Peripheral Dopamine Receptors in Cardiovascular Therapy

The Legacy of Leon Goldberg (1927–1989)

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Leon Isodore Goldberg, Professor of Pharmacology and Medicine and Chairman of the Committee on Clinical Pharmacology at The University of Chicago, died May 8, 1989, after a brief illness and an illustrious career. In recognition of his outstanding contributions to cardiovascular pharmacology and medicine, Hypertension invited us, Leon's colleagues during the major part of his career, to review the breadth of innovation he brought to the treatment of cardiovascular disease.

Although we will shortly describe his scientific contributions, it is appropriate to begin with a brief reflection on the personal qualities that endeared Leon to his many colleagues and friends around the world. Among the countless tributes paid after his death, one characteristic was identified above all others: his unassuming, friendly, nonconfrontational approach to life. When on the losing end of an argument there was always the graceful exit with "Well, I have only been thinking aloud!"

The circumstances under which one of us (J.D.K.) first met him illustrates the essence of his personality: "It was the summer of 1967 in Montreal. I was presenting a paper at the Canadian Federation. From the back of the room someone asked a question and, in reply, I referred him to Leon Goldberg's work. I did not realize that the person asking the question was Leon himself. That evening, at a mixer, Leon sought me out and introduced himself and we laughed at the incident. Of course neither of us knew the answer to the question. I relate this anecdote as it shows how unassuming a person Leon was. He was already well-known for his work on dopamine at the time, but he did not react to my not recognizing him, and he later went out of his way to seek me out, a relatively unknown person, to discuss something in which he was genuinely interested."

There was extraordinary personal generosity to colleagues and staff. Informal visits to his home, any time, on any day, were the norm. Junior faculty and fellows were treated to restaurants, the theater, or even the occasional football game—provided, of course, that they were willing to hear out Leon's latest theory on dopamine receptors! His willingness to sit on the floor, beer in hand, with student or fellow, casually discussing pharmacology, music, Ulysses, or Finnegans Wake (he was a perennial student of the "Great Books") made him a much sought after teacher and mentor. His popularity among medical students was also aided by his inability to fail anyone at examination time. There was always some mitigating circumstance, and the erring student would be shamed into the additional necessary study. He started the Clinical Pharmacology Training Program at Emory University in 1961 with one fellow. By 1968 he had 10 and, over his career, he attracted more than one hundred fellows for training. His course on Clinical Pharmacology at The University of Chicago was one of the most popular among undergraduates.

Although a universally popular figure among his colleagues and his peers in national and international societies, it was the product of his intellect that earned him the respect he enjoyed. The potential of this intellect was obvious at an early age.

Initial Observations

Leon was born the son of a pharmacist in Charleston, South Carolina. Following in his fa-
ther's footsteps, he trained as a pharmacist but very quickly saw that he would need a greater challenge in life. Accordingly, he returned to the Medical University of South Carolina at Charleston and received his PhD degree in pharmacology in 1951. Later that year, he entered Harvard Medical School, having impressed the selection committee—"more likely by the fact that I was principal clarinet in the Charleston Symphony than by my academic credentials" as he once said with characteristic, albeit unjustified modesty. After receipt of his MD degree (cum laude) in 1956, he underwent postdoctoral training in medicine at Massachusetts General Hospital and later in cardiology at the National Institutes of Health (NIH). It was during a postdoctoral fellowship with Albert Sjoerdsma at the NIH that he first encountered dopamine.

A major interest of Sjoerdsma’s laboratory was the effect of monoamine-oxidase inhibitors on the metabolism of endogenous amines. Rather than adopt the biochemical techniques that were dominant in the laboratory (Leon had been known to describe his new colleagues as "a bunch of biochemists who hadn’t a clue about pharmacology"), he elected to exercise his talents in pharmacology by embarking on comparative studies of the hemodynamic effects of the different sympathomimetic amines in the anesthetized dog. He soon discovered that there was a clear difference between the hemodynamic response to dopamine and that to norepinephrine. Although norepinephrine invariably caused a dose-dependent increase in blood pressure as well as in heart rate and contractility (the last measured with the Walton and Brodie strain gauge named for his mentors in pharmacology at Charleston), low dose dopamine enhanced contractility but with little change in heart rate and a reduction in blood pressure. However, when the infusion rate was increased, dopamine behaved like norepinephrine, raising both heart rate and systemic pressure (Figure 2).

This observation launched his career. As he wrote later, "It was during the course of these studies that I began to consider the possibility that dopamine might be useful in the treatment of congestive heart failure. This concept was a direct result of my training as a graduate student with Robert Walton at the Medical University of South Carolina. Professor Walton had postulated that if a sympathomimetic amine could be found which stimulates the heart without increasing heart rate or blood pressure, it would be useful in the treatment of heart failure." According to a collaboration of Horwitz and Fox at the NIH, he went on to demonstrate that dopamine exhibited these characteristics not only in the dog but also in normal human volunteers. The next step would be a trial in heart failure patients.

**First Application: Heart Failure**

With this background of scientific and clinical training and a clear view of what he wanted to study, Leon joined the faculty of Emory University, in the Department of Pharmacology, in 1961. He quickly set about the first clinical study of dopamine in patients, in collaboration with Bob McDonald and colleagues.4
The first patient produced another surprise, described in a lecture he delivered to the Royal Society of Medicine some years later: “A patient with severe congestive heart failure was brought into a metabolic unit for study. He was not responsive to the diuretics available at that time. We placed him on a constant sodium diet and found that he was excreting less than 5 mEq in 24 hours. After a period in hospital, his sodium excretion was constant. We then administered dopamine at a relatively slow rate, about 1–2 μg/kg/min, for a period of several hours, and observed a good diuresis in that sodium excretion increased to about 45 mEq/24 hours ... We later tried the effect of half the dose of dopamine, and also repeated the full dose, and found that sodium excretion was related to the dose of drug administered.”

This lecture, incidentally, was delivered during a sabbatical year at “The Hammersmith,” with Sir John MacMichael and Colin Dollery. British unfamiliarity with American academic titles led to Leon (an assistant professor at that time) being awarded all the privileges of a full professor, including that most important and rare of rights—a car parking space on the grounds of The Hammersmith. This perk, coupled with personal immunity from MacMichael’s absolute ban on smoking by staff members, sorely tested the patience of his less fortunate British colleagues but was the experience most frequently recounted by Leon in later years.

In any case, the initial conclusion from the experiment was that the diuresis had probably resulted from improved cardiac output as had been seen previously with digitalis. If this were the case, they conjectured, dopamine should have little effect on renal function in normal subjects. However, this proved not to be so. Infusion of dopamine in volunteers led to substantial increases in renal blood flow, glomerular filtration rate, and sodium excretion—in the absence of changes in heart rate or blood pressure (Figure 3).6 Discerning that this might have resulted from a specific effect in the renal vasculature, they returned to the animal laboratory to characterize the vascular distribution of the effects of dopamine in the anesthetized dog. Canine renal artery (but not femoral) vasodilation, in the presence of phenoxycbenzamine, unaffected by antihistamines or anticholinergic agents, became the “gold standard” assay for dopamine receptor activity.7 That there likely existed a specific vascular dopamine receptor became increasingly clear to him with the finding of selective blockade of the renal vasodilator effects by phenothiazines and butyrophenones, already known to block dopamine receptors in the caudate nucleus.8

At Emory from 1961 to 1973, Leon Goldberg and his colleagues studied many aspects of dopamine: physiological, pharmacological, and clinical. Their work changed the way pharmacologists and physicians looked at dopamine. It was no longer considered just another sympathomimetic amine or merely a precursor of norepinephrine; dopamine came to be recognized as an important endogenous amine with unique therapeutic potential.

**Additional Applications: Shock and Hypertension**

In the 1960s, the drug treatment of cardiovascular shock was quite unsatisfactory. Isoproterenol was used to enhance cardiac output, but it diverted blood from vital organs such as the kidney to skeletal muscle (now known to result from β2-adrenergic receptor activation). Both an α-adrenergic receptor agonist (norepinephrine) and an antagonist (phenoxycbenzamine) were variously advocated. In 1966, MacCannell and Goldberg reported results from the first patient with septic shock treated with dopamine.9 Having first ensured adequate plasma volume expansion, they demonstrated remarkable increases in cardiac output, systemic blood pressure, and urine output during dopamine infusion. The variable hemodynamic response to different infusion rates allowed titration to the desired hemodynamic effect—low dose to enhance cardiac output and renal perfusion, and higher dose if peripheral vasoconstriction was required to preserve flow to vital organs. Although individual patients differed greatly in their volume status and the extent to which their autonomic system was activated, the rate of dopamine infusion could be individualized. The ability to preserve renal function while inducing peripheral vasoconstriction was of signal importance. Consequently, dopamine was on its way to becoming the most widely used cardiovascular drug in critical care medicine.
Always anticipating clinical applications of his laboratory work, Goldberg also saw the potential for exploitation of the still putative dopamine receptor in hypertension. In a remarkable clinical experiment in 1966, with the collaboration of John McNay, he administered dopamine to a patient with severe hypertension (Figure 4). Although low dose dopamine lowered pressure to a limited extent, higher doses actually increased pressure; however, when combined with phenoxybenzamine, dopamine had a dose-dependent hypotensive effect. Recounting this experiment in later years, Leon wistfully remarked on how the climate for clinical research had changed. The "experiment" would never be performed in the 1980s with the advent of the stifling bureaucracy regulating clinical investigation. In any event, based on the findings in this patient, he predicted that a drug that activated dopamine receptors exclusively would be an ideal antihypertensive agent, combining vasodilation with diuresis, and with limited tachycardia. This would encompass "triple therapy" in a single compound. Unfortunately, it has taken almost 25 years to exploit this early observation.

Characterization of the Receptor Mechanism

Although sufficient evidence was gathered from dog studies to suggest the presence of a specific dopamine receptor in the renal and mesenteric vascular beds, pharmacokinetics of drug-receptor interactions could not be studied in such a model. Leon was acutely aware of this and was, therefore, keen to develop an isolated tissue model for studying dopamine receptors to put this concept on a firmer footing. In pursuit of this, he took a sabbatical year to work in Dr. Noburu Toda's laboratory in Kyoto, Japan. In collaboration with Toda, he developed an in vitro model: the isolated rat or canine renal or mesenteric artery, precontracted with prostaglandin F2α, and treated with phenoxybenzamine. This in vitro model had only limited success because of the inherent difficulty of studying vascular muscle relaxation in vitro. Goldberg's work, as well as an exhaustive review of the world literature on dopamine up to this point, was summarized in his citation classic article of 1972.

In 1974, The University of Chicago sought to establish a clinical pharmacology group led by an individual who could transcend the boundaries of basic and clinical science. With his background in the pharmacology laboratory and his proven ability to translate laboratory science to the bedside, Leon was selected to lead the new program. It was this approach of Goldberg and of some of his contemporaries to drug research (application of laboratory pharmacological research to clinical medicine and, of equal importance, seeking to solve clinical problems in the animal laboratory all within one department) that fostered the discipline of clinical pharmacology in the United States, and, in turn, profoundly affected the process of drug development.

Once in Chicago, he quickly set about the creation of a new group to carry forward both the basic science and clinical missions. Of the former, an urgent component was the better characterization of the dopamine receptor and determination of the structure/activity requirements of agonists and antagonists. In 1975, one of us (J.D.K.) joined him to participate in this research. Although there was sufficient evidence suggestive of a specific vascular dopamine receptor, the evidence was still somewhat tenuous. Aside from dopamine, the only other "dopamine" receptor agonist available was epinephrine, which was equipotent to dopamine, and the antagonists available had very limited specificity. Thus, neither a potency order of agonists nor a sufficiently specific antagonist was available to characterize the receptor in the classic pharmacology mode. Efforts were, therefore, directed toward gathering evidence from both angles.

One of the first compounds studied was N-N-di-n-propyl dopamine (DPDA). DPDA was found to have dopamine-like activity in the renal vascular bed with a potency 1/15-1/30 that of dopamine. Unlike dopamine, however, DPDA also produced femoral vasodilation (Figure 5). It should be recalled that, according to the criteria set for dopaminelike activity by Goldberg, a dopaminomimetic drug should not produce vasodilation in the femoral vascular bed. Thus, DPDA appeared to have some additional action. Further investigation of this DPDA-induced
Two Dopamine Receptors

In 1978, several novel N-N-di-substituted analogues of dopamine were developed and were studied in the experimental models described earlier. Interestingly, the series showed very different potency orders in the two models. Although all the compounds were nearly equipotent in the femoral vascular bed (the presynaptic receptor model), they showed three levels of potency in the renal bed (the vascular receptor). This led to speculation that the dopamine receptors in the two locations might fall into two different subtypes. In the same year the enantiomers of sulpiride, an antagonist of dopamine receptors in the central nervous system, became available from the Ravizza Company of Italy. When activity of the sulpiride enantiomers against dopamine-induced renal and DPDA-induced femoral vasodilation was studied in the anesthetized dog, d-sulpiride was more potent than the l-enantiomer in antagonizing dopamine-induced renal vasodilation (the vascular dopamine receptor). In contrast, the l-enantiomer was much more effective in inhibiting DPDA-induced femoral vasodilation. On the basis of this evidence—different orders of potency of a limited series of agonists, the reverse potencies of the two enantiomers of sulpiride as antagonists of the dopamine receptors at the two sites and some additional differences observed in other studies—classification of peripheral dopamine receptors into two subtypes, DA1 and DA2 was proposed.15

Because therapeutic exploitation was the ultimate goal, a search began for compounds with actions confined specifically to the two dopamine receptors. As regards receptor agonists, several structures represented by dopamine analogues with an open side-chain or compounds in which the dopamine side-chain was placed into rigid or semirigid structures were studied. These included phenylethylamines, aminotetralines and aminoindans, aporphines, ergolines, benzoxazolines, and benzazepines. The eventual discovery of fenoldopam at the Smith Kline and French laboratories as a highly potent and specific DA1 antagonist, lacking any DA2 activity, provided a new view of the possible conformation of dopamine side-chain essential for DA1 activity. Previous studies had suggested that a fully extended trans conformation of the side-chain, where the meta OH of the catechol had to be in β-rotameric conformation, was required. This, however, proved to be incorrect since N-propyl substitution in α-rotameric aminotetralin yielded a highly potent, though not specific, DA1 agonist. The potent specific activity of fenoldopam suggested that the required conformation of the dopamine side-chain for agonist activity was intermediate between the fully cis and fully trans configuration. Other important observations in this area included: 1) Ergolines were inactive as DA1 agonists but provided several potent and full DA2 agonists (bromocriptine, pergolide). 2) Apomorphine was a weak partial DA1 agonist but was a potent and full DA2 agonist.

In search of specific and selective dopamine antagonists, many types of structures have been studied. These include butyrophenones, phenothiazines, thioxanthines, natural products (bulbocapnine), substituted benzamides, and 3-benzazepines. Most were not specific, however, since a twofold increase in the dose would result in action on other receptors. In addition to lacking specificity vis a vis other receptor systems (5-HT, adrenergic receptors), they also discriminated poorly between the two subtypes of dopamine receptors; the selectivity ratios were limited to a 2–5 range. S-Sulpiride was the first relatively selective DA2 antagonist with a selectivity of greater than 2 log units. This was followed by the butyrophenone domperidone with a reported selectivity of 104 also as a DA2 antagonist. Thus, all early dopamine antagonists were more potent at the DA2 than at the DA1 receptor, including R-sulpiride. The last, although more potent than the S-enantiomer as a DA2 antagonist, was still five times more potent as a DA2 than as a DA1 antagonist. Thus, no selective DA2 antagonist was available until the discovery of SCH 23390 by Iorio et al16 in 1983. When selectivity and
specificity ratios of SCH 23390 were compared in the dog renal and femoral vascular beds, a ratio of 300 was noted for DA$_1$ antagonism in comparison with DA$_2$, histamine, muscarinic, 5-HT, and $\alpha$-adrenergic receptors. Availability of this highly potent and selective DA$_1$ antagonist completed the total evidence needed in support of two subtypes of vascular dopamine receptors. A clear-cut potency order of agonists was established; in fact, using a selected group of compounds, a total reverse order of potency of agonists could be shown at the two subtypes. Finally, highly selective and potent antagonists for both subtypes had also been reported.

**Dopamine and Heart Failure: Current Status**

The introduction of dopamine enhanced the acute treatment of heart failure, but its use in chronic therapy has been thwarted by two factors: poor oral bioavailability and activation of postsynaptic vascular $\alpha$-adrenergic receptors, which increase peripheral resistance and consequently myocardial work load. Efforts to overcome limited bioavailability have involved the use of prodrugs that are absorbed from the gastrointestinal tract and converted to dopamine or dopamine agonists after absorption. Lack of selectivity at peripheral receptors has been addressed by the synthesis of new dopamine agonists as described earlier.

While still at Emory, Leon saw the potential of levodopa (the immediate metabolic precursor of dopamine already in use in the treatment of Parkinson’s disease) to circumvent first-pass metabolism. In a study of parkinsonian patients, he demonstrated that levodopa produced cardiac and renal effects similar to those seen during dopamine infusion. Shortly thereafter, when confronted with a patient with severe heart failure whose symptoms worsened each time the infusion rate of dopamine was reduced, he succeeded in weaning the patient off dopamine by substituting oral levodopa. Later, in Chicago, Rajfer, Goldberg, and colleagues carried out a study in patients with severe congestive heart failure wherein they demonstrated symptomatic improvement, decreased systemic vascular resistance, and increased cardiac index. Heart rate, systemic blood pressure, and intracardiac pressures were not altered significantly. These effects were sustained for at least 3 months. Side effects included nausea and vomiting, actions mediated through DA$_2$ receptor activation in the central nervous system, but these could be minimized by gradual dose increases.

Similar results have been achieved with ibopamine, the diisobutyric ester of $N$-methylamphetamine (epinine). Once in the body, ibopamine is metabolized by plasma esterases and epinine (an agonist at peripheral DA$_1$ receptors and $\alpha$- and $\beta$-adrenergic receptors) is released. In patients with heart failure, oral ibopamine increased cardiac index, sodium and water excretion, and reduced systemic vascular resistance; nausea and vomiting were uncommon. Ibopamine has been approved for the treatment of heart failure in Italy.

In addition to dopaminergic prodrugs, novel receptor agonists have also been studied. Unfortunately, all are metabolized in the gastrointestinal system and must be administered intravenously. For example, dopexamine is an agonist at DA$_1$, DA$_2$, and $\beta$-adrenergic receptors but, unlike dopamine, has minimal activity at $\beta$-adrenergic receptors and does not activate $\alpha$-adrenergic receptors. Additionally, it blocks the reuptake of norepinephrine into sympathetic nerve terminals. Its rapid onset and short duration of action are of value in the acute treatment of congestive heart failure. Propylbutylamphetamine is active at both DA$_1$ and DA$_2$ receptors, although it is more potent at the latter. It has minimal activity at $\alpha$-or $\beta$-adrenergic receptors. Its hemodynamic effects are similar to those of low dose dopamine but, because of DA$_2$ receptor activation in the central nervous system, it produces nausea and vomiting.

It appears that dopamine agonists confer benefit in improving hemodynamic indexes on some patients with heart failure. Whether exploitation of the dopaminergic receptor system in long-term therapy improves the duration of survival has yet to be proven.

**Dopamine and Hypertension: Current Status**

We alluded earlier to the prediction made in 1966 that a drug like dopamine, but devoid of actions at $\alpha$-adrenergic receptors, would be a useful antihypertensive agent. With the recent development of fenoldopam, a benzaazepine derivative, it has become possible to test that hypothesis. Murphy and Goldberg infused it in patients with mild hypertension and observed a dose-dependent blood pressure reduction. Renal plasma flow, sodium excretion, and glomerular filtration rate increased in the face of blood pressure reduction. Because of its rapid onset and short duration of action, ideal characteristics of a parenteral agent for hypertensive emergencies, Elliott et al went on to compare fenoldopam with sodium nitroprusside in patients with severe hypertension. Both agents lowered blood pressure effectively. Although nitroprusside had little effect on sodium and water excretion, fenoldopam increased urine output, creatinine clearance, and sodium excretion despite significant reductions in blood pressure. These renal effects of fenoldopam are potentially advantageous in the treatment of patients with coexisting hypertension and renal impairment.

Aside from therapeutic implications, Leon’s initiatives have stimulated research in other areas of hypertension. Noting his finding of the natriuretic effects of dopamine, several investigators are now examining whether deficiencies in the renal metabolism of dopamine or diminished sensitivity to the effects of endogenous renal dopamine might underlie salt-sensitive hypertension. Yet others address their efforts to the role that dopamine receptor activation might play in the renal responses to different vasodilator and natriuretic agents. This research is but another testament to the importance of his work.
Dopamine Receptors: Current Status

Although the classification of dopamine receptors into two subtypes is now generally accepted, there is some question whether the Goldberg and Kohli classification of DA₁ and DA₂ vascular receptors and the Keabian and Calne classification of central nervous system receptors represent the same receptors. The D₂ receptor has been purified, cloned, and expressed. Similar characterization of the D₁ receptor is imminent, and the biochemical mechanisms of action of both receptors have been elucidated, as outlined recently by Mark Caron at an international symposium on dopamine, dedicated to Goldberg's memory. With molecular sequencing and three-dimensional modeling, it should be possible shortly to develop new drugs that will achieve, finally, the therapeutic promises heralded almost 30 years ago.

The Legacy

We have focused on Goldberg's contribution to cardiovascular pharmacology and therapeutics. Limitations of space have allowed but scant tribute to his influence on the discipline of Clinical Pharmacology and none to the several other areas of pharmacology in which he made substantial contributions or to his influence on the many young investigators he trained. We have made reference almost exclusively to work that emanated from his own laboratory, knowing well that a great number of others have claim to reference on several of the issues described. For it is the breadth of this group, the great number of scientists, basic and clinical, who followed in his path in search of the role of dopamine, that testifies to the enormity of his legacy.

References


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