AMINOACYL DERIVATIVES OF DOPAMINE AS ORALLY EFFECTIVE RENAL VASODILATORS

J. H. BIEL[1], P. SOMANI[1], P. H. JONES[1], F. N. MINARD[1] and L. I. GOLDBERG[2]

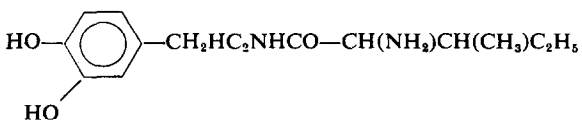
[1]Division of Pharmacology and Medicinal Chemistry, Abbott Laboratories, North Chicago Illinois, 60064, U.S.A. and [2]Department of Clinical Pharmacology, Emory University School of Medicine, Atlanta, Georgia, 30303, U.S.A.

THE FINDING by Goldberg and associates [J. L. McNAY, R. H. McDONALD and L. I. GOLDBERG, *Circ. Res.* **16,** 510 (1965)] that dopamine produced a selective dilatation of the renal vascular bed prompted the synthesis and pharmacological investigation of a large variety of dopamine derivatives, in an effort to find a clinically useful agent which would be orally effective and exert its effect over a relatively prolonged period of time (4–6 hr). An agent of this type would be an important adjunct in the drug treatment of congestive heart failure, hypertension, and acute renal shutdown. Many of the currently available antihypertensive drugs reduce renal blood flow in hypertensive patients. Increased renin secretion is believed to be due to reduced renal blood flow (RBF) and may result in the overproduction of angiotensin, thereby perpetuating the hypertensive process. An effective and selectively acting renal vasodilator would be useful both in incipient hypertension and in overcoming the deficiencies of the present drugs used in the treatment of moderate to severe hypertension. Reduced RBF also prevails in congestive heart failure and conventional diuretic therapy could be rendered significantly more effective in the presence of decreased renal vascular resistance.

While dopamine produces a pronounced increase in RBF in both animals and man which is accompanied by substantial diuresis and natriuresis, it has to be infused continuously because of its poor absorption from the G.I. tract and short duration of action. The instability of dopamine in the gut is primarily due to the presence of monoamine oxidase (MAO). On the other hand, the gut could act as a useful repository for the gradual absorption of a "protected" or latentiated dopamine which would be absorbed intact and then converted by appropriate enzymes to the active dopamine, preferably at the target site, i.e., the kidney.

Several hundred derivatives of dopamine were prepared protecting the molecule at its metabolically most vulnerable sites, the amino and phenolic hydroxyl groups. The protecting groups had to be of such a nature, as to be cleaved by the body's enzyme systems at an optimal rate to afford the release of significant quantities of dopamine over a protracted period of time, thereby producing a significant rise in renal blood flow of several hours duration without greatly compromising other hemodynamic parameters.

The present report deals with one such compound, ABBOTT-41596(N-L-isoleucyl-dopamine):



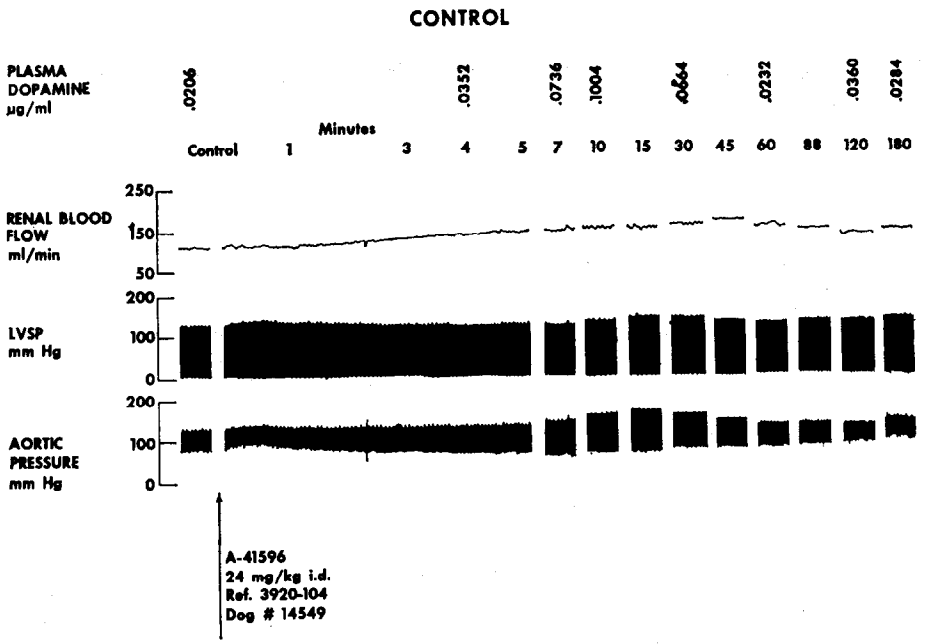


FIG. 1.—Effect of intraduodenal injection of A-41596 in an anesthetised dog. In each panel, data shown represent from top to bottom: plasma dopamine, renal blood flow, left ventricular systolic pressure (LVSP) and aortic blood pressure. The drug was given at the arrow. Tracings obtained at various time intervals after the drug administration are included to show a prolonged increase in plasma dopamine and renal blood flow.

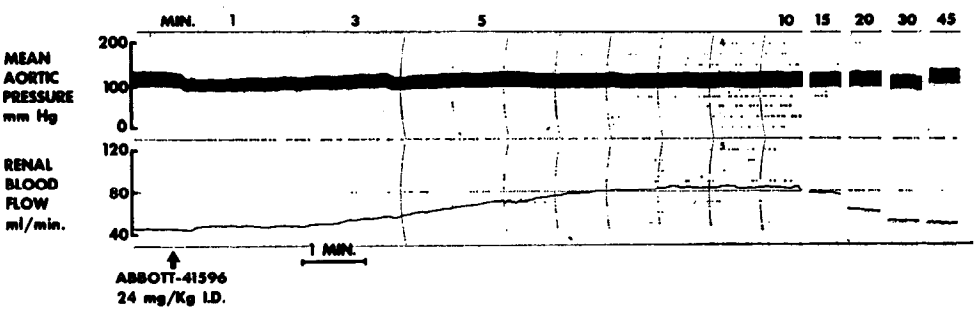


FIG. 2.—Effect of intraduodenal injection of A-41596 in an anesthetised monkey. The drug was administered at the arrow in a dose of 24 mg/kg, which is equimolar to 15 mg/kg of dopamine. Note the selective increase in renal blood flow which remained elevated for 38 min in this animal.

which fulfills some of these requirements. This amide of dopamine is cleaved at a rather slow rate by the enzyme, aminoacylarylarylamidase, which is particularly abundant in renal tissue.

The intraduodenal administration of 12 or 24 mg/kg of ABBOTT-41596 to anesthetised dogs produced a significant increase in RBF for 155 and 172 min, with a peak increase of 31 and 44 per cent respectively. RBF was measured by an electromagnetic flow probe around the renal artery. Plasma samples taken from these

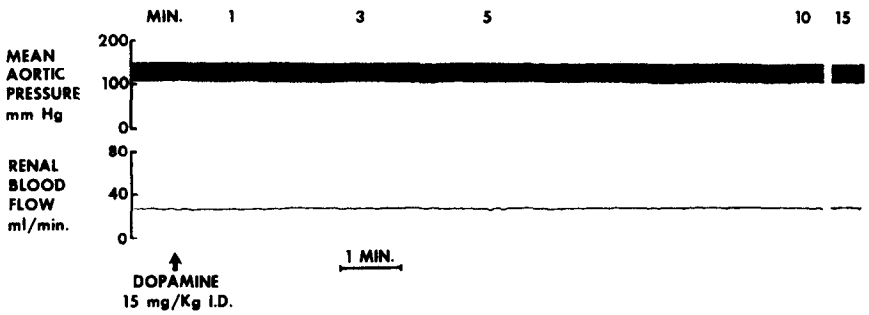


FIG. 3.—Effect of intraduodenal injection of dopamine in an anesthetised rhesus monkey. In each panel, aortic blood pressure and renal blood flow are shown. Dopamine was given at the arrow in a dose of 15 mg/kg.

animals demonstrated the presence of both intact amide and markedly increased concentrations of dopamine. The drug produced only minimal systemic hemodynamic effects at the lower dose; at the higher dose, pharmacological responses characteristic of both α and β-adrenoreceptor stimulation were seen also. Pretreatment with both phenoxybenzamine and propranolol increased RBF by 55–75% at doses of 12–24 mg/kg/i.d., suggesting that the renal vasodilator effect is independent of α or β-adrenoreceptor stimulation. In Rhesus monkeys, 12 and 24 mg/kg/i.d. of ABBOTT-41596 increased RBF by an average of 25 and 37 per cent respectively, with an onset time of 3–5 min and a duration greater than 30 min. No changes in heart rate or systemic blood pressure were observed in these animals.

ABBOTT-41596 is the first in a series of latentiated derivatives of dopamine which produces significant increases in RBF in both dog and monkey over a protracted period of time, when administered by the i.d. route. The increase in RBF can be accomplished at doses which give only minimal systemic hemodynamic changes. Slow but consistent hydrolysis by the enzyme, aminoacylarylamidase, of ABBOTT-41596 appears to be responsible for the prolonged presentation of physiologically active quantities of free dopamine to the renal vasculature, resulting in a substantial decrease in renal vascular resistance.