Table 1. Changes in the mean arterial pressure following intravenous administration of captopril (3 mg kg^{-1}) alone and with indomethacin or aprotinin in anephric dogs.

	Δ MBP (mmHg) after captopril					
Baseline BP (mmHg)	+10 min	+20 min	+30 min	+40 min	+50 min	+60 min
Captopril alone						
103 ± 5	−21 ± 2	−17 ± 2	−12 ± 2	−7 ± 1	−6 ± 1	−5 ± 1
Indo. + captopril						
104 ± 4	−5 ± 1*	−7 ± 1*	−7 ± 1*	−6 ± 1	−5 ± 1	−3 ± 1
Aprotinin + captopril						
104 ± 7	−21 ± 3	−17 ± 2	−11 ± 2	−6 ± 1	−3 + 1	−1 ± 1

All values represent mean ± s.e.m. of 5 animals.
* $P < 0.05$, compared with 'captopril alone' or 'aprotinin + captopril' group.

inhibitor (YS-980: (4*R*)-3-[(2*S*)-3-mercapto-2-methyl-propanoyl]-4-thiazolidine carboxylic acid) was blunted by aprotinin in dogs, both compounds being administered via the renal artery.

The effective inhibition of captopril's effect on BP with indomethacin in the anephric state strongly implicates involvement of extrarenal prostaglandins. In doca/salt hypertensive rats, which were also characterized by a low-renin state (0·3 vs 4·4 ng AI ml^{-1} h^{-1} in normal controls), Miyamori et al (1980) showed that the hypotensive effect of captopril was inhibited by indomethacin. Furthermore, a recent clinical study (Moore et al 1981) demonstrated that inhibition of prostaglandin synthesis with indomethacin or aspirin inhibited the depressor response to captopril in some hypertensive patients and appeared to be related to suppression of prostaglandin E2 generation. However, the linking events between ACE inhibition by captopril and activation of vasoactive prostaglandins remain to be elaborated.

In conclusion, the present results indicate that extrarenal prostaglandins, but not kinins contribute significantly to the hypotensive effect of captopril in anephric dogs.

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The ability of iprindole to antagonize the biochemical central effects of clonidine

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Iprindole, a clinically active antidepressant, has no effect on noradrenaline (NA) or 5-hydroxytryptamine (5-HT) uptake, on monoamine oxidase (MAO) activity or on reserpine effects characteristic of typical antidepressant drugs (Gluckman & Baum 1969; Lahti & Maickel 1971; Rosloff & Davis 1974). Iprindole does not change the brain level of NA or of MOPEG, or the NA turnover (Freeman & Sulser 1972; Rosloff & Davis 1978; Sugrue 1981). Binding studies have also indicated that iprindole has a low activity with respect to α_1, α_2, 5-HT or others receptors (e.g. Peroutka & Snyder 1980; Hall & Ögren 1981). It therefore appears to be a drug with no definite action in an acute experiment.

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In the course of our studies on atypical antidepressants, we have found that iprindole affects changes in the brain 3-methoxy-4-hydroxyphenylethyleneglycol (MOPEG) level and in the utilization of NA (after inhibition of its synthesis), both induced by clonidine. These findings are the subject of the present communication.

Methods

The experiments were carried out on male Wistar rats, 180–220 g. All drugs were given i.p. Iprindole and clonidine were dissolved in 0.9% NaCl (saline). The total MOPEG level was estimated by gas liquid chromatography with electron capture detection as the pentafluoropropionyl derivative, according to Braestrup (1973). The supernatant from the whole brain

Table 1. Effect of iprindole (IPR) on the clonidine (CLO)-induced decrease in brain total MOPEG level in rats.

Dose (mg kg^{-1})	Brain MOPEG levels (ng g^{-1}) ± s.e.m.			
	Control	IPR	CLO	IPR + CLO
5	91·3±2·7	92·6±3·9	60·4±3·8*	90·3±8·4††
10	101·3±6·4	108·9±6·8	59·6±3·4*	89·1±8·1††
20	106·4±9·5	108·2±10·1	63·0±4·9*	105·1±2·4†††
40	95·2±2·4	96·8±7·9	60·9±5·3*	81·6±6·5†

IPR was administered 3 h, CLO (0·2 mg kg^{-1}) 2·5 h before decapitation. Both drugs were given i.p. dissolved in saline. MOPEG level was determined according to Braestrup (1973). Each result is the mean of at least 5 determinations.

* Differs from control, $P < 0·01$ (Student's t-test).
† Differs from CLO treated group, $P < 0·02$.
†† Differs from CLO treated group, $P < 0·01$.
††† Differs from CLO treated group, $P < 0·001$.

Table 2. Effect of IPR on the CLO-induced decrease in NA disappearance produced by FLA-63 in rats.

Dose (mg kg^{-1})	Brain NA level (ng g^{-1}) ± s.e.m.				
	Control	FLA-63	IPR + FLA-63	CLO + FLA-63	IPR+CLO+ FLA-63
10	382·9 ± 16·9	231·6 ± 7·7	224·5 ± 10·3	402·5 ± 18·9**	325·0 ± 25·4*†
20	397·3 ± 26·3	217·7 ± 12·3	211·5 ± 12·3	329·1 ± 13·3**	270·2 ± 19·4*†
40	404·7 ± 18·0	247·2 ± 18·6	248·3 ± 12·4	369·9 ± 18·5**	268·5 ± 26·0†

IPR was given 3 h, CLO (0·2 mg kg^{-1}) 2·5 h, FLA-63 (30 mg kg^{-1}) 2 h prior to decapitation. All drugs were injected i.p. as solution in saline (IPR and CLO) or suspension in 1% Tween 80 (FLA-63).

NA level was determined according to Earley and Leonard (1978). Each result is the mean of at least 6–7 determinations.

* Differs from FLA-63 group, $P < 0·05$ (Student's t-test).
** Differs from FLA-63 group, $P < 0·001$.
† Differs from CLO+FLA-63 group, $P < 0·05$.

extract was hydrolysed overnight with glusulase (Endo Laboratories, Inc.). Iprindole was administered 3 h and clonidine (0·2 mg kg^{-1}) 2·5 h before decapitation. The controls received saline.

The utilization of brain NA was evaluated by measuring its disappearance after treatment with dopamine β-hydroxylase inhibitor, FLA-63 (bis(4-methyl-1-homopiperazinylthiocarbonyl) disulphide) in a dose 30 mg kg^{-1} (suspension in 1% Tween 80). NA was determined spectrofluorimetrically (Earley & Leonard 1978). Iprindole was given 3 h, clonidine (0·2 mg kg^{-1}) 2·5 h and FLA-63 2 h before decapitation.

Results

Iprindole (5–40 mg kg^{-1}) did not change the total brain MOPEG level (Table 1). The MOPEG levels at other times (1, 2, 8 h) were also not modified (data not given here). The ability of clonidine to lower the brain MOPEG level was antagonized by pretreatment with iprindole (Table 1). A similar antagonism was observed in preliminary experiments when a lower dose of clonidine (0·1 mg kg^{-1}) was used (data not presented).

Iprindole (10, 20, 40 mg kg^{-1}) did not change the NA level in the brains of normal rats (data not presented here). Clonidine decelerated the utilization of NA by the brains of rats treated with FLA-63 (Table 2). Iprindole given alone (10, 20, 40 mg kg^{-1}) to FLA-63-treated rats did not affect the utilization of NA, but significantly counteracted the clonidine-induced decelerating effect.

The findings that iprindole given alone had no effect on the brain MOPEG level of normal rats or on the disappearance of brain NA in FLA-63 treated rats are in accordance with reported results (Freeman & Sulser 1972; Rosloff & Davis 1978; Sugrue 1981). The antagonism of iprindole towards clonidine, evaluated here by means of the MOPEG level or the disappearance of NA, resembles the similar action of yohimbine, a α_2-adrenoceptor blocker (Andén & Grabowska 1976; Braestrup & Nielsen 1976). Yohimbine, however, given alone, elevates the MOPEG level and increases the utilization of NA, hence the anti-clonidine action of iprindole we observed would not seem to result from blockade of α_2-adrenoceptors. This is also supported by the findings that iprindole does not antagonize the functional effects of clonidine, like sedation, hypothermia and analgesia (own data, unpublished). The latter fact also excludes the possibility of pharmacokinetic interactions. On the other hand, the inhibition by iprindole of the biochemical, but not the pharmacological, effects of clonidine may suggest that those effects could be induced by different mechanism, among others an influence on different populations of adrenoceptors.

Sugrue (1981) did not observe any influence of iprindole (10 mg kg^{-1}) on the clonidine-induced decrease in MOPEG level. This discrepancy may be due to the fact that he used a different dose of clonidine and determined MOPEG-SO_4 but not total MOPEG.

Although our findings may point to the possibility of an action of iprindole on the NA system, an indirect effect via another system(s) cannot be excluded, e.g. via the β-adrenergic system. Iprindole has been found to block the 6-hydroxydopa-induced depletion of brain adrenaline and consequently the presynaptic potentiating effect of iprindole at adrenaline synapses was hypothesized (Von Voigtlander & Losey 1978). On the other hand the interaction of noradrenergic and adrenergic neurons has been reported (Fuxe et al 1974). Also clonidine, at the dose used here, may not be selective and may therefore affect other central transmitter systems.

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Evidence for a saturable component in isoniazid transfer across rat small intestine in vitro

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It is well known that isoniazid is a drug that is rapidly absorbed after oral administration (Genazzani et al 1966; Gelber et al 1969). As a weak base it is probably absorbed mainly in the small intestine (Schanker 1961). Studying isoniazid transport across rat small intestine in vitro, Barley et al (1972) concluded that the drug was transported by passive diffusion. However, its good water solubility and the almost total dissociation of its hydrazine moiety (pK_a = 10·8) at physiological pH cannot be regarded as favourable for penetration through lipid barriers like intestinal epithelium by passive diffusion. Since Barley et al (1972) based their conclusion on experiments with a limited number of relatively high isoniazid concentrations, we have re-examined the problem of intestinal transfer of isoniazid using a wider range of concentrations (0·5–50 mM) and a modified perfusion technique of rat small intestine in vitro.

An everted isolated segment of the rat proximal ileum, approximately 10 cm long was suspended in 70 ml phosphate buffer ($KH_2PO_4/Na_2HPO_4.12H_2$, pH = 6·0) representing the mucosal compartment into which isoniazid was introduced at the beginning of the experiment. Continuous bubbling by air ensured mixing of the entire volume of this compartment. The serosal side of the segment was continuously washed by Ringer solution from a reservoir (volume 500 ml) by means of a peristaltic pump (Desaga Resomat 14700, Dibbern, FRG) at a rate of 3·5 ml min^{-1}. The solution in the reservoir was continuously mixed by means of a magnetic mixer assuring a constant concentration in all of the system. The temperature of both solutions was maintained at 37 °C thermostatically.

The concentrations of isoniazid in the serosal compartment were continuously recorded for 10 min after its introduction into the mucosal compartment, by means of a u.v. monitor (Chiratic, Chirana, Czechoslovakia) at 266 nm the wavelength of absorption maximum. The rate of isoniazid transfer across the intestinal barrier was expressed as the increase in amount of drug in the serosal compartment per unit time (μg min^{-1}). The experimental design is depicted in Fig. 1.

The following models were considered as possible alternatives to describe the dependence of transport rates of isoniazid on its mucosal concentrations:

(a) A simple first order process (Model I) representing the usual assumption made on the drug's absorption from the gastrointestinal tract (Ellard et al 1972):

$$v = p.c_m$$

where v is the initial transport rate measured in μg min^{-1}, p a 'permeability' constant having the dimension 'volume/unit of time' and c_m the initial drug concentration in the mucosal compartment.

(b) A capacity-limited process of the Michaelis-Menten type (Model II):

$$v = \frac{c_m}{K + c_m} \cdot V_{max}$$

where v and c_m are defined as above, V_{max} is the maximal transport rate and K represents that drug concentration in the mucosal compartment corresponding to the transport rate which is half of the maximal ($V_{max}/2$).

(c) A combination of both—the capacity-limited and first order processes—described by the relationship (Model III):

$$v = \frac{c_m}{K + c_m} \cdot V_{max} + p.c_m$$

Fitting of the experimental data to model equations was performed using unweighted non-linear regression analysis based on the Gauss-Newton computing algorithm. Asymptotic standard deviations (s.d.) of the

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