Asymmetric Dimethylarginine and Kidney Disease—Marker or Mediator?

Patrick Vallance and James Leiper
Division of Medicine, University College London, London, United Kingdom


Asymmetric dimethylarginine (ADMA) is a naturally occurring amino acid that circulates in blood and is excreted in urine (1). It is also a competitive inhibitor of all three isoforms of nitric oxide synthase (NOS). ADMA competes with arginine for the binding site of NOS with an IC₅₀ of about 10 μM depending on the prevailing concentration of arginine (2). Combine these observations and it is possible to make the statement that ADMA is an endogenous inhibitor of NOS. Although correct, this implies only that endogenously generated ADMA has the capacity to act as an inhibitor of NOS, and does not necessarily mean that this is either a physiologic or pathophysiologic role of ADMA.

Ever since the first description of ADMA as an endogenous inhibitor of NOS (1), two approaches have been taken to try to answer the question of its biologic importance. One approach has been to explore the relationship between the circulating concentration of ADMA and disease states, and the other has been to undertake experiments designed to test causal relationships. The first disease association established was in renal failure (1). The idea was simple: Because ADMA is excreted in the urine, it should accumulate as the kidneys fail, and, as a consequence, the inhibition of NOS would produce adverse effects in many different organ systems. Reassuringly, ADMA fulfils many of the characteristic features of a uremic toxin. It is a guanidino compound, a product of protein metabolism, accumulates in renal failure, is removed by dialysis, and has a clear mechanism of action (inhibition of NO generation) to produce pathophysiology. Studies have already indicated that plasma ADMA levels are predictive of cardiovascular morbidity and mortality in renal failure (3,4) and now, in this issue of the Journal of the American Society of Nephrology, two articles describe that ADMA levels also predict progression to renal failure (5,6). It might also be reasonable to expect other effects on NO systems to affect the gut and the immune and nervous systems (1).

Despite the encouraging results, the literature on ADMA levels in disease states is not easy to interpret with any degree of certainty. Different laboratories have reported widely differing ranges for ADMA concentration in plasma (7,8), and the use of laborious HPLC techniques to measure ADMA has meant that samples sizes for clinical studies have usually been relatively small. The two studies reported here are of 177 and 131 patients with kidney failure. One assessed ADMA by liquid chromatography–mass spectrometry and the other used a newly described ELISA. Taking into account differences in age and degree of renal failure in the subjects, ADMA concentrations were similar between the two studies and both found that those patients with the highest ADMA had the greatest progression to end stage disease, and gave comparable estimates of risk. The predictive power of ADMA appears to be independent of other markers, and may be additive in predictive value when combined with brain natriuretic peptide and C-reactive protein (9). Even allowing for the relatively low event rates, small sample sizes, and the possibility of publication bias, it does now appear likely that ADMA is a risk marker for death, cardiovascular mortality, and renal progression in patients with kidney failure. A meta-analysis of the available studies may be useful to get a better estimate of risk, but would be hampered by the lack of standardization in ADMA measurement techniques.

As well as noting the predictive power of ADMA, it is clear that markers of renal function also predict cardiovascular risk (10) and that the best predictor of ending up with no renal function is starting off with reduced renal function. In this context it is worth noting that the predictive power of cystatin C, creatinine, and symmetric dimethylarginine (SDMA) is probably better than that of ADMA (5,6,10). This is important because creatinine has not been proposed as a biologic mediator, and SDMA, unlike ADMA, does not inhibit NOS (1) and does not have a clear biologic rationale to act as a mediator of cardiovascular risk. Two questions follow: First, is the accumulation of ADMA simply due to failed renal clearance? Second, is ADMA more than just another marker of renal dysfunction? SDMA is not metabolized to any great extent and, as expected, its concentration in plasma correlates closely with creatinine. In contrast, ADMA is actively metabolized to dimethylamine and citrulline by the action of the dimethylarginine dimethylamionohydrolases (DDAH I and II) (11,12). Indeed, the major route of elimination of ADMA from the body is by metabolism rather than by urinary excretion (13). Therefore, as the kidneys fail ADMA does indeed accumulate, but the extent of accumulation is limited because metabolism continues. Thus, though the...
study of Fliser et al. (5) suggests that both SDMA and ADMA predict progression of renal disease and poor cardiovascular outcome, it seems that only the effect of ADMA is independent of creatinine (it would also be useful to know if it is also independent of cystatin C). The reason that ADMA may accumulate to different degrees in different patients with renal disease is not known, but it is worth noting that the kidney expresses very high levels of both isoforms of DDAAH (12) and is the major arginine-handling organ of the body. It is conceivable therefore that renal pathologies not only affect the ability to excrete ADMA but also exert a major and differential effect on the ability to metabolize ADMA.

The key question then comes down to causality. In simple terms, the case for ADMA as a causal agent rather than simple plasma marker looks strong. It inhibits all three isoforms of NOS, and experimental data indicate that ADMA produces the expected physiologic changes when infused in vivo (1,13,14). Furthermore, animal models have shown that other NOS inhibitors enhance atherosgenesis and promote renal damage consequent upon reduced NO generation (15,16). However, the absolute levels of ADMA and the differences between groups in the current clinical studies are small. It seems difficult to accept that a 0.1 μmol/L increase in ADMA could cause a 20% or greater increase in event rate. Indeed, it would be expected that such a change would have virtually no effect on NOS activity. This sort of paradox in the NO field is not new. Indeed, based on the enzymology and the nature of competition between arginine (substrate) and the asymmetric methylarginines (inhibitors), it would be predicted that it would be necessary to give ADMA or Nω-monomethyl-L-arginine (L-NMMA) in very high doses to achieve a pharmacologic effect and overcome the near mM concentrations of arginine within cells. Yet the functional data tell us that relatively low doses of methylarginines inhibit NOS in vivo and that very large amounts of exogenous arginine need to be administered to overcome the inhibition (17). This may be because methylarginines are compartmentalized in some way and linked to the distribution of the cationic amino acid transporters. All cells seem to make ADMA and the plasma concentration presumably reflects release from many different sources. It seems prudent to conclude that it is very unlikely to be the circulating concentration of ADMA that is the mediator of effects, but rather some local higher concentration, either because of cellular uptake from plasma, or because of high levels of generation of ADMA within certain cell types or tissues. This would not be surprising given the high levels of methylarginine generation within cells and the existence of intracellular machinery to regulate ADMA concentrations (19). Alternatively, the raised ADMA that predicts risk may simply be a marker of some other important biologic process, such as an increase in protein arginine methylation in proteins (the synthetic route of ADMA), altered breakdown of proteins, or DDAAH dysfunction (19). Ultimately, to answer the question of causality with any degree of certainty, it will be necessary to generate animal models with elevated ADMA levels, and to identify therapeutic maneuvers that would increase ADMA elimination. Until such time, we are left with a novel risk marker and a tantalizing possibility of a very plausible route by which it may produce pathophysiology.

References


