

Captopril and immune regulation

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Captopril and immune regulation. We examined the *in vitro* effect of captopril (2.5 to 5 $\mu\text{g/ml}$) on the primary antibody response of human B cells. Captopril suppresses (by 50%) the specific anti-trinitrophenyl (TNP) response of unfractionated peripheral blood mononuclear cells (PBM) but not that of nonadherent PBM. The susceptibility to captopril suppression can be restored in the latter cell cultures by 10% adherent radioresistant cells. This suppression is independent of prostaglandins. In transfer experiments, cells preincubated with 5 $\mu\text{g/ml}$ captopril suppress the antibody response of autologous nonadherent PBM. The inductive phase of this suppression requires both adherent cells and radiosensitive T cells. Once induced, the suppression can be transferred by isolated T effector cells. *In vivo* after a unique oral intake of captopril a moderate suppressor activity can be demonstrated in adherent cells from normal individuals. We conclude that captopril interferes with the immune regulation by inducing a suppressor circuit involving monocytes and a T_8 suppressor effector lymphocyte.

Le captopril et la régulation immunitaire. Nous avons examiné l'effet de captopril (2,5 à 5 $\mu\text{g/ml}$) sur la réponse anticorps primaire de cellules B humaines. Le captopril supprime (de 50%) la réponse spécifique anti-trinitrophénol (TNP) de cellules mononucléées (PBM) non fractionnées mais non celles de PBM non-adhérents. Dans les cultures de cellules, la susceptibilité à la suppression par le captopril peut être restaurée par l'addition de 10% de cellules adhérentes radio-résistantes. Cette suppression est indépendante des prostaglandines. Dans des expériences de transfert, les cellules préincubées avec 5 $\mu\text{g/ml}$ de captopril suppriment la réponse anticorps de PBM non-adhérents autologues. L'induction de cette suppression nécessite à la fois des cellules adhérentes et des cellules T radiosensibles. Une fois induite, la suppression est transférable par des cellules T isolées. Après une prise orale unique de captopril, les cellules adhérentes de volontaires normaux font preuve d'une activité suppressive modérée. Ainsi, le captopril semble modifier la régulation immunitaire en induisant un circuit suppresseur qui fait intervenir les monocytes et un effecteur de suppression de phénotype T_8 .

Captopril (Capoten[®], Squibb Pharmaceutical Company, Paris, France), the first oral inhibitor of angiotensin-converting enzyme (ACE), could have broadest indications than renin-dependent hypertension, including some forms of essential hypertension or cardiac congestive heart failure [1, 2]. However, this drug has serious side-effects in about 5% of long-term treated patients, particularly in hypertensive patients with impaired renal function, or those initially treated with a dose higher than 400 mg/day [1]. The nature of these complications as well as the possible occurrence of autoantibodies on treatment suggests that captopril can interfere with immune regulation. This is supported by recent investigations in animal models [3, 4] and *in vitro* studies of human T cell proliferative response [5, 6].

We analyzed the effect of captopril on the primary *in vitro* antibody response of human peripheral blood mononuclear (PBM) cells [7]. This model allows the analysis of cellular interactions taking place in the differentiation of cells producing specific IgM. The B cell response is positively and negatively regulated by T cells and monocytes [8, 9]. We show that captopril induces a moderate transferable suppressor activity which requires monocytes at the inductive phase and is mediated by the T_8 lymphocyte subset.

Methods

***In vitro* antibody response.** The *in vitro* antibody response was induced and tested as previously described [7, 8]. Blood was drawn from normal volunteers. Peripheral blood mononuclear cells (PBM) were separated and cultured at 2.5×10^6 cell concentration in RPMI 1640 medium supplemented with 10% fetal bovine serum in flat-bottomed wells (Costar 3524, Cambridge, Massachusetts) (0.5 ml final volume). The antigen, a trinitrophenyl conjugate of polyacrylamide (TNP-PAA) was prepared and used as already described [7]. After 7 to 8 days cells were collected and separated from the beads; the anti-TNP response was measured by a Jerne-type plaque assay using TNP-conjugated sheep red blood cells (TNP-SRBC) and unconjugated SRBC as target erythrocytes. The response was expressed as the number of anti-TNP plaque-forming cells (PFC) per 10^6 collected cells (PFC/ 10^6). At least three cultures were performed in each experimental group. The cell recovery and viability were identical in the various experimental groups. In each experiment, cultures without antigen were performed: The background anti-TNP response was usually negative and never exceeded 5% of the response of the stimulated cultures. Unless otherwise stated, the results are the mean (\pm SE) responses from different experiments involving different donors. The Student's *t* test was used for statistical analysis. Captopril was obtained from Squibb Laboratory, Paris, France (SQ 14 225, lot no. 230002). It was dissolved in culture medium immediately before use in the cultures.

The responding system. Two different preparations were used as responding cells: unfractionated PBM isolated on

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Ficoll-Hypaque and non-adherent PBM, additionally filtered on a nylon wool column [8, 9]. Nylon filtration resulted in a decrease in the proportion of peroxidase (Pox) positive cells from 15 to 30% to 3 to 5% without modification of the T-B lymphocyte ratio or of the T₄ and T₈ cell proportions [8].

Cell separations. In some experiments adherent cells were isolated from unfractionated PBM by plastic adherence [9]. They contained at least 90% Pox positive cells.

T cells were separated from nonadherent PBM by E-rosette formation using neuraminidase-treated SRBC. T cells contained 95% E-rosette forming cells. T cell subpopulations were isolated with an anti-T₈ antibody OKT₈ (Ortho Pharmaceutical Corporation, Raritan, New Jersey). After incubation with OKT₈ antibody, T₈⁺ and T₈⁻ cells were separated by the panning technique [10]. The purity of these populations was assessed by indirect fluorescence using OKT₈ and OKT₄ monoclonal antibodies. T₈⁺ cells contained more than 95% OKT₈⁺ cells and less than 5% OKT₄⁺ cells. T₈⁻ cells contained more than 90% OKT₄⁺ cells and less than 5% OKT₈⁺ cells. They will be referred to as T₈ cells and T₄ cells, respectively. In some experiments cells were 2000 rd irradiated before culture.

Suppressor cell induction and assay. Suppressor cells were induced as follows. Cells were incubated for 2 days alone (control cells), with captopril (5 µg/ml) or with concanavalin A (Con A, 2 µg/ml) as a positive control for suppression. After incubation preincubated cells were washed with α methyl mannoside for Con A cells and added in a proportion of 10% to cultures of autologous nonadherent PBM (responding cells). The incubated cells were added to the responding cultures on day 2 of the response according to the protocol we previously described for Con A-induced suppressors [11]. The responding cells were cultured alone (control response) or with the different preincubated cells, and their anti-TNP response was measured on day 7. To express the suppressive effect of the various preincubated cells, the results are provided as the percent of the control response in each experiment. The following preparations were preincubated: unfractionated PBM, adherent cells, T cells, adherent cells + T cells (20 to 80%, respectively). In some experiments, preincubated adherent + T cells were separated at the end of the incubation, in T₈, T₄ subsets.

Dosage of PGE₂ production in cultures. Cultures of 5.10⁶ unfractionated PBM were set up and at 48 hr the supernatants were collected, and prostaglandin E₂ (PGE₂) concentration was measured by radioimmunoassay [9]. In four different experiments endogenous PGE₂ production was evaluated in culture in the presence or the absence of captopril (5 µg); no difference was found: 378 ± 62 nM PGE₂ in control cultures versus 356 ± 50 in cultures with captopril.

In vivo drug intake. Five normal volunteers (having signed an informed consent) absorbed 200 mg captopril orally. Blood was drawn before and 90 min after drug intake. At least 1 month later the same protocol was performed with 160 mg propranolol.

Results

Adherent cell requirement for suppression by captopril. Captopril when present in the culture medium at a 2.5 to 5 µg/ml concentration inhibits by 50% the in vitro antibody response (Table 1). This effect requires a threshold concentration of monocytes. The response of unfractionated PBM is suppressed whereas that of nonadherent PBM is unaffected. The addition of

Table 1. Adherent cell requirement for suppression of the antibody response by captopril

Cells in culture	Anti-TNP response (PFC/10 ⁶)		Number of experiments	P value
	Without captopril	With captopril		
Unfractionated ^a	120 ± 28	51 ± 6	11	<0.02
Nonadherent ^b	381 ± 90	334 ± 78	9	NS
Nonadherent + adherent ^c	292 ± 68	133 ± 37	9	<0.01

^a The culture contains 15 to 30% POX positive cells.

^b The culture contains 3 to 5% POX positive cells.

^c The cultures have 10% adherent cells containing greater than 90% POX positive cells.

10% adherent cells to nonadherent PBM cultures restores their sensitivity to the inhibitory effect of captopril. A similar suppression is observed when irradiated adherent cells are used (57 ± 8% with adherent cells as compared to 54 ± 3% with irradiated adherent cells in three experiments). Captopril does not modify the kinetics of the response in cultures of unfractionated PBM. The response is suppressed by 46 ± 15% on day 5, by 64 ± 5% on day 8, and by 57 ± 5% on day 10 (three experiments). The inhibition is observed only when captopril is added during the first 24 hr of culture (results not shown).

Lack of prostaglandin involvement in the suppressive effect. When indomethacin (3 × 10⁻⁶ M) is present in the culture medium, a moderate (and nonstatistically significant) enhancement of the response is observed: from 140 ± 41 PFC/10⁶ to 223 ± 98 PFC/10⁶ in seven experiments. However, the relative suppression by captopril is not affected by indomethacin (50 ± 5% as compared to 58 ± 3% in control cultures). We verified that captopril does not modify the in vitro production of PGE₂ by unfractionated PBM (see **Methods**). In addition the drug does not increase the suppressive effect of exogenous PGE₂ on the in vitro antibody response, evaluated as previously described [9] (results not shown).

Transferable suppression induced by captopril. Unfractionated PBM pretreated with 5 µg/ml captopril can suppress the response of autologous nonadherent PBM (Table 2). This suppression is no longer observed when nonadherent PBM are preincubated with captopril (see experiment 3). Thus in contrast with Con A-induced suppression, captopril-induced suppression requires a threshold concentration of adherent cells at the inductive phase.

Suppression by captopril: interaction between a monocyte and a suppressor T cell. To better characterize the cellular interactions, we tested the ability of captopril and Con A to generate a suppressor activity in cultures of isolated T cells or of T cells cocultured with 20% adherent cells (Fig. 1). Con A-activated T cells were fully suppressive whereas in the case of captopril only the combination of T cells and adherent cells exerted a suppressive effect. Irradiation of T cells before the preculture period abolished both suppressions.

Additional experiments were performed to define the nature of the effector suppressor cell. Upon recovery of captopril, incubated cells (adherent cells + T cells) were either transferred to responding cultures or submitted to an additional separation step. Nonadherent cells were separated into T₄ and T₈ cells

Table 2. The suppression by captopril is transferable by unfractionated PBM

Nature of incubated cells	Expt no.	Anti-TNP response ^a of responding cultures in the presence of cells incubated ^b with		
		0	Con A	Captopril
Unfractionated	1	91	16	36
Unfractionated	2	74	—	10
Unfractionated	3	420	20	113
Nonadherent	3	309	64	418

^a The anti-TNP response is expressed as PFC/10⁶ collected cells.

^b Unfractionated or nonadherent cells were cultured for 2 days, alone or with Con A (2 µg/ml) or captopril (5 µg/ml), then washed, and added to cultures of fresh autologous nonadherent PBM, the anti-TNP response of which is provided.

(Fig. 2). Upon Con A activation both T₄ and T₈ cells were suppressive ($P < 0.05$). In contrast, on preculture with captopril only T₈ cells exerted a suppressor effect ($P < 0.001$).

In vivo effect of captopril in normal subjects. Five normal volunteers received 200 mg captopril orally. Their PBM were isolated from blood drawn before (control cells) and 90 min after (treated cells) drug intake. The responses were identical in cultures of control or treated nonadherent PBM (195 ± 46 PFC/10⁶ and 168 ± 33 PFC/10⁶, respectively). To test the hypothesis that the adherent cell was involved in the initiation of the suppression, we compared the effect of 10% control or treated adherent cells on the response of control nonadherent cells (Fig. 3A). In four patients a clearcut suppressive effect was observed after captopril intake. As a mean, treated adherent cells significantly suppressed the response (by $58 \pm 7\%$; $P < 0.002$) whereas control adherent cells did not exert a significant suppression (by $24 \pm 18\%$).

As a control, the same five volunteers received 160 mg propranolol at least 1 month later, and the same experiments were performed (Fig. 3B). The *in vitro* response of their nonadherent cells was comparable (220 ± 41 PFC/10⁶) and was not significantly suppressed by either control or treated adherent cells (by 18 ± 8 and $24 \pm 8\%$, respectively).

Discussion

Adverse reactions occurred during long-term treatment by captopril with a relatively high frequency in patients with renal failure or treated with high dose protocol [1]. The nature of these side effects (leucopenia adenopathies, membranous glomerulonephritis, and serum sickness-like syndrome), the occurrence of autoantibodies suggested an immunological mechanism [12–15]. It is thus of interest to analyze the possible interaction of this drug with the immune regulation. As reported by other investigators who used T cell proliferation assays [5, 6], we observed that captopril can suppress the primary *in vitro* antibody response of human PBM. This effect is obtained with concentrations of 2.5 to 5 µg/ml, which is slightly above the serum levels found in patients treated with moderate doses of the drug [16]. We took advantage of the fact that the human B cell response involves the interaction of various immunocompetent cells to analyze the mechanism of this suppression.

The effect of captopril on the *in vitro* antibody response

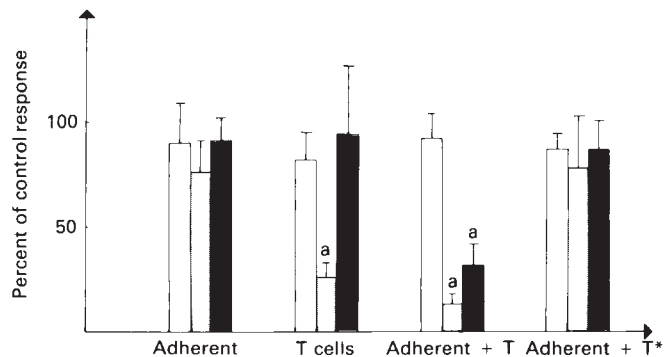


Fig. 1. The induction of the suppression by captopril requires an adherent cell and a radiosensitive T cell. Anti-TNP response (% of control) in three experiments (mean \pm SE) of nonadherent PBM responding cultures in the presence of 10% preincubated cells of four different preparations included: adherent cells, T cells, adherent cells + T cells or adherent cells + irradiated T cells (adherent + T*); preincubated cells were pretreated with: control medium, □; Con A, ▨; or captopril, ▩. The a represents $P < 0.02$ as compared to the appropriate control group. The anti-TNP response of control cultures (receiving no incubated cells) was 245 ± 158 PFC/10⁶ in these three experiments.

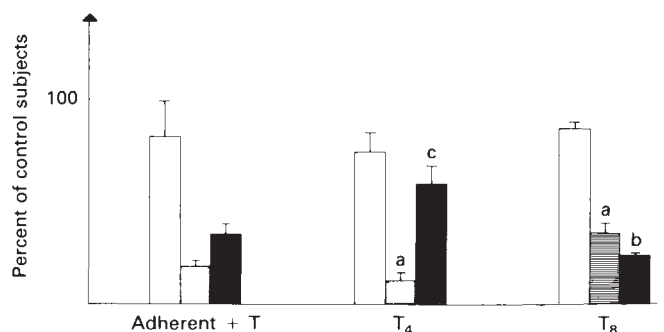


Fig. 2. The effector of captopril-induced suppression: a T₈ cell. Anti-TNP response (% of control) in three experiments (mean \pm SE) of nonadherent PBM responding cultures, with 10% preincubated cells, was observed. Adherent cells + T cells were preincubated with control medium, □; Con A, ▨; or captopril, ▩. The following preincubated cells were transferred: adherent + T; T₄ or T₈ (see **Methods**). This group of cells was compared with the respective control group: a, $P < 0.05$; b, $P < 0.001$; c, nonsignificant. The anti-TNP response of control cultures (receiving no incubated cells) was 806 ± 352 PFC/10⁶ in these three experiments.

depends on the percentage of monocytes present in the culture. The anti-TNP response can be induced in cultures of unfractionated PBM (containing 15 to 30% monocytes) or in cultures of nonadherent PBM (containing 3 to 5% monocytes) [8]. The latter preparations contain enough monocytes to support the B cell response, which is depressed only when less than 1% monocytes are left. Both the responses of unfractionated and nonadherent PBM are T dependent [7, 8] requiring a radioresistant T cell, localized in the T₄ subpopulation [17]. We show that captopril suppresses only the response of unfractionated PBM or that of nonadherent PBM supplemented with 10% monocytes. The monocytic nature of these latter cells is indicated by the following properties: they are adherent, radioresistant, and 90% peroxidase positive.

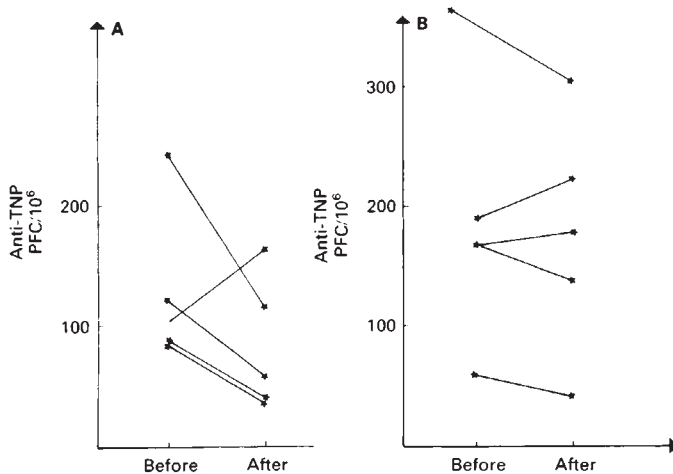


Fig. 3. *In vivo* effect of captopril. Anti-TNP response (PFC/10⁶) of nonadherent PBM responding cultures from five normal individuals (mean \pm SE) cocultured with autologous adherent cells collected before or 90 min after the intake of 200 mg captopril (A) or 160 mg propranolol (B). The intake of the drugs was separated by at least 1 month in each subject.

This suggested that captopril does not directly suppress the B cell response but induces a suppressor phenomenon. Indeed, pretreatment of unfractionated PBM (but not of nonadherent PBM) with the same concentration of captopril induces a transferable suppression. This suppression can be induced in cultures of T cells provided monocytes are present. The two activities are clearly separated as the suppressor T cells are radiosensitive. Cell separation experiments showed that the effector of the suppression is in the T₈ subpopulation. The suppressor cells induced by captopril differed from those induced by the T cell mitogen Con A at least in two respects: The monocyte requirement was not apparent in our conditions for Con A suppression; the effectors of Con A suppression belong to the T₈ and the T₄ subsets, which agrees with the report of Thomas et al [18]. We did not investigate the inductive phase of the suppression induced *in vitro* by captopril. However, the fact that adherent cells collected after an intake of captopril are suppressive suggests that monocytes can initiate a suppressor circuit when transferred *in vitro*. They could be the target of captopril.

The latter results are indicative of an *in vivo* relevance for our *in vitro* findings. Indeed both human and animal studies show that captopril can suppress the immune and inflammatory responses [3–6]. Several mechanisms can be discussed for this effect: (1) An interaction with prostaglandins which can modulate the immune response [19] was suggested by two *in vivo* studies [5, 20]. However, we found no argument in favor of a role of prostaglandins in the *in vitro* effect of captopril. (2) Two elements may suggest that, regardless of its effect on the kinin-prostaglandin pathway, captopril action on the ACE activity could be implicated in its immunological effects. The anti-inflammatory effect of captopril *in vivo* is correlated with the decrease in ACE activity [3, 4]. Human monocytic cells which seem to be responsible for the initiation of the *in vitro* suppression (this study) are ACE producers in normal subjects and in sarcoidosis [21]; this production is influenced by T cells [22]. (3)

Conversely, the immunological effects of captopril may be unrelated to its activity on ACE. In this respect they can be compared with those reported for D-penicillamine. These drugs have a strikingly similar chemical structure and comparable side-effects. The immunosuppressive action of D-penicillamine was established in animal and human studies [23]. However, D-penicillamine suppresses human B cell response through a negative effect on T helper cell function [23]. It will be of interest to compare the occurrence of side-effects with new inhibitors of ACE activity devoid of a sulfhydryl radical [24] and to determine whether they can interfere with immune regulation.

Our results provide new data on the mechanism of the effect of captopril on the immune system. The suppressor circuit we have defined *in vitro* may be determinant in the anti-inflammatory effect of this drug [3, 4]. The possible role of such a circuit in the occurrence of autoimmune or hypersensitivity phenomena is more difficult to determine. *In vitro* immunoregulatory effects of the drugs that have the capacity to induce the production of autoantibodies are variable [25–28]. The anomalies induced by captopril could be one aspect of a more general dysregulation of the immune response as described with other drugs, which could favor an abnormal response in otherwise susceptible individuals [29, 30]. Recently, the potential importance of autoanti-idiotypic antibodies in the maintenance of self-tolerance have been outlined [31]. Captopril-induced suppressor T cells could preferentially interfere with such a circuit, thus leading to the occurrence of autoantibodies, particularly in hypertensive patients [32]. Alternatively, these suppressor cells could contribute to the clinical tolerance to the drug. Predisposed individuals could develop a sensitization to the captopril molecule as described in the case of D-penicillamine. Such a sensitization would lead to the clinical occurrence of side-effects mediated by immune complexes in those subjects concomitant presenting a deficit in suppressor cell function. Such defects have been implicated in the pathogeny of autoimmune diseases [33, 34].

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