Hypotensive Effect of a Phosphorus-Containing Novel Angiotensin Converting Enzyme Inhibitor, (S)-1-[6-Amino-2[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline (SQ 29 852) in Conscious Hypertensive Dogs

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The hypotensive efficacy of (S)-1-[6-amino-2[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline (SQ 29 852), a phosphorus-containing novel angiotensin converting enzyme inhibitor (ACEI) was examined in conscious two-kidney, one-clip Goldblatt hypertensive dogs. The acute hypotensive effect of SQ 29 852 was compared with that of captopril or enalapril at 3 mg/kg, p.o., for each, and the potencies were ranked as follows, enalapril > SQ 29 852 > captopril. On the other hand, the hypotension caused by repetitive dosing with SQ 29 852 (3 mg/kg, p.o./d for 7 d followed by another 7-d treatment with 10 mg/kg, p.o./d) was somewhat more marked than that by enalapril at the same dosage. Blood urea nitrogen (BUN) increased in all the animals given enalapril, while that in all of the SQ 29 852-treated animals did not increase. These results indicate that SQ 29 852 is a potent, and long-lasting ACEI with a possible low incidence of side effects.

Keywords — (S)-1-[6-amino-2[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline (SQ 29 852); enalapril; captopril; conscious hypertensive dog.

Introduction

Since captopril was introduced in 19771) as a new tool in the therapy of hypertension, a number of ACEIs have been developed, and introduced into clinical use in the last decade. Now they have already been regarded as one of the major groups of antihypertensive drugs including β-adrenoeceptor blocking agents, calcium blockers, and diuretics. ACEIs are currently divided into 3 groups of compounds according to their molecular structures, each providing binding sites which combine with zinc ion in angiotensin converting enzyme (ACE) molecule.2,3) The first group consists of sulfhydryl-containing compounds including captopril. Several side effects of captopril were reported, and the sulfur element of the ACEIs has caused the side effects.2,3) Therefore ACEIs of the second group containing a carboxyl group instead of the sulfur moiety were developed to avoid the side effects. One of the most widely used compounds in this group may be enalapril. On one hand, in the therapy of hypertension, once-a-day dosing is beneficial because of the frequently required long-term control of blood pressure which sometimes spreads over one’s life time. Therefore ACEIs with a long-lasting efficacy have been sought. Enalapril was probably the first product for this purpose.

Very recently, the third group of phosphorus-containing ACEIs, fosinopril and (S)-1-[6-amino-2[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline (SQ 29 852) have developed potent ACEIs with the long-lasting efficacy and low toxicity.4,5) Fosinopril is an ACEI prodrug with a favorably potent and long-lasting hypotensive activity.6,7) In contrast, SQ 29 852 is not a prodrug but a molecule very similar to fosinopril except for an ester residue of fosinopril.4,5,8) About the pharmacological profile of SQ 29 852, we have already studied, and found its favorable hypotensive efficacy in anesthetized dogs.9) In the present study, we examined the hypotensive effect of SQ 29 852 in comparison with that of enalapril, and captopril in conscious hypertensive dogs.

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Materials and Methods

Conscious Hypertensive Dogs — Thirteen female beagle dogs weighing 7.4—10.6 kg were trained to sit quietly on an observation platform for monitoring blood pressure and heart rate. The trained animals were anesthetized with sodium pentobarbital (30 mg/kg, i.v.), and the right femoral artery was catheterized with a polyethylene tube which was filled with sterile heparin-saline. This catheter was led subcutaneously toward the back, out at the shoulder extracorporeally and fixed. The exposed end of the catheter was plugged with a metal stopper which was removable for the measurement of blood pressure, and blood sampling for biochemical measurements.

Seven to 10 days after the implantation of the catheter, the blood pressure and heart rate of the animals were measured (the control observation). Then the animals were anesthetized again, and the left renal artery was exposed via a retroperitoneal incision. A non-cannulating type probe of an electromagnetic flow meter was attached around the renal artery for monitoring the renal blood flow and the renal artery was constricted with silk thread in order to decrease blood flow by 70—75% of the pre-constriction level. The animals were regarded as hypertensive when a consistently high blood pressure was confirmed on the 7th—10th day after the operation (Blood pressure of the hypertensive animals was at least 20 mmHg as high as the pre-constriction level).

Single Administration — Six hypertensive dogs weighing 9.2—10.4 kg were used. After the control observations of blood pressure and heart rate, SQ 29 852, captopril or enalapril at 3 mg/kg for each, or the placebo (a gelatin capsule) was given orally, and changes in the parameters were monitored for 30 min. Thereafter an hourly 20-min monitoring was carried out at each time point of observation 1—8 h after dosing. Moreover, the recovery of blood pressure and heart rate was also observed at 24 and 48 h after dosing. Arterial blood samples were taken before, and at 4, 8, 24, and 48 h after dosing for determination of the levels of serum angiotensin converting enzyme (ACE) and plasma renin (PRA).

The animals were used repetitively, and given ACEIs or the placebo in a cross-over fashion at a recovery interval for 7—10 d. The effects of ACEIs and the placebo were examined in 5 animals for each treatment.

Repetitive Administration — Seven hypertensive dogs weighing 7.4—10.6 kg were used. Blood pressure and heart rate of the animals were measured at 9:00—11:00 in the morning throughout this experiment. Immediately after the daily measurement of blood pressure and heart rate, SQ 29 852, enalapril or the placebo (a gelatin capsule) was orally administered. The treatment with ACEI was started at 3 mg/kg/d for 7 d which was followed by another 7-d treatment at 10 mg/kg/d. Additionally, blood pressure and heart rate were measured for 7 d after the withdrawal of dosing. ACE, PRA, plasma levels of angiotensin I (Ang I), angiotensin II (Ang II), and aldosterone (Aldo), electrolytes (Na⁺, K⁺ and Cl⁻), and BUN were determined using arterial blood samples collected in the morning on the day starting the treatment, the 7th and 14th days during the treatment, and on the 7th day of the recovery period. Twenty-four-hour urine was collected on these days for measuring urinary volume, urinary excretion of Na⁺, K⁺, Cl⁻, and creatinine. Moreover, circulating blood volume was measured on these days. For this purpose, 0.4 mg/kg of Evans blue was injected intravenously, and arterial blood was taken 10 min after the injection. Then plasma concentration of the dye was determined by spectrophotometry, and the circulating blood volume was calculated from the dilution ratio of the dye in plasma and the hematocrit value.

The animals were used repetitively following the cross-over fashion protocol at a recovery interval of 2 weeks or longer, and the results were compared among 5-animal groups.

Apparatuses for the Measurement and Recording — Blood pressure was measured by a pressure transducer (45363, NEC-San-ei, Tokyo) and a pressure-force displacement amplifier (1829, NEC-San-ei). Heart rate was determined from the systolic pulse curves of blood pressure by a tachometer (1332, NEC-San-ei). These parameters were recorded on a rectigraph.
(Recti-Horiz 8S53, San-ei, Tokyo).

**Biochemical Measurements** — Serum ACE activity was measured by fluorescein antibody technique according to the method of Cushman and Cheung.\(^{10}\) Plasma renin activity (PRA) was measured using Renin RIA heads\(^\circledast\) (Dinabot, Tokyo), and Aldo was determined by a two-antibody method using Aldosterone RIA kit\(^\circledast\) (Dinabot). Both levels of Ang I and Ang II were measured by radiimmunoassay after purification with high-performance liquid chromatography. Creatinine concentration in blood and urine was measured by the Folin-Wu method\(^{11}\) using Creatinine-Test Wako\(^\circledast\) (Wako, Osaka). BUN was measured by the diacetylmonoxime method using BUN-Test Wako\(^\circledast\) (Wako).

**Chemicals** — The following chemicals were used in the present study: Evans blue (Wako), pentobarbital sodium (Tokyo Kasei, Tokyo), SQ 29 852 and captopril (Squibb Japan, Tokyo), and enalapril (Renivace\(^\circledast\), Ban-yu, Tokyo).

**Statistics** — Values in the present study are represented as means ± S.E.M. The statistical significance of the difference between two group mean values before and after treatments was evaluated by a paired \(t\)-test. Time-matched values between groups, which were treated with the placebo and a drug, were compared by ANOVA followed by Dunnett’s test for multiple comparison. In the experiments with repeated measures, the mean values after dosing were compared with the pre-dosing values using ANOVA and Dunnett’s test for repeated measures. \(p\) values less than 0.05 were considered to be statistically significant.

**Results**

**Establishment of Hypertension**

**Fig. 1. Acute Effects of ACEIs or Placebo on Blood Pressure and Heart Rate in Conscious Hypertensive Dogs**

Three mg/kg, p.o., of SQ 29 852 ( ), enalapril ( ), captopril ( ) or placebo [gelatin capsule ( )] was administered orally ( ), and blood pressure and heart rate were measured up to 48 h after dosing. The mean values with S.E.M. of 5 animals are shown. MBP, mean blood pressure; HR, heart rate. \(a\) \(p<0.05\), \(b\) \(p<0.01\), significantly different from the pre-dosing values (Dunnett’s test for repeated measures). \(c\) \(p<0.05\), \(d\) \(p<0.01\), significantly different from the time-matched values in the placebo-treated group (Dunnett’s test).

**Fig. 2. Acute Effects of ACEIs or Placebo on Plasma Levels of Renin and Angiotensin Converting Enzyme in Conscious Hypertensive Dogs**

Changes in plasma levels of renin and ACE before and at 4, 8, 24 and 48 h after dosing with 3 mg/kg, p.o., of SQ 29 852 ( ), enalapril ( ), captopril ( ) and placebo [gelatin capsule ( )] are summarized as the mean values with S.E.M. of 5 animals. PRA, plasma renin activity; ACE, angiotensin converting enzyme activity. \(a\) \(p<0.05\), \(b\) \(p<0.01\), significantly different from the pre-dosing values (Dunnett’s test for repeated measures). \(c\) \(p<0.05\), \(d\) \(p<0.01\), significantly different from the time-matched values in the placebo-treated group (Dunnett’s test).
The changes in the renal blood flow before and after the constriction of the renal artery were measured under anesthesia during the operation, and recorded in 7 of 13 animals. The renal blood flow decreased from 97.7 ± 11.5 ml/min to 31.6 ± 10.0 ml/min (N = 7, p < 0.001, paired t-test) by the constriction. The blood pressure (measured at 9:00 — 11:00 in the morning) started to increase on the following day of the operation, and the hypertension lasted for more than 7 d. The mean blood pressure was 137.5 ± 3.4 mmHg (N = 13) on the 7th — 10th day after the operation which was significantly higher than the preconstriction value (115.5 ± 2.4 mmHg, N = 13, p < 0.001, paired t-test). The changes in blood pressure of the two-kidney, one-clip renovascular hypertensive dogs have been observed in detail in our laboratory, and reported elsewhere. 12)

Effects of Single Oral Administration of ACEIs

A single oral administration of SQ 29 852 at 0.3 mg/kg failed to decrease blood pressure in the hypertensive dogs (Data not shown). At 3 mg/kg, in contrast, blood pressure decreased markedly compared with the control value. This hypotension lasted at least for 8 h after dosing without any concomitant changes in heart rate.

Fig. 3. Effects of Repetitive Administration of Placebo in Conscious Hypertensive Dogs

Placebo (gelatin capsule) was administered (●) for 14 d. Symbols indicate mean values with S.E.M. of 5 animals. SBP, systemic blood pressure; HR, heart rate. a) p < 0.05, significantly different from the pre-dosing values (Dunnett's test for repeated measures).

Fig. 4. Effects of Repetitive Administration of SQ 29 852 in Conscious Hypertensive Dogs

SQ 29 852 was given orally at 3 mg/kg/d (△) for 7 d and 10 mg/kg/d (●) for consecutive 7 d. Symbols indicate mean values with S.E.M. of 5 animals. SBP, systemic blood pressure; HR, heart rate. a) p < 0.05, b) p < 0.01, significantly different from the pre-dosing values (Dunnett's test for repeated measures). c) p < 0.05, d) p < 0.01, significantly different from the time-matched values in the placebo-treated group shown in Fig. 3 (Dunnett's test).

Fig. 5. Effects of Repetitive Administration of Enalapril in Conscious Hypertensive Dogs

Enalapril was given orally at 3 mg/kg/d (△) for 7 d and 10 mg/kg/d (●) for consecutive 7 d. Symbols indicate mean values with S.E.M. of 5 animals. SBP, systemic blood pressure; HR, heart rate. a) p < 0.05, significantly different from the pre-dosing values (Dunnett's test for repeated measures). b) p < 0.05, c) p < 0.01, significantly different from the time-matched values in the placebo-treated group shown in Fig. 3 (Dunnett's test).
Thus the hypotensive effect of SQ 29 852 was compared with that of captopril or enalapril at 3 mg/kg for each.

As shown in Fig. 1, all the ACEIs at 3 mg/kg decreased blood pressure within 30 min after dosing. Captopril-induced hypotension was especially marked at 30 min after dosing, and the blood pressure returned gradually to the pre-dosing level. Enalapril revealed the most potent and long-lasting hypotensive effect among these ACEIs. SQ 29 852 showed a mild hypotension, and no prompt decrease in blood pressure like captopril was observed. At 1—8 h after dosing the hypotensive potency of SQ 29 852 appeared to be in-between two other ACEIs.

PRA and ACE activity which were measured before, and at 4, 8, 24, and 48 h after dosing with ACEIs are shown in Fig. 2. PRA was elevated by the ACEIs, and was highest at 8 h after dosing. Every ACEI decreased ACE activity and enalapril most effectively inhibited the activity among them. Both enalapril and SQ 29 852 markedly decreased ACE activity compared with time-matched values of the placebo-treated group. In contrast, the captopril-induced decrease was slight and no differences were observed as compared with the vehicle-treated animals. The time courses of PRA and ACE activity appeared to be parallel with those of the hypotension. The placebo had no effects on any parameters monitored.

**Comparison of Effects in Repetitive Oral Administrations of SQ 29 852 and Enalapril**

The changes in blood pressure and heart rate in the animals given placebo, SQ 29 852 and enalapril were shown in Fig. 3, 4 and 5, respectively. In contrast to the acute hypotensive effects, the hypotension caused by repetitive administration of SQ 29 852 appeared somewhat more marked than that by enalapril (Fig. 4 and 5). The blood pressure was gradually decreased by repetitive dosing with SQ 29 852, and the mean blood pressure became significantly lower than the pre-dosing level on the 6th day during the 3-mg/kg/d treatment (Fig. 4), whereas enalapril caused no more than a slight decrease in blood pressure throughout the 7-d period of 3 mg/kg/d treatment (Fig. 5). When the treatment with SQ 29 852 at 10 mg/kg/d was started, an additive decrease in blood pressure occurred immediately. By enalapril, on the other hand, a statistically significant decrease in the mean blood pressure appeared on the 3rd day during 10-mg/kg/d treatment. After the withdrawal of dosing, significantly lower blood pressure than the pre-dosing level continued longer in SQ 29 852-treated group than enalapril-treated one (Fig. 4 and 5). Neither of the treatments

![Graphs showing changes in plasma levels of Angiotensin I and II and the ratio of Angiotensin I to Angiotensin II](image)

**Fig. 6.** Changes in Plasma Levels of Angiotensin I, Angiotensin II and the Ratio of Angiotensin I to Angiotensin II by Repetitive Oral Administrations of ACEIs and Placebo in Conscious Hypertensive Dogs

Effects of SQ 29 852 (□), enalapril (■) or placebo [gelatin capsule (○)] on plasma levels of angiotensin I, angiotensin II and on the ratio of angiotensin I to angiotensin II (Ang I/Ang II) are shown. Symbols indicate mean values with S.E.M. of 5 animals. C, the control (pre-dosing) value. 3, 10, values on the 7th day of 3 and 10 mg/kg/d-treatment, respectively. Rec, values obtained on the 7th day of recovery observation. *a) p<0.05,* significantly different from the pre-dosing values (Dunnnett's test for repeated measures).
changed heart rate markedly (Fig. 3, 4 and 5).

By the repetitive treatment with SQ 29 852, plasma levels of Ang I and Ang II were not changed, whereas both Ang I and Ang I/Ang II were increased by enalapril (Fig. 6). PRA increased in both groups given SQ 29 852 and enalapril, and the magnitude of the increment in the latter was larger than that in the former (Fig. 7). ACE activity decreased by both ACEIs (Fig. 7) Aldo tended to be decreased slightly after 10 mg/kg/d-treatment with both ACEIs, and circulating blood volume did not change markedly in any of the groups (Fig. 7).

No marked changes occurred in the renal function throughout the ACEI treatments except a slight increase in BUN in the group given enalapril (Fig. 8). Enalapril increased BUN in all 5 animals during the treatment, while the placebo and SQ 29 852 increased it in 1—2 and 2—3 out of 5 animals, respectively.

**Discussion**

At 3 mg/kg captopril caused a transient hypotension followed by a mild, and continuous one which lasted up to 8 h after dosing. SQ 29 852 did not cause such a prompt decrease in blood pressure, but SQ 29 852-induced hypotension also continued for 8 h after dosing, and was slightly more marked than that by captopril. On the other hand, enalapril caused similarly potent hypotension compared with that by captopril at 30 min after dosing, and this hypotension continued. The hypotension caused by enalapril at 1 — 8 h after dosing was the most potent among those by the ACEIs examined in the present study. Therefore it is demonstrated in the conscious hypertensive dogs that the onset of hypotension by SQ 29 852 is mild and its hypotensive potency is in-between enalapril and captopril.

The increase in PRA and decrease in ACE ac-
Fig. 8. Effects of Repetitively Administered ACEIs and Placebo on the Renal Function in Conscious Hypertensive Dogs

Effects of SQ 29 852 (□), enalapril (■) or placebo [gelatin capsule (○)] on 24-h urinary excretion (UV), creatinine clearance (Ccr) blood urea nitrogen concentration (BUN), clearances of electrolytes (Cna, Ck and Ccl) and sodium reabsorbing rate (sodium reabsorption) are shown. Symbols indicate mean values with S.E.M. of 5 animals. C, the control (pre-dosing) value. 3, 10, values on the 7th day of 3 and 10 mg/kg/d-treatment, respectively. Rec, values obtained on the 7th day of recovery observation. a) p<0.05, significantly different from the pre-dosing values (Dunnett’s test for repeated measures).

tivity by SQ 29 852 were also in-between two other ACEIs. However, in contrast to the similar hypotensive properties of SQ 29 852 and captopril at 4, 8, 24 and 48 h after dosing, the inhibition of ACE activity by SQ 29 852 at these time points was far more potent than that by captopril, and rather equipotent to enalapril. Namely, the decreased ACE activity by both SQ 29 852 and enalapril indicated their longer-lasting ACEI effects than that of captopril. ACE activity in the group given captopril was not changed markedly compared with the time-matched value in the placebo-treated animals. The maximal inhibition of ACE activity by captopril might be over within 4 h after dosing. In the time courses of PRA and ACE activity, the maximal increase in PRA was observed behind the minimal ACE activity. The delayed increase in PRA may be accounted for by subsequent changes in PRA to that in ACE activity.

It has been reported that the acute oral administration of SQ 29 852 to rats shows equipotent inhibition of Ang I-response compared with that by enalapril.6) Actually in the present study both ACEIs were equipotent in the inhibition of ACE activity, although lower bioavailability of SQ 29 852 in dogs than rats has been reported.13) Although the inhibition of ACE activity by SQ 29 852 was far more potent compared with that of captopril and was, moreover, even comparable to that by enalapril, the hypotensive potency of SQ 29 852 was similar to captopril and less than enalapril. Therefore, the long-lasting hypotension by SQ 29 852 was not neces-
sarily anticipated from the results of the single-dose experiment, although a long-lasting inhibition of ACE activity by SQ 29 852 was observed. In order to evaluate the hypotensive efficacy of SQ 29 852 further, we compared its effect with that of enalapril in the repetitive oral administrations. In contrast to the results of the single-dose experiment, the repetitive administration of SQ 29 852 caused a somewhat stronger hypotension than enalapril. In the inhibition of ACE activity in sera and tissue homogenates of spontaneously hypertensive rats, SQ 29 852 has been reported to be far less potent than that of enalapril.\(^8,14\) Moreover, as mentioned previously, the bioavailability of SQ 29 852 has been reported to be low especially in dogs compared with that in rats.\(^13\) Therefore, there should be pharmacokinetic differences between SQ 29 852 and enalapril, which can be revealed more clearly in a repetitive administration. Although there are no reports dealing with pharmacokinetics of SQ 29 852 in detail, the long-lasting effects of SQ 29 852 in repetitive treatment may be due to accumulation of the agent in the body. The slight longer duration of the withdrawal effect of SQ 29 852 than with enalapril may also indicate such differences.

The hypertensive dogs used in the present study were of the acute phase with presumably stimulated RAAS.\(^15,16\) Thus, the inhibition of RAAS probably play a large part in the mechanisms of hypotensive effect of the ACEIs in these animals. In contrast, the changes in the renal function by the ACEIs might play few roles, with regard to the hypotension. Actually, few changes in UV, clearances of electrolytes, and in sodium-reabsorption rate were found during the treatment with both SQ 29 852 and enalapril.

Enalapril has been reported to be excreted mainly from the kidney,\(^2,17\) and has undesirable effects at the organ.\(^17–19\) The repetitive dosing with enalapril tended to increase BUN especially after 7-d treatment at 10 mg/kg. Although this increase in BUN was very slight, it was observed in all 5 animals given enalapril. On the other hand, SQ 29 852 did not show such an increase in BUN in spite of its renal excretion route which is the same as that in enalapril.\(^13\) Thus the slight change in BUN by enalapril might be some sign of undesirable effects, although the elevated BUN in these animals was still around the normal levels.

The increase in PRA by the repetitive administration of enalapril was more marked than that by SQ 29 852. Moreover, enalapril increased plasma levels of Ang I and Ang I/Ang II, whereas SQ 29 852 did not change them. These results suggest the more potent ACEI activity of enalapril than that of SQ 29 852, since the inhibition of ACE activity is to decrease Ang II formation which results in compensatory increases in Ang I and PRA. However, the hypotensive effect of SQ 29 852 was comparable or somewhat potent compared with that of enalapril. In the case of enalapril, the marked increase in the level of Ang I by the inhibition of ACE activity may result in a consecutive increase in the level of Ang II, since the conversion from Ang I to Ang II is in some part catalyzed also by proteases like tonin,\(^20,21\) kallikrein\(^22\) and angiotensin II-producing enzyme III.\(^21\) The increased Ang II might partly offset the hypotension which should have been induced by enalapril, if the absolute amount of plasma Ang II affects blood pressure. In contrast, SQ 29 852 decreased blood pressure without changing the level of Ang II. There are no reports which demonstrate any other hypotensive mechanisms of SQ 29 852, that is, \(\alpha\)-blocking and Ca\(^{2+}\) channel-blocking activities, than those as an ACEI. Moreover, in our previous experiments on the acute effects of intravenously administered SQ 29 852 in anesthetized dogs,\(^9\) no particular signs of the effects of the agent except those as an ACEI were observed. Thus, the changes in PRA, and plasma levels of Ang I and Ang II may not be directly correlated with the potency of the hypotensive effect of an ACEI, even though the relative changes in PRA, ACE and angiotensins may reflect the potency of the ACEI alone. Actually, in the hypotensive effects of ACEIs, the tissue (local) RAAS has been focused as a more important system than the circulating RAAS.\(^24–26\) Between SQ 29 852 and enalapril, therefore, there may be a difference in the preference of affinity to tissue or circulating ACE at least in dogs.

The present results in hypertensive dogs suggest that SQ 29 852 possesses a somewhat
stronger hypotensive efficacy than enalapril in repetitive oral administrations, although the acute hypotension caused by the former was less marked than that by the latter. The repetitive administration of SQ 29 852 revealed no apparent effects on the renal function, whereas a small but statistically significant elevation of BUN was caused by enalapril. SQ 29 852 appears to be a favorable ACEI at least in the renal hypertensive dogs, and the clinical virtue of this agent is anticipated as a potent ACEI with fewer side effects than previously developed ACEIs. There were differences between the changes in biochemical parameters in plasma [PRA, ACE activity, Ang I and Ang II] caused by SQ 29 852 and enalapril, although the hypotensive effects were generally comparable. The underlying mechanisms for the discrepancy between the effects of these drugs are remains to be elucidated.

References


