Hypertension induced by blockade of ET<sub>B</sub> receptors in conscious nonhuman primates: role of ET<sub>A</sub> receptors

GLENN A. REINHART, LEE C. PREUSSER, SANDRA E. BURKE, JERRY L. WESSALE, CRAIG D. WEGNER, TERRY J. OPGENORTH, AND BRYAN F. COX
Pharmaceutical Discovery, Abbott Laboratories, Abbott Park, Illinois 60064-6119

Received 18 April 2002; accepted in final form 23 May 2002

Reinhart, Glenn A., Lee C. Preusser, Sandra E. Burke, Jerry L. Wessale, Craig D. Wegner, Terry J. Opgenorth, and Bryan F. Cox. Hypertension induced by blockade of ET<sub>B</sub> receptors in conscious nonhuman primates: role of ET<sub>A</sub> receptors. Am J Physiol Heart Circ Physiol 283: H1555–H1561, 2002.—The role of endothelin-B (ET<sub>B</sub>) receptors in circulatory homeostasis is ambiguous, reflecting vasodilator and constrictor effects ascribed to the receptor and diuretic and natriuretic responses that could oppose the hypertensive effects of ET excess. With the use of conscious, telemetry-instrumented cynomolgus monkeys, we characterized the hypertensive production by ET<sub>B</sub> blockade and the role of ET<sub>A</sub> receptors in mediating this response. Mean arterial pressure (MAP) and heart rate (HR) were measured 24 h/day for 24 days under control conditions and during administration of the ET<sub>B</sub>-selective antagonist A-192621 (0.1, 1.0, and 10 mg/kg bid, 4 days/dose) followed by coadministration of the ET<sub>A</sub> antagonist atrasentan (5 mg/kg bid) + A-192621 (10 mg/kg bid) for another 4 days. High-dose ET<sub>B</sub> blockade increased MAP from 79 ± 3 (control) to 87 ± 3 and 89 ± 3 mmHg on the first and fourth day, respectively; HR was unchanged, and plasma ET-1 concentration increased from 2.1 ± 0.3 pg/ml (control) to 7.24 ± 0.99 and 11.03 ± 2.37 pg/ml. Atrasentan + A-192621 (10 mg/kg) decreased MAP from hypertensive levels (89 ± 3) to 75 ± 2 and 71 ± 4 mmHg on the first and fourth day, respectively; plasma ET-1 and HR increased to 26.64 ± 3.72 and 28.65 ± 2.89 pg/ml and 113 ± 5 (control) to 132 ± 5 and 133 ± 7 beats/min. Thus systemic ET<sub>B</sub> blockade produces a sustained hypertension in conscious nonhuman primates, which is mediated by ET<sub>A</sub> receptors. These data suggest an importance clearance function for ET<sub>B</sub> receptors, one that influences arterial pressure homeostasis indirectly by reducing plasma ET-1 levels and minimizing ET<sub>A</sub> activation.

endothelium-derived factors; blood pressure; endothelin receptor blockade

ENDOTHELIN (ET) peptides are a family of structurally related 21-amino acid peptides capable of exerting an array of physiological effects, many with the potential to alter arterial pressure and circulatory function. Of the three isoforms, ET-1 is recognized as the most physiologically relevant isoform and is synthesized as a precursor molecule by endothelial cells and other cell types (14, 21, 33). ET-1 is cleaved from a larger, inactive precursor polypeptide through a sequence of highly specific proteolytic steps. It potently constricts the peripheral vasculature, alters renal hemodynamic and tubular function, stimulates mitogenesis in vitro, and interacts with an array of cell and tissue types through activation of cell surface, ligand-specific receptors (14, 21, 33).

The physiological effects of ET-1 are mediated by two distinct, differentially expressed receptor subtypes designated ET<sub>A</sub> and ET<sub>B</sub>, each coded by a specific gene and possessing some overlap in their tissue distribution (1, 30). In the peripheral vasculature, ET<sub>A</sub> receptors are expressed primarily on the surface membrane of vascular smooth muscle cells where they mediate, in a large part, the potent and characteristically sustained vasoconstrictor response associated with administration of exogenous ET peptides. ET<sub>B</sub> receptors are also expressed by vascular smooth muscle cells albeit less densely than ET<sub>A</sub> receptors and may mediate a portion of ET-induced vasoconstriction in many vascular beds (14, 19, 33). Also, in contrast to ET<sub>A</sub> receptors, ET<sub>B</sub> receptors are highly expressed on vascular endothelial cells, where they mediate the rapid, transient vasodilation produced by exogenous ET through the enhanced generation of nitric oxide and prostaglandin-related substances (14, 15, 21, 33). Relative to ET<sub>A</sub> receptors, the role of ET<sub>B</sub> receptors in vascular homeostasis has been difficult to define, because ET<sub>B</sub> receptors are known to mediate constriction in some vascular beds (3, 19, 27, 32) but also mediate transient hypotension when challenged appropriately (14, 21, 33). Acute blockade of ET<sub>B</sub> receptors produces prompt increases in plasma concentrations of immuno-reactive ET-1 in both the dog and rat, suggesting that the receptor functions as a clearance receptor and eliminates ET-1 from the plasma compartment (8, 9). The clearance function of the ET<sub>B</sub> receptor is aided by equal affinity for all three ET isoforms, whereas the ET<sub>B</sub> receptor selectively binds only ET-1 at physiological concentrations of the peptide (14).

Genetic disruption of ET<sub>B</sub> receptor expression has been reported to increase arterial pressure in both
mice and rats in association with increased circulating ET-1 levels (10, 22). Also, chronic administration of the ET<sub>B</sub>-selective antagonist A-192621 produces or exacerbates experimental hypertension in rats (2, 20, 28, 35). Given the potential for ET<sub>B</sub> activation to alter both vascular and renal function, the mechanism by which ET<sub>B</sub> suppression induces hypertension is of considerable interest. In conscious mice in which ET<sub>B</sub> expression is reduced to approximately one-eighth of normal (complete ET<sub>B</sub> knockout is a lethal construct), arterial pressure is elevated relative to wild-type controls; acute ET<sub>A</sub> blockade reduces but does not normalize blood pressure compared with control animals (22). In rats, sustained pharmacological blockade of ET<sub>B</sub> receptors produces hypertension (28, 35), a response that is abolished by subsequent ET<sub>A</sub> + ET<sub>B</sub> blockade (28). Thus ET<sub>A</sub> receptors may at least partly mediate the hypertension produced by suppression or blockade of ET<sub>B</sub> receptors in rats.

The objective of the present study was to characterize the effects of sustained systemic ET<sub>B</sub> receptor blockade on arterial pressure homeostasis and plasma ET-1 levels in conscious cynomolgus primates by using radiotelemetry techniques. In addition, we tested the hypothesis that the increase in arterial pressure produced by ET<sub>B</sub> receptor blockade is indirectly mediated by activation of the ET<sub>A</sub> receptor.

**METHODS**

**Animal preparation.** Seven male cynomolgus primates weighing 5.3–8.2 kg were used in this study. All procedures were approved by Abbott Laboratories’ Institutional Animal Care and Use Committee and carried out in American Association for Accreditation of Laboratory Animal Care accredited facilities. For surgical implantation of the telemetry transmitter, anesthesia was induced with ketamine (10 mg/kg im) followed by isoflurane (1–1.5%) as described previously (29). With the use of aseptic techniques, a ventral midline incision was made, and a telemetry transmitter (model TL10M2-D70-PC or D70-PCT, Data Sciences International) was anchored in the abdominal cavity with nonabsorbable suture. A gel-filled catheter connected to the transmitter was tunneled to the femoral area. Via a small femoral incision, the catheter was inserted into a femoral artery, advanced into the abdominal aorta, and secured, and the femoral incision was closed. The abdominal incision was closed in layers. In addition, a venous vascular access port (Access Technologies) was implanted subcutaneously and contralateral to the telemetry transmitter; the connecting catheter was secured in the femoral vein in a manner similar to the arterial catheter. Preoperatively, the animals were treated with K<sup>+</sup>-penicillin (20,000 U/kg iv) and gentamicin (2 mg/kg iv). Postoperatively, buprenorphine (0.01 mg/kg im bid) was given to provide analgesia. Amoxicillin (5 mg/kg) and trimethoprim and sulfadiazine (Tribrissen, 30 mg/kg) were given postoperatively for a period of 5–7 days. The vascular access ports were flushed with sterile saline biweekly or after each use and filled with a sterile solution of saline containing heparin (1,000 U/ml) and gentamicin (3.2 mg/ml).

After several weeks the animals were housed in individual cages in a room maintained at 22 ± 1°C with a 14:10 h light-dark cycle. They were fed a standard primate diet (Purina Primate Diet 5038), and water was provided ad libitum. Fresh fruit (banana) was given twice daily as part of the dosing regimen throughout the entire 24-day protocol.

To allow continuous measurement of mean arterial pressure (MAP) and heart rate while the animals moved freely in their home cages, the telemetry receivers were mounted to the front of each cage. The connecting wires extended through a wall port to a data collection computer (Compaq DeskPro/133M) located in an adjoining room. MAP and heart rate data were sampled continuously from each animal in 10-s bursts at 2-min intervals, 24 h/day. Daily values for MAP and heart rate were determined for each animal for each 24-h period beginning at 7:30 AM, excluding the 2.5-h feeding and maintenance period (10:30 AM to 1:00 PM). Thus each daily average was calculated from the 645 data points collected during a 21.5-h period.

**Experimental protocol.** A 4-day control period was carried out to establish baseline values for MAP, heart rate, hematocrit, and plasma concentrations of ET-1 and electrolytes before treatment. Throughout the entire 24-day protocol, the animals were fed banana (or banana containing the active drug) twice daily at 12-h intervals (7:30 AM and 7:30 PM). On completion of the 4-day control period, the ET<sub>B</sub> antagonist A-192621 (35) was placed in cored bananas and administered twice daily. Dose-dependent systemic ET<sub>A</sub> receptor blockade was accomplished by administering A-192621 at 0.1, 1.0, and 10 mg/kg (bid) in ascending order; each dose was administered for a period of 4 days. After completion of the fourth day of high-dose (10 mg/kg) ET<sub>B</sub> blockade, the animals were coadministered A-192621 (high dose) and the ET<sub>A</sub>-selective antagonist atrasentan (5 mg/kg bid) (24) for another 4 days. Subsequently, the animals were given plain banana during a final, 4-day posttreatment period. Atrasentan, also known as ABT-627 or A-147627, is a pharmacologically active enantiomer of A-127722, a chiral ET<sub>A</sub> antagonist that has been described previously (23).

Throughout the experimental protocol and on the first and fourth day of each sequential treatment period, the animals were removed from their home cages and placed in restraining chairs beginning at 10:30 AM, 3 h following administration of the morning banana (or banana + drug). Venous blood (10 ml) was collected via the vascular access port into chilled tubes (Vacutainer; Beckton Dickson) containing EDTA (for determination of plasma concentrations of ET-1) or lithium heparin (for plasma electrolyte concentrations), and the animals were returned to their home cages. Blood samples were stored on ice until centrifuged under refrigeration. Aliquots of EDTA-plasma were stored frozen (−80°C) until assayed for plasma concentrations of ET-1.

**Analytic methods.** Plasma concentrations of sodium and potassium were measured in fresh heparinized plasma by using a Synchron El-Ise Electrolyte System (Beckman). Hematocrit was determined by using a micromethod. Plasma concentrations of ET-1 were determined by ELISA (Quantiglo, R&D Systems; Minneapolis, MN).

**Statistical analysis.** Results are expressed as the group mean ± SE. Experimental and recovery data were compared with control using ANOVA with Dunnett's t-test for repeated measures (7). Values obtained on the last day of the control period were used for statistical comparison.

**RESULTS**

Daily values for 24-h MAP and heart rate and responses to increasing levels of systemic ET<sub>B</sub> blockade followed by simultaneous blockade of ET<sub>A</sub> + ET<sub>B</sub> receptors are summarized in Fig. 1. Administration of
the ET\textsubscript{B} antagonist A-192621 at the low dose (0.1 mg/kg bid) had no effect on MAP or heart rate. MAP tended to increase in response to 1.0 mg/kg A-192621, but these changes were not statistically significant. In contrast, MAP increased from a control value of 79 ± 3 to 87 ± 3 mmHg (P < 0.05) during the first day of the high-dose ET\textsubscript{B} blockade and to 89 ± 3 mmHg (P < 0.05) on the fourth day. Subsequently, when ET\textsubscript{A} blockade was superimposed on ET\textsubscript{B} blockade by coadministration of A-192621 and atrasentan, MAP fell from the hypertensive value of 89 ± 3 to 70 ± 3 or 9 mmHg below control; MAP was 71 ± 4 mmHg (P < 0.05) on the fourth day of ET\textsubscript{B} + ET\textsubscript{A} blockade. MAP remained suppressed at or near these hypertensive levels throughout the 4-day posttreatment period. Thus sustained hypertension was produced by the high dose of A-192621 and reversed to below baseline levels by dual ET\textsubscript{B} + ET\textsubscript{A} blockade, suggesting ET\textsubscript{A} receptors mediate the hypertensive effects of ET\textsubscript{B} blockade in nonhuman primates.

Heart rate was not significantly different from control values on any day during administration of the ET\textsubscript{B} receptor antagonist A-192621 (Fig. 1). However, coblockade of ET\textsubscript{B} + ET\textsubscript{A} receptors subsequent to ET\textsubscript{B} blockade-induced hypertension elicited a pronounced and sustained tachycardia in association with marked hypotension; heart rate increased from a control value of 113 ± 5 to 132 ± 5 beats/min (P < 0.05) during the first day of dual ET\textsubscript{B} + ET\textsubscript{A} blockade and increased to 133 ± 7 beats/min on the fourth day of the treatment period. Subsequently, heart rate remained elevated throughout the 4-day posttreatment period. Heart rate declined toward control values during the second day and was not significantly different from control values thereafter.

The hematocrit (control = 47 ± 1%) was not significantly affected by the low dose of A-191621 but did decrease modestly, but significantly, on subsequent days; hematocrit decreased to 44 ± 1% (P < 0.05) on the first day of the 1 mg/kg dose of A-192621 and was 45 ± 1% (P < 0.05) 8 days later, following the first coadministration of A-192621 + atrasentan. After 4 days of dual ET\textsubscript{B} + ET\textsubscript{A} blockade, hematocrit fell to 41 ± 1% (P < 0.05) and declined to 40 ± 1% (P < 0.05) 4 days after treatment was terminated.

Plasma sodium (control = 145.3 ± 1.6 meq/l; n = 5) and plasma potassium (control = 3.8 ± 0.2 meq/l; n = 5) concentrations were not significantly different from control at any time during the experimental protocol.

The effects of dose-dependent ET\textsubscript{B} blockade and subsequent coblockade of ET\textsubscript{B} + ET\textsubscript{A} receptors on the plasma concentration of ET-1 in conscious primates are summarized in Fig. 2. Plasma ET-1 concentration was not significantly affected by the low and middle dose of the ET\textsubscript{B} antagonist A-192621. In contrast, plasma ET-1 concentration increased from a control value of 2.1 ± 0.3 to 7.24 ± 1.0 pg/ml (P < 0.05) 3 h after administration of the first high dose (10 mg/kg) of A-192621; on the fourth day of ET\textsubscript{B} blockade, plasma ET-1 concentration increased to 11.03 ± 2.37 pg/ml.
Subsequent coadministration of A-192621 + atrasentan caused plasma ET-1 concentration to increase further to 26.64 ± 3.72 and 28.65 ± 2.89 pg/ml ($P < 0.05$) on the first and fourth day of the dual treatment period, respectively. On the first day when administration of A-192621 + atrasentan was terminated, plasma ET-1 concentration remained elevated at 25.54 ± 4.23 pg/ml ($P < 0.05$); at 4 days posttreatment, plasma ET-1 concentration had declined and was not different from pretreatment values.

**DISCUSSION**

In a recent study from our laboratory, we demonstrated that ETA receptor blockade in normal conscious cynomolgus primates produces a sustained hypotension and a modest elevation in plasma ET-1 concentration (29). In the present study, also in conscious primates, we demonstrate a dose-dependent hypertension in response to sustained, systemic ETB receptor blockade; this hypertension is completely abolished by subsequent dual blockade of ETB + ETA receptors. Thus selective, systemic blockade of ETA or ETB receptors produces markedly different effects on arterial pressure and ET-1 levels in the conscious primate, whereas the hypertension produced by ETB blockade is mediated by activation of the ETA receptor.

Acute systemic blockade of ETB receptors increases arterial pressure or systemic vascular resistance in experimental animals and healthy human volunteers (34), respectively. Genetic suppression of ETB receptor expression has been shown to produce hypertension in mice (22) and salt-dependent hypertension in rats (10, 20). In normal rats on a normal salt intake, prolonged administration of the selective ETB antagonist A-192621 produces hypertension (27, 33) and exacerbates the hypertension produced by a high-salt diet (28). Chronic administration of A-192621 also exacerbates angiotensin II-induced hypertension in rats (2) but has been reported to either increase (26) or have no effect (20) on systolic pressure in deoxycorticosterone acetate-salt rats. Finally, blockade of ETB receptors with A-192621 has been shown to markedly increase plasma levels of ET-1 in the rat, whereas the effects of ETA blockade on plasma ET-1 concentration are modest to negligible in rats and primates (24, 29).

Whereas the hypertensive effects of ETB suppression have been relatively consistent between studies, the mechanism by which ETB deficiency produces hypertension in experimental animals has been unclear. Because ETB activation can lead to transient hypotension and dilation of some vascular beds, a loss of ETB-dependent vasodilator tone (leading to increased vasoconstriction) has been suggested as a possible mediator of this hypertensive response. Second, elevations in plasma ET-1 levels and increased ETA activation as a result of reduced clearance of ET-1 is another potential mechanism and one supported by the present study. Finally, given the dominant role of the kidney in regulating arterial pressure (6, 12), the renal effects of altered ETB activity must also be considered. Because low-level exogenous ET-1 (and ETB receptor activation) elicits acute diuretic and natriuretic responses in vivo (31, 33), it has been hypothesized that intrarenal blockade of ETB receptors may increase sodium and fluid reabsorption at the level of the renal tubule, thereby producing antinatriuretic effects that, if maintained, would lead to retention of fluid and electrolytes and possible increases in arterial pressure (17).

In the present study, subacute, oral administration of the ETB-selective antagonist A-192621 produced a
sustained increase in MAP and concomitant increases in plasma ET-1 concentration. To our knowledge, this is the first demonstration of hypertension produced by ETB receptor blockade in a nonrodent species. At the highest level of ETB blockade tested, 24-h MAP values remained elevated throughout the 4-day treatment period, achieving values 10 mmHg above control while plasma ET-1 concentration increased fivefold.

Once ETB blockade-induced hypertension was established for 4 days, we quantified the contribution of ETA receptors in mediating this response by coadministering the orally active, ETA-selective antagonist atrasentan while continuing the hypertensive dose of A-192621. As a result, MAP fell promptly from hypertensive levels to values significantly below control on the first day of dual ETB + ETA blockade. Moreover, MAP continued to decrease, and, by the second day of dual blockade, MAP fell another 5 mmHg. This hypotensive response was accompanied by a marked and sustained tachycardia that likely reflects a compensatory response to the sustained fall in MAP. Finally, compared with baseline values, the hypotension produced by ETA blockade in monkeys made hypertensive by ETB antagonism was similar to that of monkeys possessing a fully intact ET system (29). Viewed collectively, these data suggest that the hypotension produced by ETA blockade in the present study was not appreciably altered by, or dependent on, pretreatment with the ETB antagonist A-191621. Thus these data indicate that hypertension produced by sustained ETB receptor blockade in the conscious nonhuman primate is mediated indirectly, but completely, by activation of ETA receptors, presumably through increased circulating concentrations of ET-1.

A similar ETA dependency of ETB-induced hypertension has been reported recently in several studies in rats. In telemetry-instrumented rats fed a low-salt diet and studied under a paradigm similar to that used in the present study, chronic administration of A-192621 produced hypertension that was abolished by subsequent coadministration of A-192621 + atrasentan (28). In the same study, rats fed a high-salt diet displayed increased arterial pressure, a response that was exacerbated by ETB blockade with A-192621. Subsequent coadministration of A-192621 + atrasentan did not ameliorate the salt-dependent hypertension but did negate the additional increase in arterial pressure produced by A-192621.

In hypertensive ETB receptor-deficient mice (22) or ETB-deficient rats (10), acute administration of an ETA receptor antagonist reduced but failed to completely normalize arterial pressure within several hours of treatment; the effects of long-term treatment were not assessed. It is our view that the partial amelioration of hypertension in ETB-deficient rodents by acute ETA blockade is consistent with the present study in which the hypertensive effects of ETA antagonism were not fully apparent until the second 24-h period.

In addition to causing hypertension in conscious nonhuman primates, systemic blockade of ETB receptors by A-192621 produced a dose-dependent increase in the plasma ET-1 concentration. At hypertensive levels of ETB blockade, the plasma ET-1 concentration increased to more than threefold above control values within 3 h of treatment. This relatively rapid increase suggests that reduced clearance of ET-1 is the primary contributor to enhanced plasma ET-1 levels produced by acute ETB blockade, because the temporal response is not consistent with increased protein synthesis.

When ETA blockade was superimposed on preexisting ETB blockade, the plasma ET-1 concentration increased again, also within 3 h of treatment, achieving levels ~2.5-fold above those produced by ETB blockade alone or ~14-fold above control. This novel observation is in contrast to the effects of ETA-selective blockade where plasma ET-1 levels remained unchanged during the first day and nearly doubled after 4 days (29). These data are consistent with acute studies in rats (18) and data generated in rats studied after 3 days of combined or selective ETA or ETB receptor blockade (24). In the present study, the acute, additive effects of ETB blockade on ET-1 levels during preexisting ETB blockade suggest a modest, net clearance function for the ETA receptor, an observation that is consistent with reports of cellular internalization of ETA-ET-1 receptor–ligand complexes (4). The effects of sustained ETB blockade and elevated ET-1 levels on ETA receptor expression and turnover patterns are unknown.

Because the ET system is largely viewed to function as a paracrine or autocrine system, it is important to consider the relevance of plasma ET-1 to changes in circulatory and end-organ function. Numerous studies have reported increased plasma levels of ET-1 in association with hypertension and other pathologies in patients and experimental animals (21, 36). In the present study, a threefold increase in plasma ET-1 concentration occurred in association with marked hypertension during ETB blockade in conscious primates. These results are similar to those reported by Wilkins et al. (37) in which chronic chronically instrumented dogs were infused with ET-1 to produce sustained increases in plasma ET-1 levels two- to threefold above baseline, causing chronic hypertension. Thus, in both conscious dogs and nonhuman primates, modest increases in plasma ET-1 concentration produced through independent means (intravenous ET-1 infusion or systemic ETB receptor blockade) caused a sustained hypertension. Therefore, excess plasma ET-1, whether derived directly from intravenous infusion or through spillover caused by reduced clearance of ET-1 during ETB receptor blockade, produces sustained hypertension, suggesting the circulating peptide is freely accessible to functional sites in the kidney and other tissues involved in the long-term control of arterial pressure.

Studies in the anesthetized rat (13, 16), anesthetized dog (5), and conscious dog (31) demonstrate that low-level ET-1 or ETB receptor activation produces natriuretic and diuretic effects. Studies performed in isolated rat nephron segments are consistent with these in vivo observations (11, 25). Thus it has been hypothesized that at normal levels of endogenous activation,
ETB receptors exert a natriuretic tone such that loss of this tone through ETB suppression or ETB blockade may produce antinatriuretic effects and therefore cause hypertension (17). However, this hypothesis is not supported by the present study in the conscious nonhuman primate or other studies in rats (28), because the hypertension produced by ETB blockade was completely abolished by adding ETA receptor blockade to the treatment regimen in both species.

The present data provide important insight regarding the function of ETB and ETA receptors and their influence on circulatory function. The ETB receptor appears to play an important, overall clearance function that allows the receptor to modulate arterial pressure homeostasis indirectly, by minimizing ETA tone through the clearance of ET-1 from the plasma. Because the ETB receptor displays equal affinities for the other ET isoforms, the receptor is well suited to perform a clearance function. In addition, these data and those from our previous study point to the importance of the ETA receptor in the long-term maintenance of normal arterial blood pressure in the nonhuman primate and an important interdependence of ETA and ETB receptors in determining the influence of endogenous ET-1 on circulatory homeostasis.

In summary, the present study demonstrates that continuous, systemic blockade of ETB receptors in conscious primates produces a sustained hypertension and concomitant marked elevations in plasma ET-1 concentration. Moreover, the hypertensive effects of systemic ETB blockade were completely abolished by subsequent ETA blockade, with arterial pressure falling to below baseline values despite further increases in plasma ET-1 concentration. These results demonstrate that in the nonhuman primate, hypertension induced by ETB blockade is wholly mediated through the indirect activation of ETA receptors, presumably via increased circulating ET-1. These data suggest a critical clearance function for ETB receptors, one that, by virtue of the potent ability of ETA receptors to alter long-term blood pressure control, is especially relevant to normal circulatory homeostasis.

The authors gratefully acknowledge the diligent efforts of Richard L. Marsh, Richard H. Scheller, and Kathleen Hamel for measuring plasma ET-1 concentrations, Dr. M. K. McKay for the figures, and Pam Rakestraw for technical assistance. We are also pleased to acknowledge the many Abbott scientists involved in the discovery and characterization of A-192621 and atrasentan.

REFERENCES


