
3
4
5
5-HT (Log nM)

Fig. 32

Effect of indapamide on the concentration-response curve of KCl in the presence of verapamil in the rat isolated aorta. The abscissa depicts concentration of KCl and the ordinate the responses as percentage of control maximum responses. Open circles (o—o) represent control concentration response curve, closed circles (●—●) in the presence of verapamil (1.1×10^{-6}M) and closed triangles (▲—▲) in the presence of indapamide + verapamil. Vertical lines denote S.E.M. (n = 5). The level of significance ($P < 0.05$) is indicated by asterisk (*) in relation to control and by ⊕ in relation to verapamil treated preparations.

FIG:32

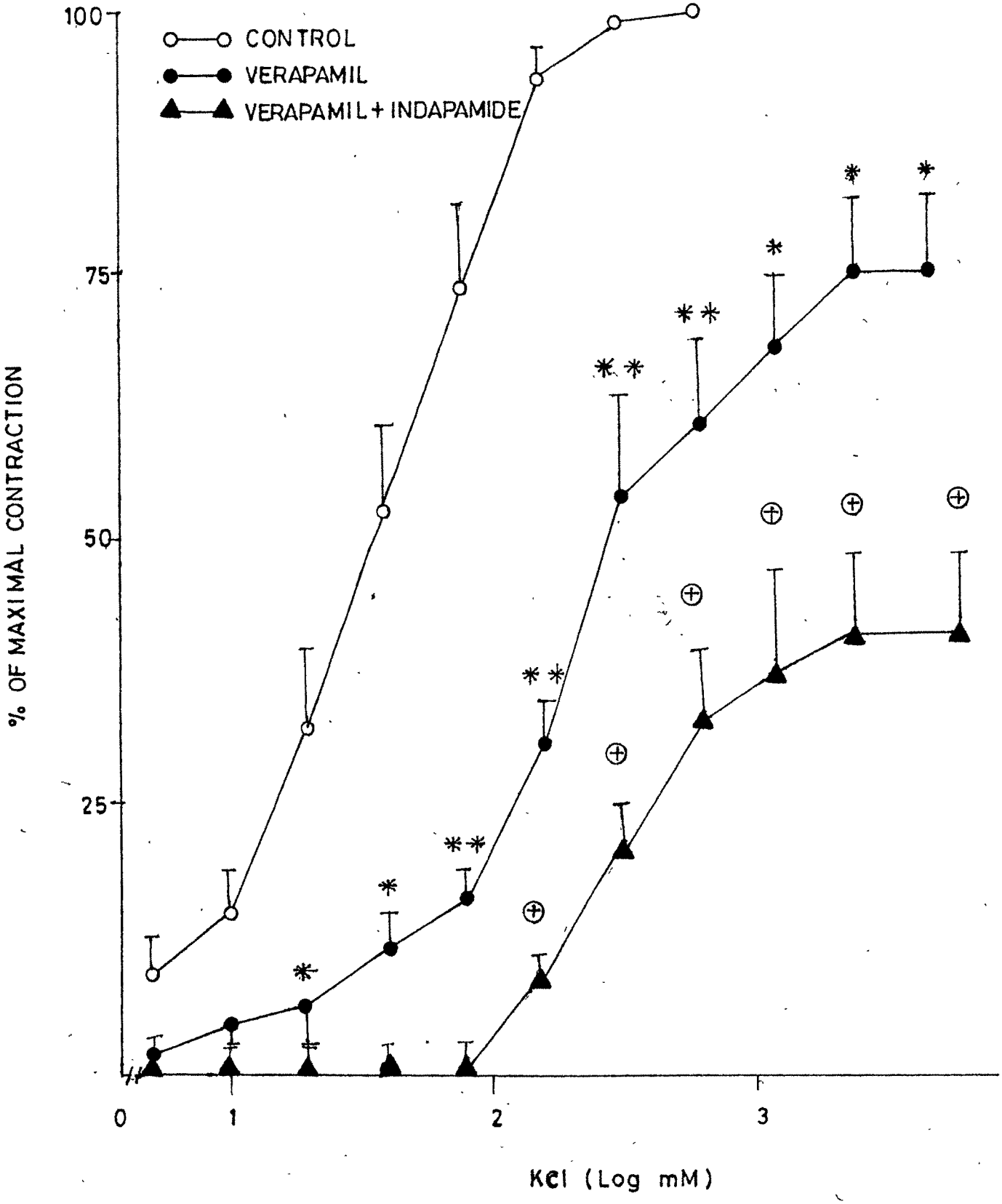

100
75
50
25
0
1
2
3
CONTROL
VERAPAMIL
VERAPAMIL + INDAPAMIDE
% OF MAXIMAL CONTRACTION
Kcl (Log mM)

Fig. 33

Effect of indapamide on the concentration-response curve of NA in the presence of indomethacin in the rat isolated aorta. The abscissa depicts the concentration of NA and the ordinate the responses as percentage of control maximum response. Open circles (○—○) represent control concentration response curve, closed circles (●—●) in the presence of indomethacin (2.8×10^{-5}M) and closed triangles (▲—▲) in the presence of indomethacin + indapamide. Vertical lines denote S.E.M. (n = 5). The level of significance is indicated by asterisks (*$P < 0.05$ and **$P < 0.01$) in relation to control and by ⊕ in relation to indomethacin treated preparations.

FIG: 33

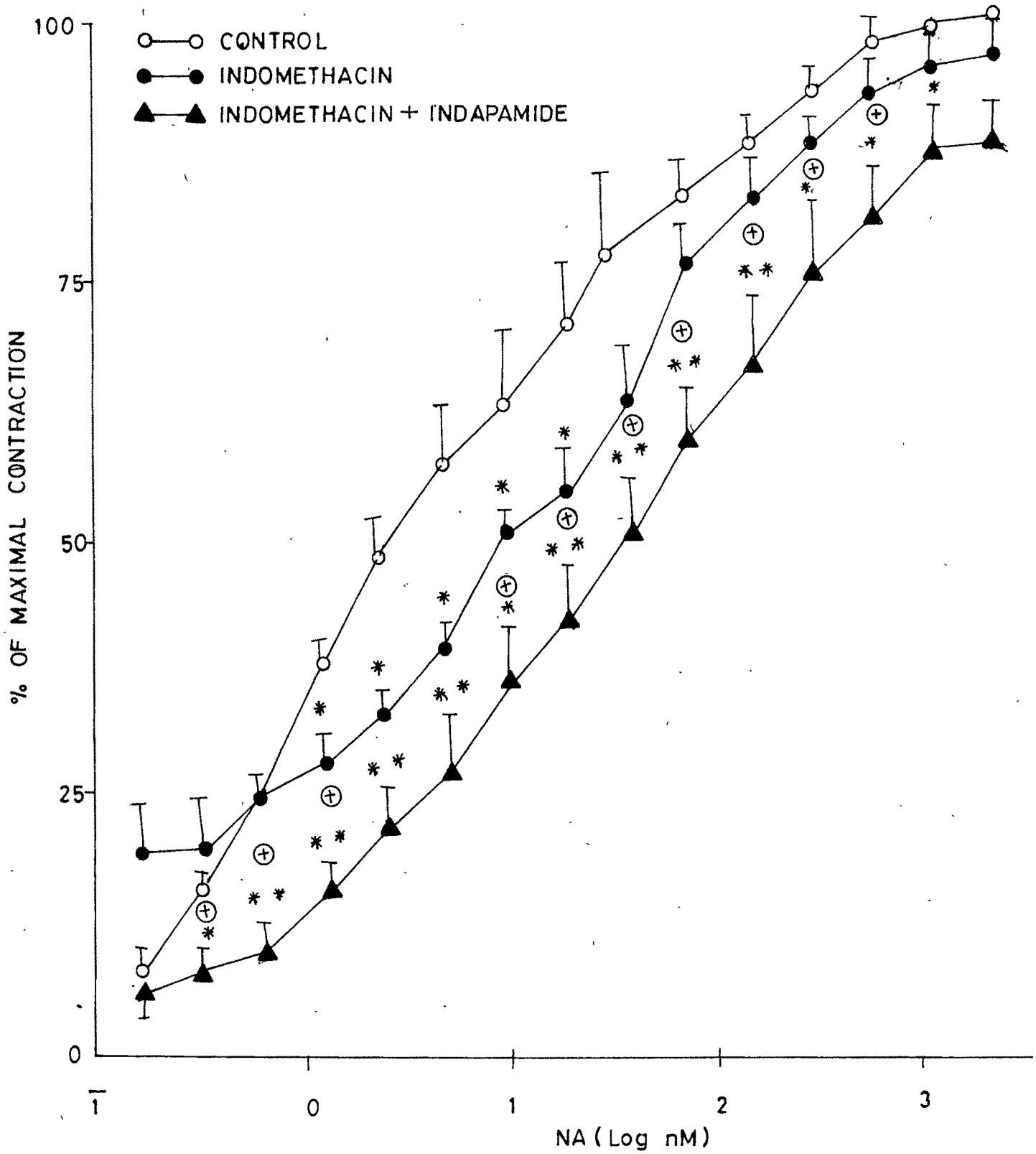
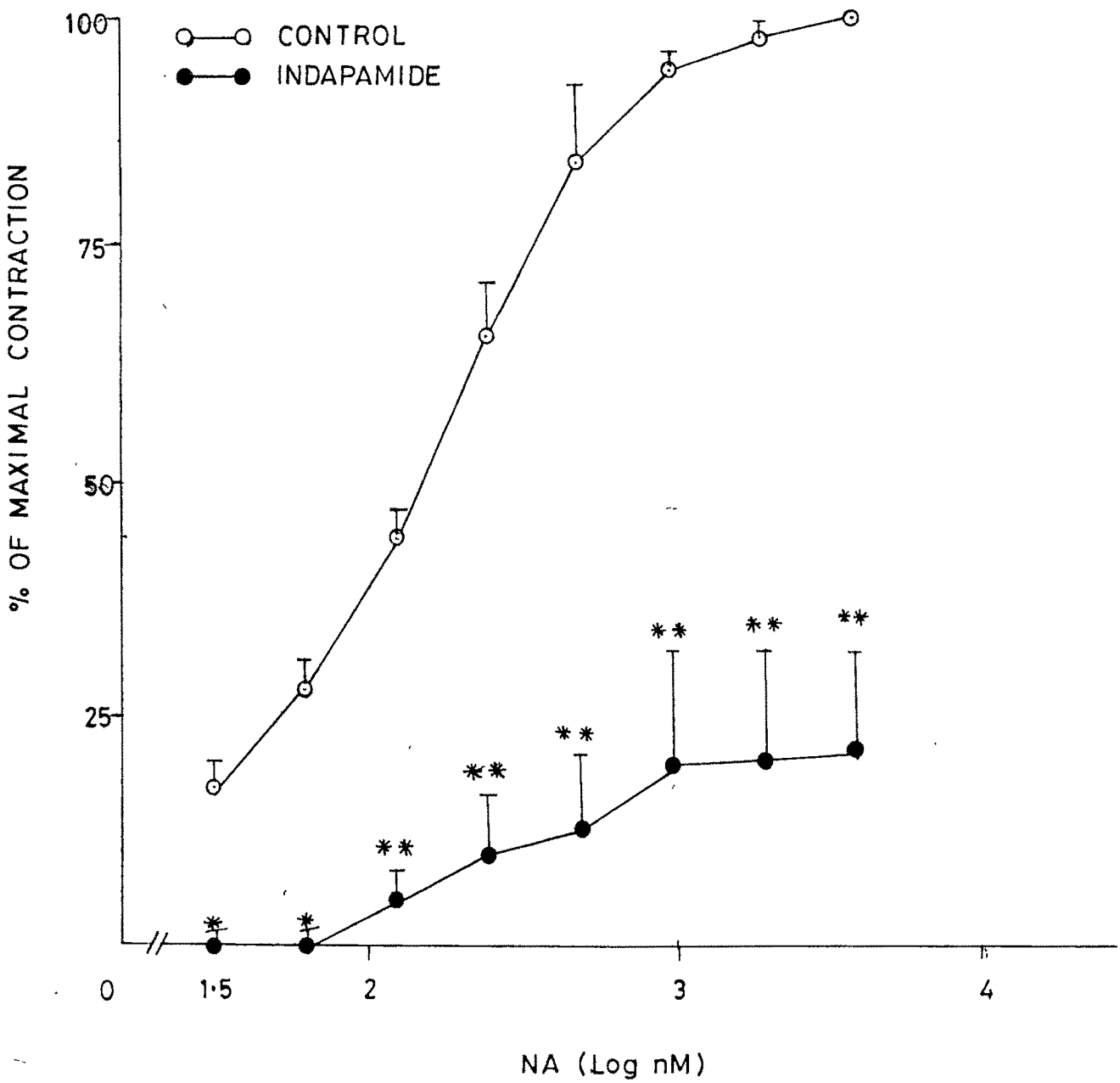

CONTROL
INDOMETHACIN
INDOMETHACIN + INDAPAMIDE
100
75
50
25
0
% OF MAXIMAL CONTRACTION
1
0
1
2
3
NA (Log nM)

Fig.34

Effect of indapamide on the concentration-response curve of NA in the portal vein of rat. The abscissa depicts concentration of NA and the ordinate the responses as percentage of control maximum response. Open circles (o——o) represent control concentration response curve and closed circles (●——●) in the presence of indapamide (3.0×10^{-5}M). Vertical lines denote S.E.M.(n = 4). The level of significance is indicated by asterisks *P $<$ 0.05 and **P $\leq$ 0.01.

FIG : 34


100
75
50
25
0
1·5
2
3
4
CONTROL
INDAPAMIDE
% OF MAXIMAL CONTRACTION
NA (Log nM)
**

(ii) Contractile responses to KCl: KCl produced dose related contractions. Indapamide (3.0×10^{-5}M) inhibited the responses with depression of the maxima (Fig.35).

(iii) Contractile responses to $CaCl_2$: $CaCl_2$ produced dose related contractions. Indapamide (3.0×10^{-5}M) inhibited the responses with the depression of the maxima (Fig.36).

(iv) Contractile responses to ANG: ANG produced dose related contractile responses. Indapamide (3.0×10^{-5}M) inhibited the responses with the depression of the maxima (Fig.37).

(3). Vas deferens

(i) Contractile responses to NA: NA produced dose related contractile responses. Indapamide (3.0×10^{-5}M) did not modify the DRC of NA (Fig.38a). A higher concentration of indapamide (3.0×10^{-4}M) inhibited the responses with the depression of the maxima (Fig.38b).

(ii) Contractile responses to KCl: KCl produced concentration related contractile responses. Indapamide (3.0×10^{-5}M) did not modify responses to KCl (Fig.39a). A higher dose (3.0×10^{-4}M) inhibited the responses with the depression of maxima (Fig.39b).

Fig. 35

Effect of indapamide on the concentration-response curve of KCl in the portal vein of rat. The abscissa depicts concentration of KCl and the ordinate the responses as percentage of control maximum response. Open circles (O—O) represent control concentration response curve and the closed circles (●—●) in the presence of indapamide (3.0×10^{-5}M). Vertical lines denote S.E.M. (n = 4). The level of significance is indicated by asterisks *$P < 0.05$ and **$P < 0.01$.

FIG:35

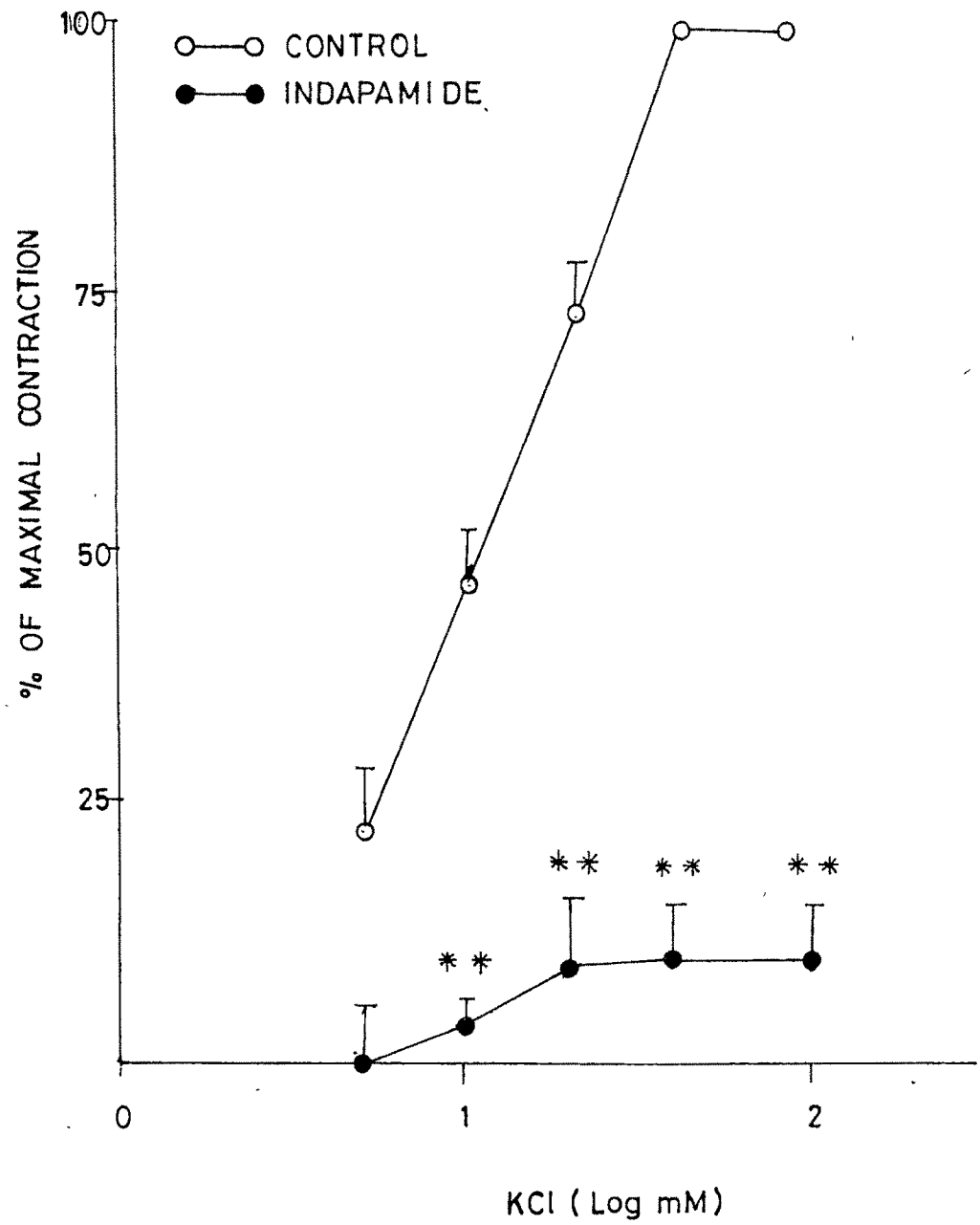

100
75
50
25
0
1
2
CONTROL
INDAPAMIDE
% OF MAXIMAL CONTRACTION
KCl (Log mM)
**
**
**
**

FIG:36

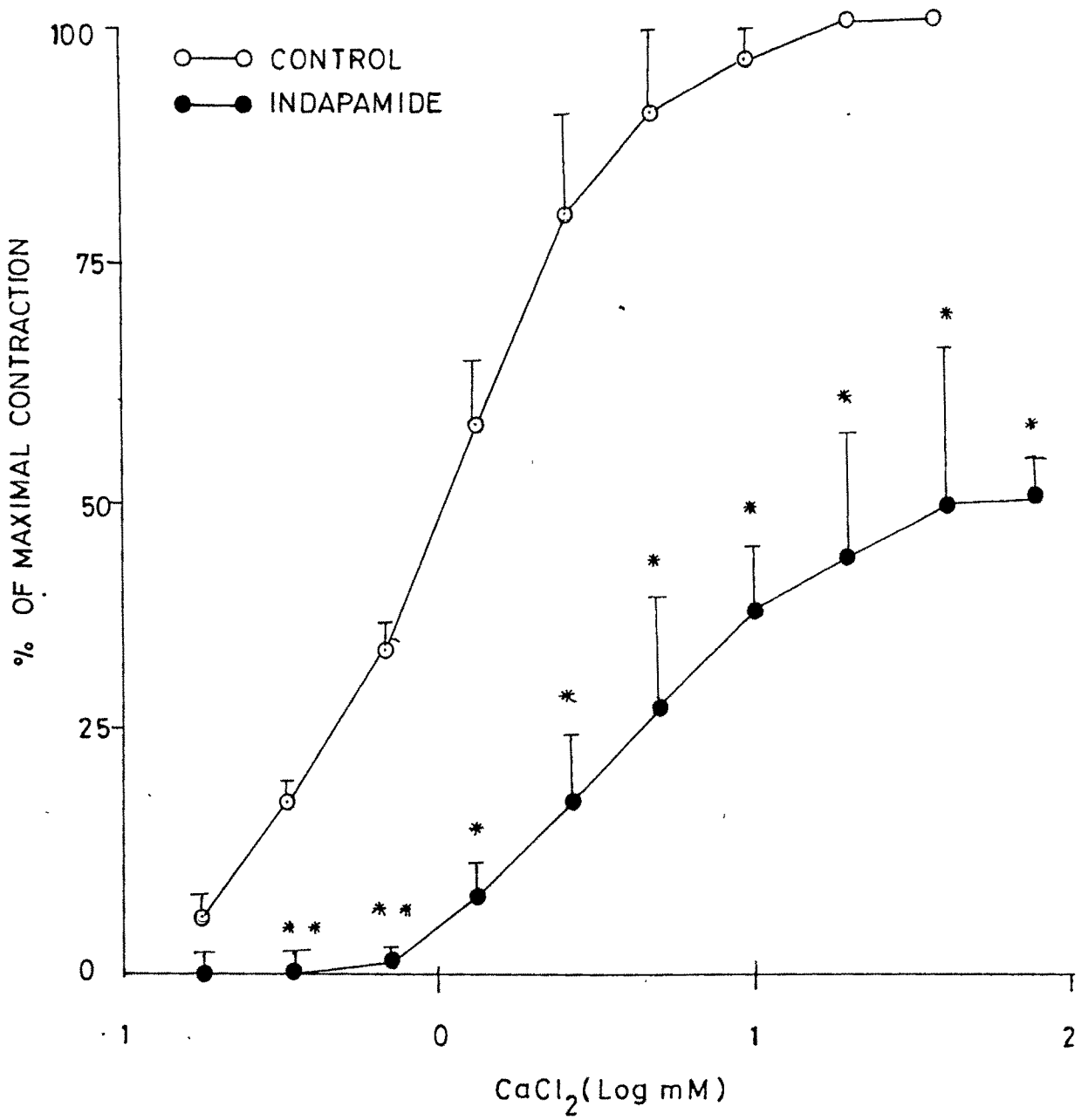

100
75
50
25
0
% OF MAXIMAL CONTRACTION
CONTROL
INDAPAMIDE
-1
0
1
2
CaCl2(Log mM)

Fig.43

Effect of indapamide on the concentration-response curve of NA in the presence of indomethacin. The abscissa depicts the concentration of NA and the ordinate the responses as percentage of control maximum response. Open circles (O—O) represent control concentration response curve, closed circles (●—●) in the presence of indomethacin (2.8×10^{-5}M) and closed triangles (▲—▲) in the presence of indomethacin + indapamide (3.0×10^{-4}M). Vertical lines denote S.E.M. (n = 5). The level of significance ($P < 0.05$) is indicated by asterisk (*).

Fig.36

Effect of indapamide on the concentration-response curve of $CaCl_2$ in the portal vein of rat. The abscissa depicts concentration of $CaCl_2$ and the ordinate the responses as percentage of control maximum response. Open circles (O—O) represent control concentration response curve and closed circles (●—●) in the presence of indapamide (3.0×10^{-5}M). Vertical lines denote S.E.M. ($n = 3$). The level of significance ($P < 0.05$) is indicated by asterisk (*).

Fig.37

Effect of indapamide on the concentration-response curve of ANG in the portal vein of rat. The abscissa depicts the concentration of ANG and the ordinate the responses as percentage of control maximum response. Open circles (o——o) represent control concentration response curve and the closed circles (●——●) in the presence of indapamide (3.0×10^{-5}M). Vertical lines denote S.E.M. (n = 3). The level of significance ($P < 0.05$) is indicated by asterisk (*).

FIG :37

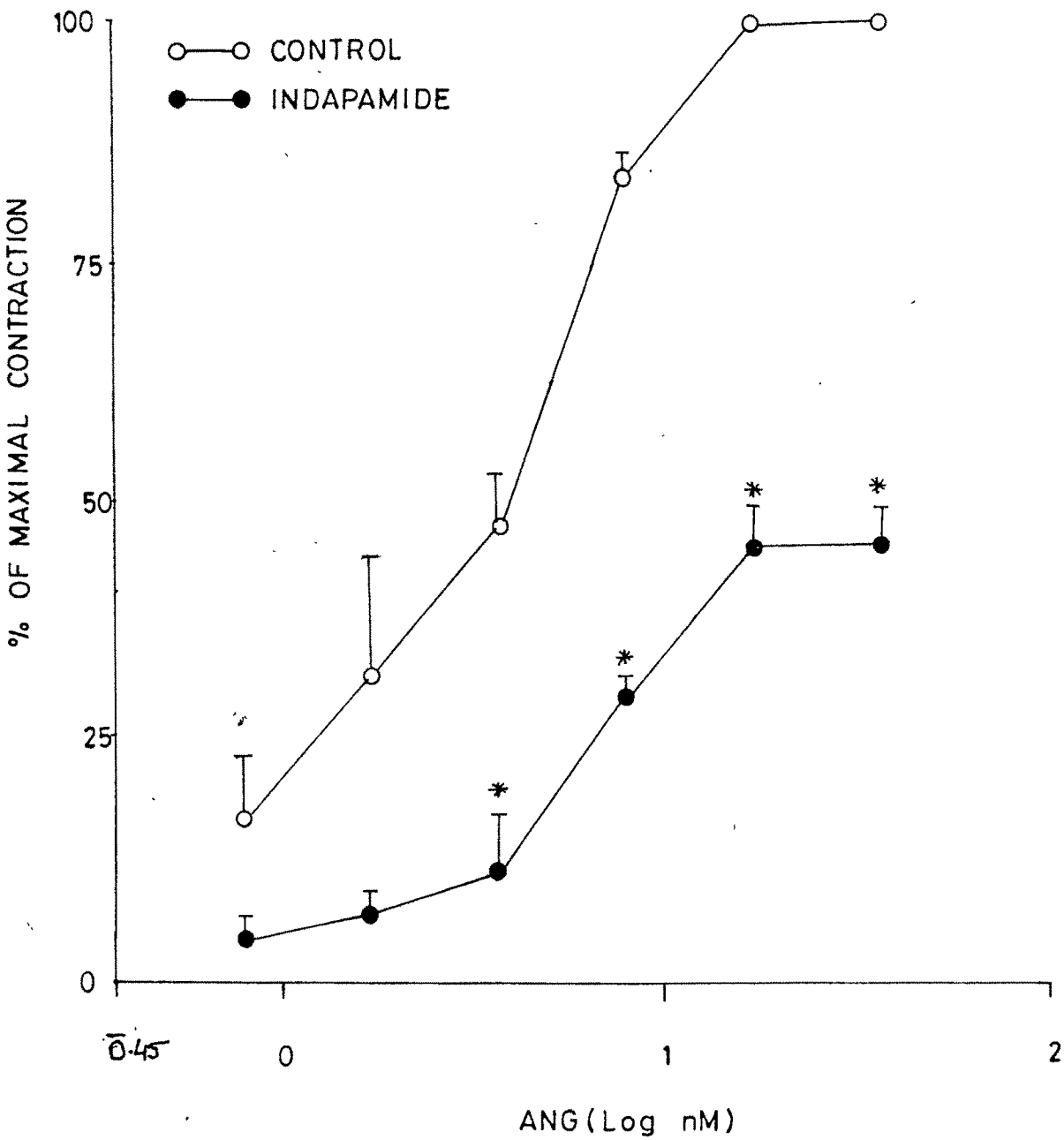

100
75
50
25
0
CONTROL
INDAPAMIDE
% OF MAXIMAL CONTRACTION
0·45
0
1
2
ANG (Log nM)

Fig. 38

Effect of indapamide on the concentration-response curve of NA in the rat isolated vas deferens. The abscissa depicts concentration of NA and the ordinate the responses as percentage of control maximum response. Open circles (o—o) represent control concentration response curve, closed triangles (▲—▲) in the presence of vehicle and the closed circles (●—●) in the presence of indapamide (3.0×10^{-5}M in a and 3.0×10^{-4}M in b). Vertical lines denote S.E.M. (n = 5 to 6 for each observation). The level of significance is indicated by asterisks *$P < 0.05$ and **$P < 0.01$.

FIG: 38

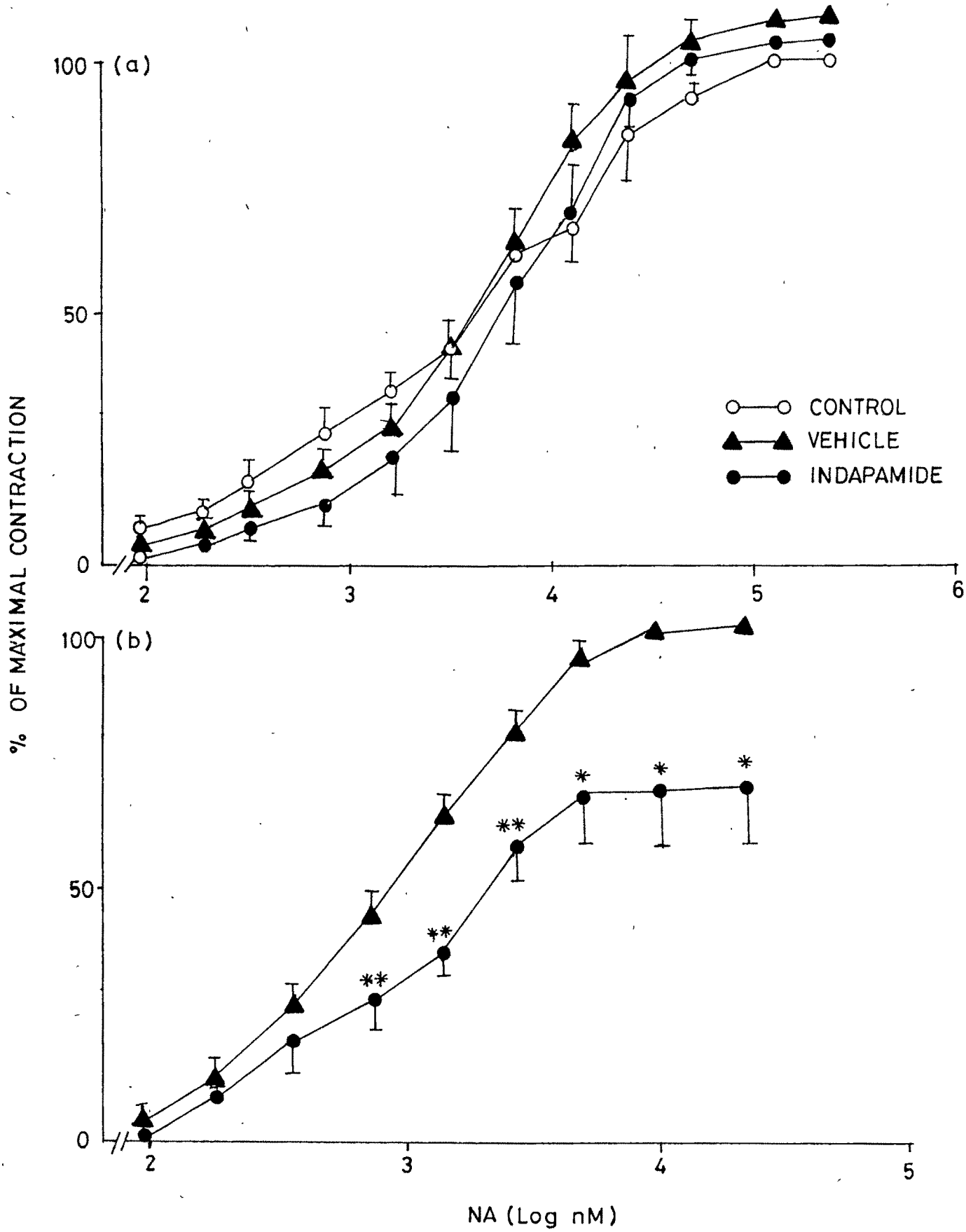
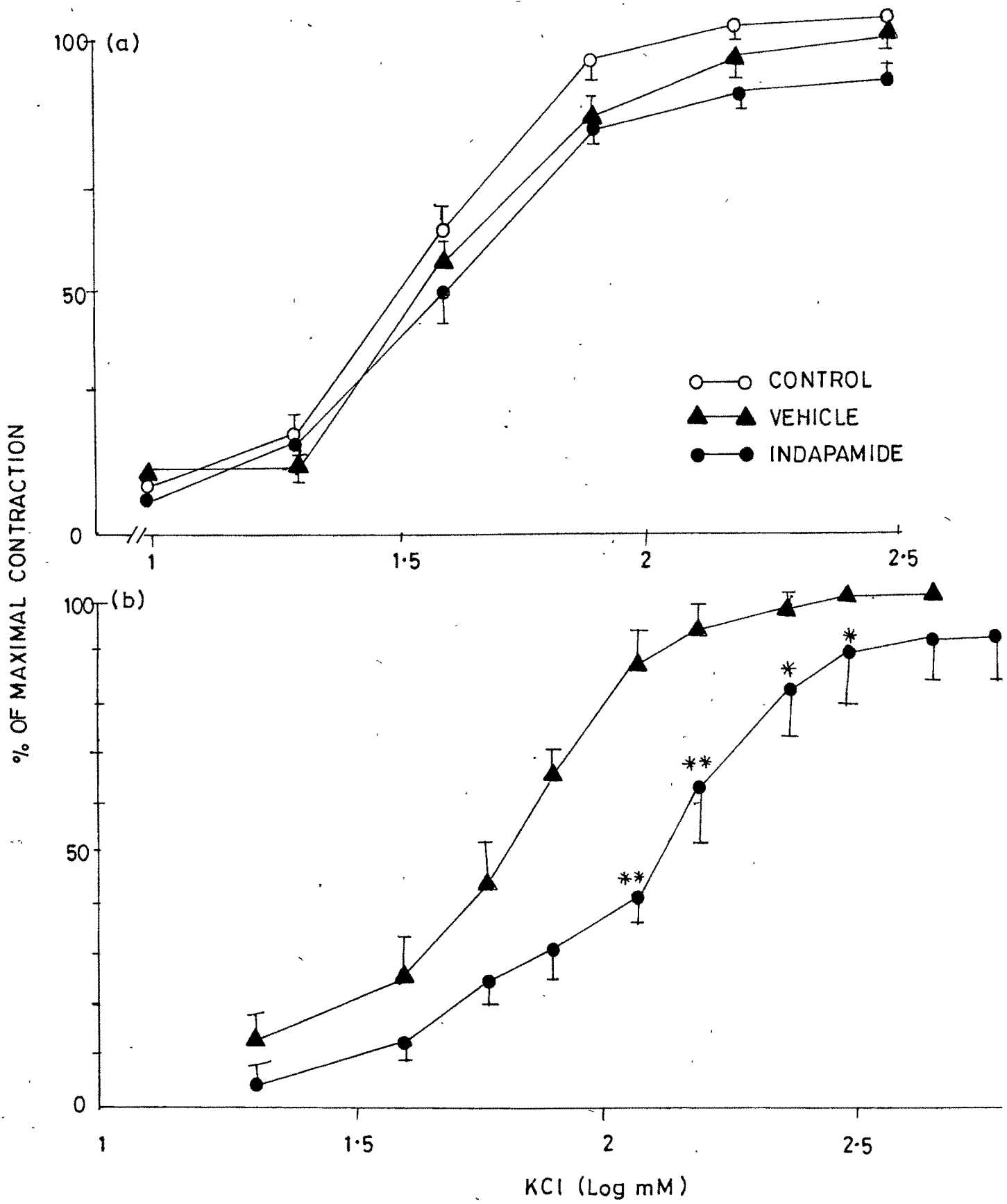

100
(a)
50
0
2
3
4
5
6
CONTROL
VEHICLE
INDAPAMIDE
100
(b)
50
0
2
3
4
5
*
**
% OF MAXIMAL CONTRACTION
NA (Log nM)

Fig.39

Effect of indapamide on the concentration-response curve of KCl in the rat isolated vas deferens. The abscissa depicts concentration of KCl and the ordinate the responses as percentage of control maximum response. Open circles (o—o) represent concentration response curve in control, closed triangles (▲—▲) in the presence of vehicle and closed circles (●—●) in the presence of indapamide (3.0×10^{-5}M in a and 3.0×10^{-4}M in b). Vertical lines denote S.E.M. (n = 5 to 6 for each observation). The level of significance is indicated by asterisks *$P < 0.05$ and **$P < 0.01$.

FIG:39


100
(a)
50
0
1
1·5
2
2·5
CONTROL
VEHICLE
INDAPAMIDE
100
(b)
50
0
1
1·5
2
2·5
% OF MAXIMAL CONTRACTION
KCl (Log mM)
*
*
**
**

(iii) Contractile responses to $CaCl_2$: $CaCl_2$ produced dose related contractile responses. Indapamide (3.0×10^{-5}M) did not modify responses to the $CaCl_2$ (Fig.40a); however, the higher dose (3.0×10^{-4}M) shifted the curve towards the right with depression of the maxima (Fig.40b).

(iv) Effect of indapamide on submaximal contraction with TYR, 5-HT and ANG: Indapamide (3.0×10^{-5}M) inhibited submaximal responses to TYR and ANG while it did not modify response to 5-HT (Fig.41).

(v) Effect of indapamide on responses to KCl in the presence of verapamil: KCl produced dose related contractions. Verapamil (1.0×10^{-6}M) inhibited responses to KCl. Indapamide (3.0×10^{-4}M) further inhibited responses to K^+ in the presence of verapamil (Fig.42).

(vi) Effect of indapamide on responses to NA in the presence of indomethacin: NA produced dose related contractile responses. Indomethacin (2.8×10^{-5}M) did not modify responses to NA. Indapamide (3.0×10^{-4}M) inhibited responses to NA in the presence of indomethacin (Fig.43).

Fig.40

Effect of indapamide on the concentration-response curve of $CaCl_2$ in rat isolated vas deferens. The abscissa depicts concentration of $CaCl_2$ and the ordinate the responses as percentage of control maximum response. Open circles (o—o) represent control concentration curve, closed triangles (▲—▲) in the presence of vehicle and closed circles (●—●) in the presence of indapamide (3.0×10^{-5}M in a and 3.0×10^{-4}M in b). Vertical lines denote S.E.M. (n = 5 to 6 for each observation). The level of significance is indicated by asterisks *$P < 0.05$ and **$P < 0.01$.

FIG : 40

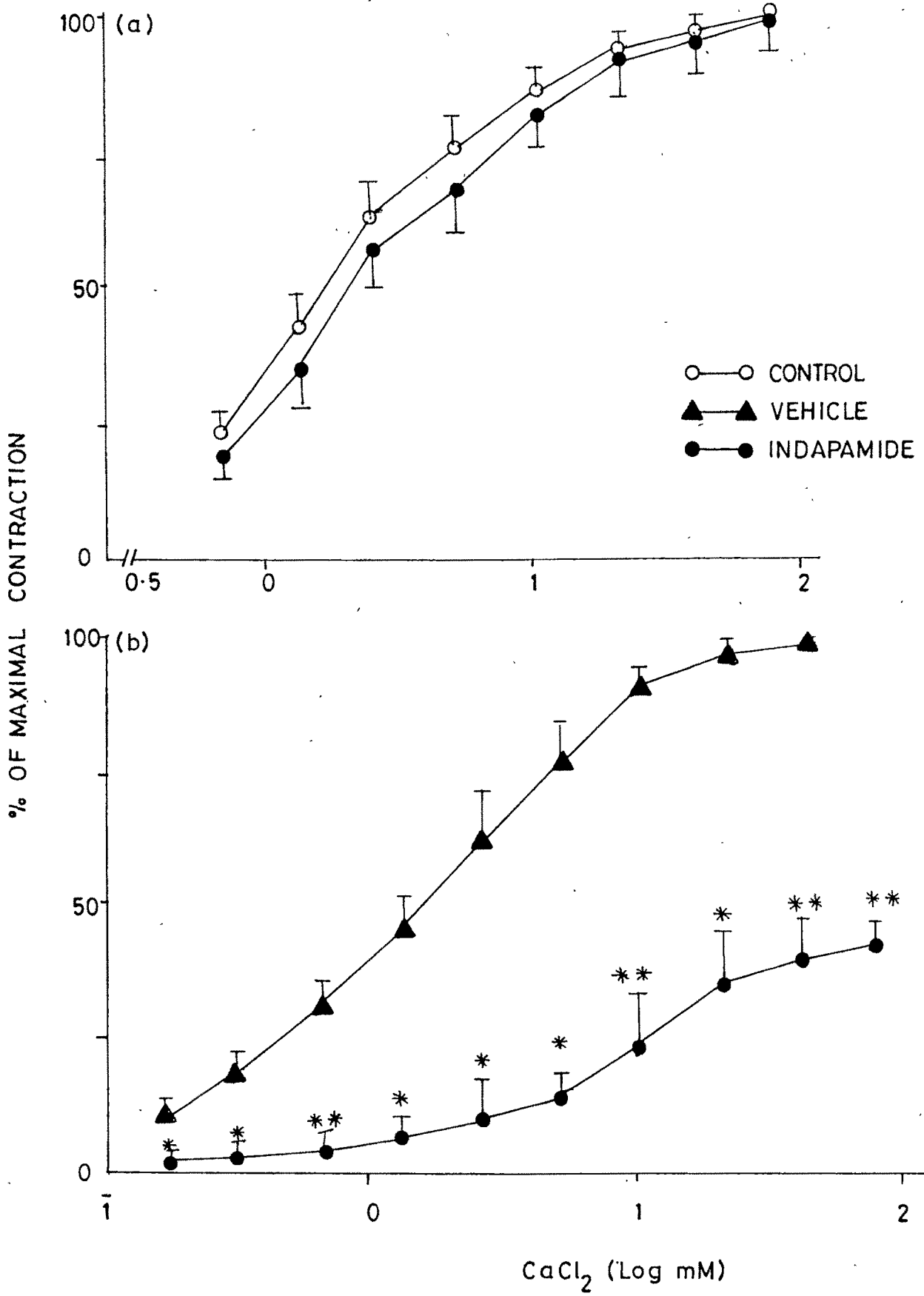

100
(a)
50
0
0·5
0
1
2
CONTROL
VEHICLE
INDAPAMIDE
100
(b)
50
0
1
0
1
2
% OF MAXIMAL CONTRACTION
CaCl2 (Log mM)

Fig.41

Effect of indapamide on the submaximal responses to different agonists in rat isolated vas deferens. The abscissa depicts responses to TYR (9.6×10^{-5}M), 5-HT (3.9×10^{-5}M) and ANG (6.4×10^{-7}M) and the ordinate the responses expressed as percentage of maximal PE (3.0×10^{-5}M) responses. Open bars (□) represent control responses to TYR, 5-HT and ANG respectively and closed bars (■) represent responses in the presence of indapamide (3.0×10^{-5}M). Vertical lines denote S.E.M. ($n = 7$). The level of significance ($P < 0.01$) is indicated by asterisks.

FIG:41

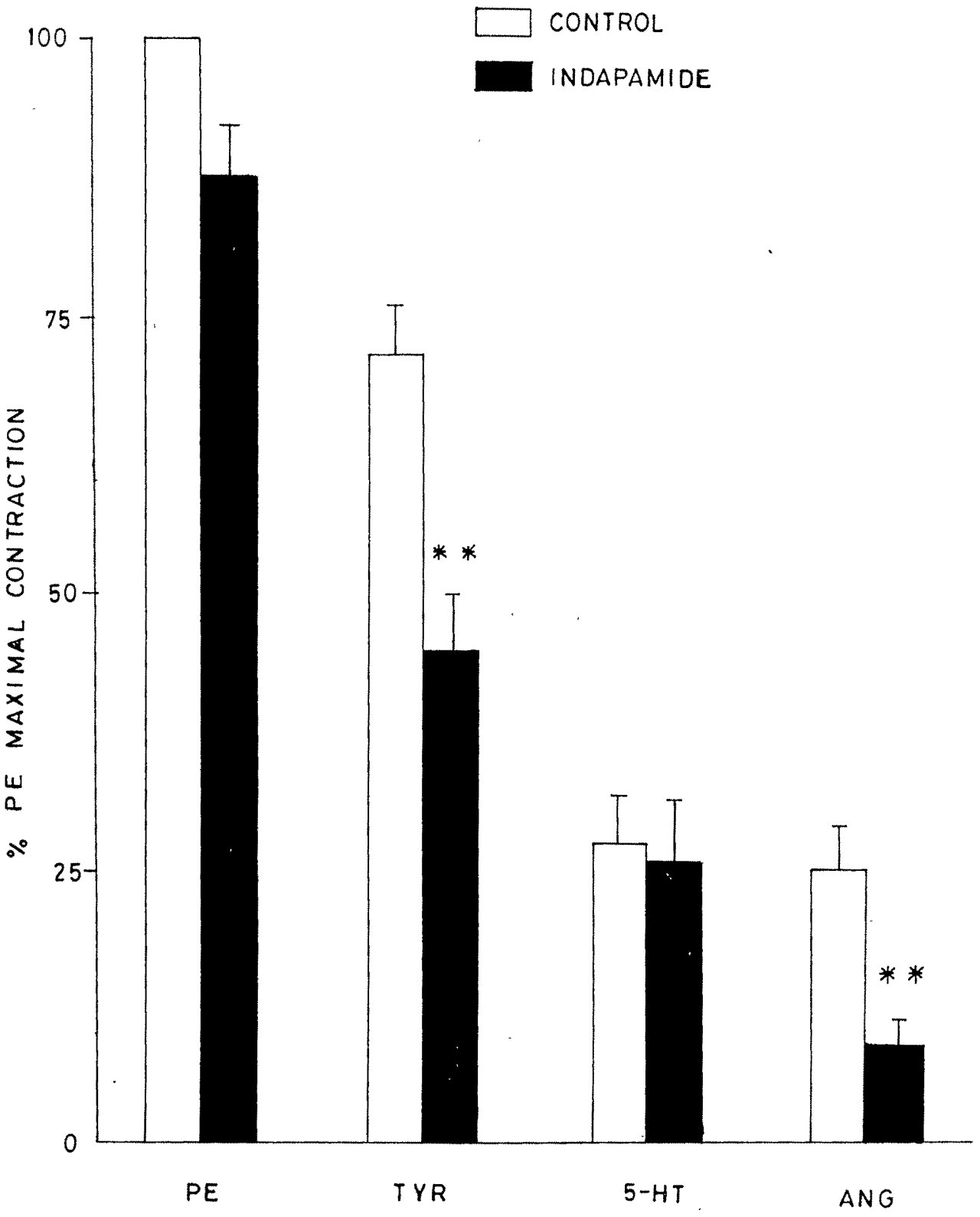

CONTROL
INDAPAMIDE
100
75
50
25
0
% PE MAXIMAL CONTRACTION
* *
* *
PE
TYR
5-HT
ANG

Fig.42

Effect of indapamide on the concentration-response curve of KCl in the presence of verapamil in the rat isolated vas deferens. The abscissa depicts the concentration of KCl and the ordinate the responses as percentage of control maximum response. Open circles (○—○) represent control concentration response curve, closed circles (●—●) in the presence of verapamil (1.0×10^{-6}M) and closed triangles (▲—▲) in the presence of indapamide + verapamil. Vertical lines denote S.E.M.(n = 5). The level of significance is indicated by asterisks (*$P < 0.05$ and **$P < 0.01$) in relation to control and by ⊕ in relation to verapamil treated preparations.

FIG: 42

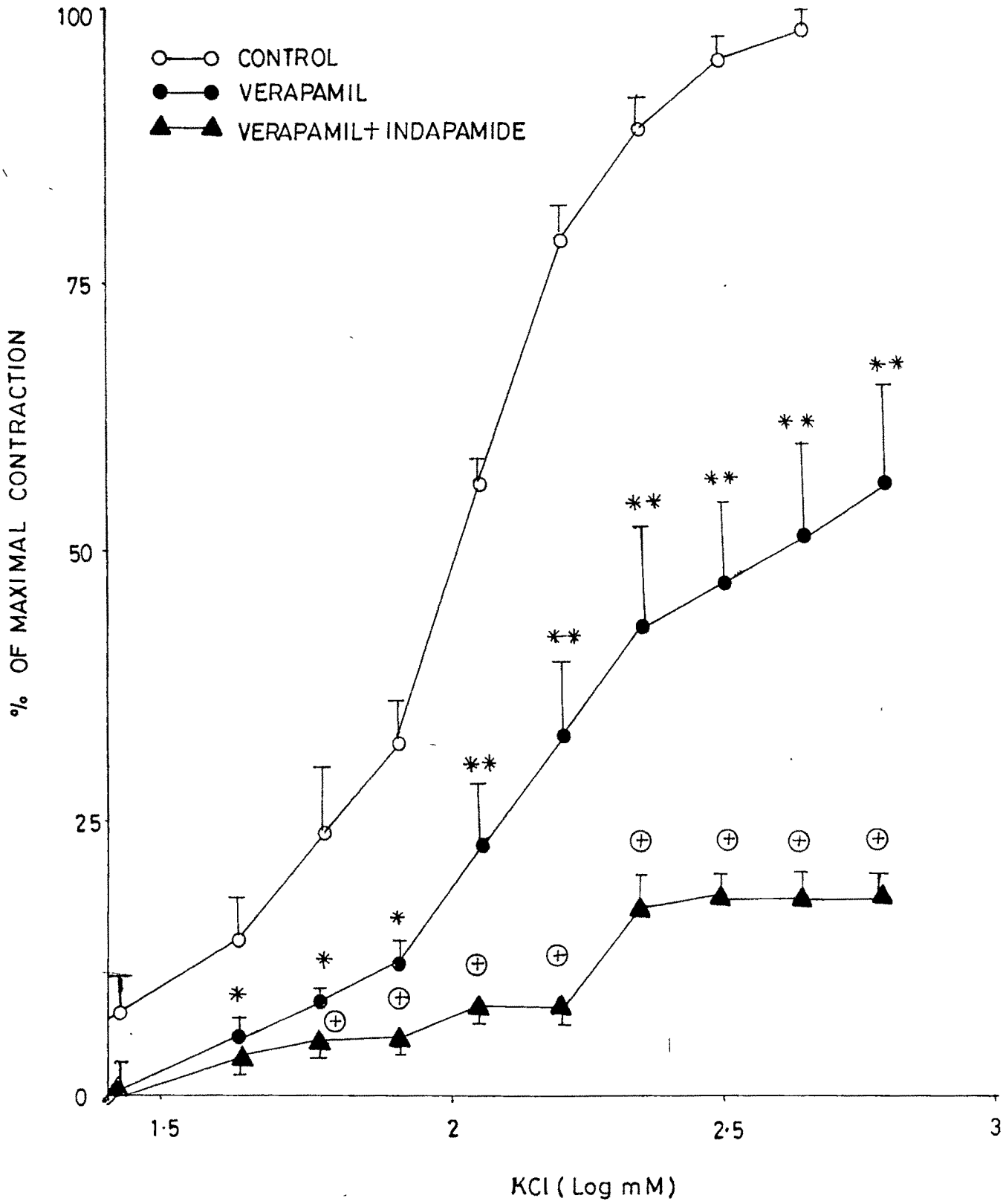
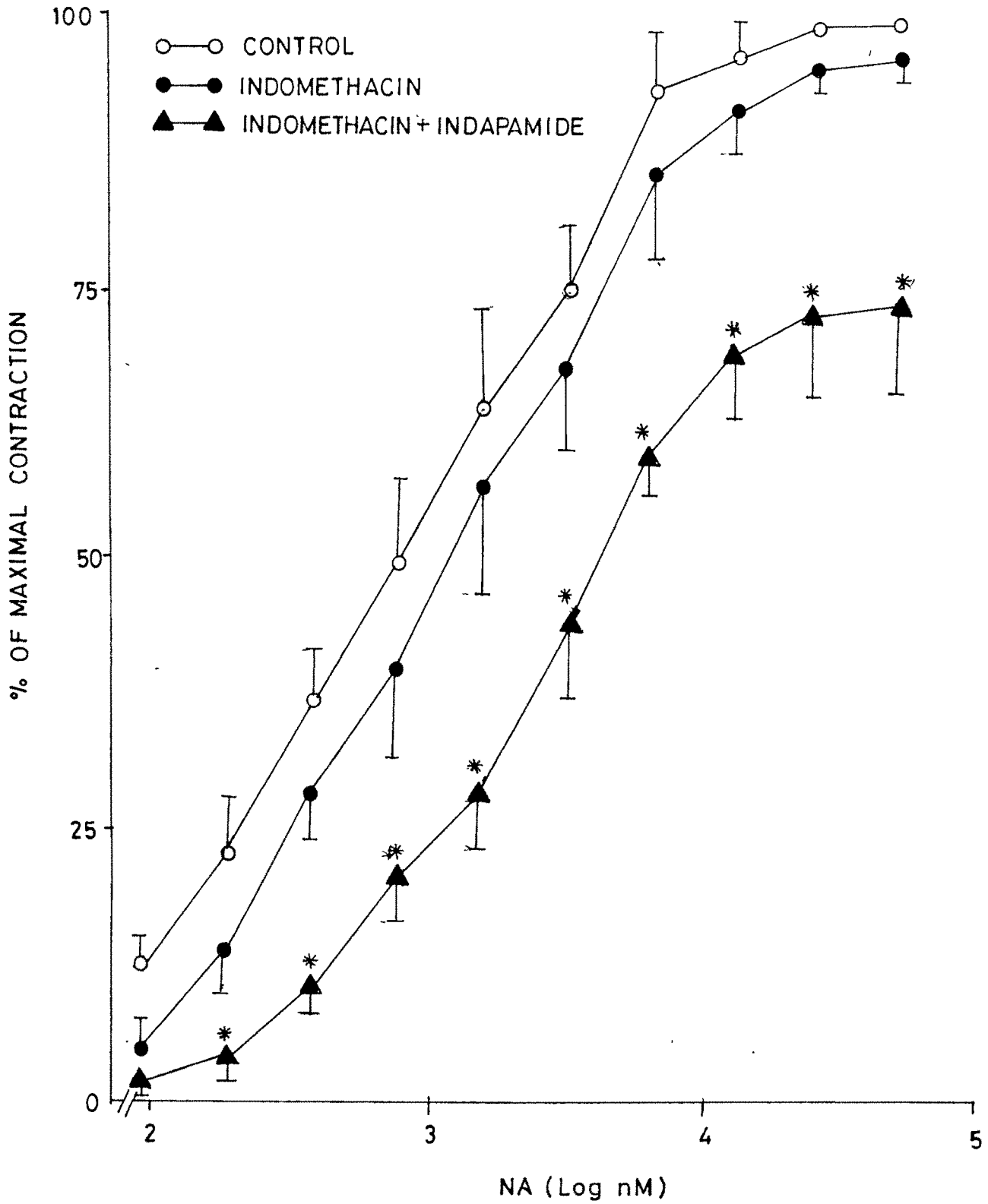

100
75
50
25
0
% OF MAXIMAL CONTRACTION
CONTROL
VERAPAMIL
VERAPAMIL+ INDAPAMIDE
1·5
2
2·5
3
KCl (Log mM)

FIG: 43


100
75
50
25
0
% OF MAXIMAL CONTRACTION
CONTROL
INDOMETHACIN
INDOMETHACIN + INDAPAMIDE
2
3
4
5
NA (Log nM)