Editorial Commentary

Rapid Effects of Aldosterone Relevant in Cardiac Ischemia?

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Not long ago, scientists celebrated the 50th birthday of aldosterone. And yet miracles around this dinosaur steroid hormone are creeping out of the bushes. For a long period, peaceful consentement overwhelmed even critical minds in the light of tremendous successes: the classical way of steroid action through a genomic machinery starting from the well-known intracellular receptors was close to being ideal in explaining both in vitro and in vivo data.

The more recent findings on rapid effects of steroid hormones such as aldosterone including those of Fujita et al1 in this issue of Hypertension have stirred up our thinking about the mineralocorticoids and virtually all other steroid hormones. They cannot involve only genomic mechanisms because of their hasty appearance and, therefore, have been termed “nongenomic” effects.

Such effects are all but new with the first report for a steroid hormone—progesterone—dating back to the 1940s;2 and those for aldosterone dating back to the 1950s and 1960s.3,4 However, as a consequence of vigorous efforts, the general scientific audience has gradually accepted their existence, and the mechanisms involved are being progressively investigated, at least up to a certain level.

Over the past decade, it has become increasingly clear that those novel steroid actions use very common intracellular signaling pathways that are seemingly promiscuous and, thus, recruited by many other hormones that induce rapid signaling (eg, catecholamines). Though differing from steroid hormone to steroid hormone and from tissue to tissue to some extent, common themes seem to be involvement of MAP kinases, phospholipase C, PI3 kinase, free intracellular calcium, and intracellular pH to name just a few.5,6

It is obvious that the receptors involved in such actions need to be identified, but this has been more difficult than the investigation of second messengers: divergent pharmacology and assumed membrane localization induced a wide search for novel steroid hormone receptors in the membrane; 4 of those have been cloned to date (eg, one presumably for estrogen7). Unfortunately, an aldosterone membrane receptor is still not among them.

However, things have turned out to be much more complicated than originally thought. It is now clearly established that classic intracellular receptors belonging to the superfamily of nuclear hormone receptors can mediate nongenomic responses as well, as shown in transfection experiments. Given the histories of scientists dedicated to classical receptors and those coming from somewhere else, an increasingly emotionally, sometimes even intellectually, violent debate has arisen regarding where to assume classical versus non-classical receptors are involved. Opinions almost stretch from one extreme end to the other, with most effects mediated through classical versus mediated through novel receptors, with the truth certainly lying somewhere in between, as critically reviewed recently for aldosterone.8

Having introduced the reader to a highly active new area of endocrinology still left with major unsolved questions and controversies, where would the findings of Fujita et al fit into the plot? Do they contribute to the virulent debate on receptors?

No, they do not.

This, however, does not matter at all. They are yet more significant in addressing an even greater and more important deficiency in our knowledge on these nongenomic steroid actions not mentioned here before their biological relevance.

Though observations in experimental animals initially opened the field (rats being instantly anesthetized by intraperitoneal injection of progesterone)2 and neurosteroid actions have even been used clinically (Althesin for anesthesia induction), most findings in this context are derived from in vitro experiments with comparably little reflection into their in vivo significance. Partially, this holds true for rapid aldosterone effects as well, although a very early article clearly demonstrated acute cardiovascular effects in humans (Reference 7 in Fujita’s article). Subsequently, data were generated in clinical trials involving human volunteers demonstrating vasoconstrictory responses at the level of systemic resistance, blood pressure,9 or renal arterioles.10 However, forearm vasculature seems to react variably to aldosterone, depending on concomitant pharmacological interventions,11 and controversies in the orientation of renal effects also exist (Reference 9 in Fujita’s article claims an acute vasodilatory effect of aldosterone on renal arterial arterioles).

Though these studies point to acute cardiovascular effects of aldosterone, their contribution to cardiovascular disease is still completely unclear. It is safe to assume that aldosterone can cause cardiovascular damage as blockade of its receptors by spironolactone or eplerenone can save lives in heart failure.

The opinions expressed in this editorial commentary are not necessarily those of the editors or of the American Heart Association.

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(RALES study) or post-myocardial infarction patients (EPHESUS trial).

For the first time to our knowledge, Fujita et al show a nongenomic, detrimental effect of aldosterone in a cardiac disease model. The authors demonstrate the early onset of the effect in an in vivo dog model of myocardial ischemia. Their experiments reveal the same dose–response relationship in the physiological range of free hormone concentrations, the same insensitivity of aldosterone effects to spironolactone as observed in many, if not all, related in vitro studies before. Reduced coronary perfusion seems to correlate with reduced cardiac function, which therefore implies that it is more than just a small, insignificant alteration of coronary flow. In general, this has been a criticism concerning the clinical relevance of nongenomic steroid effects because they normally are not impressively large.

These findings support the hypothesis that endogenous aldosterone can be harmful through acute, not just chronic, effects; of course, the relative contributions of both mechanisms to cardiovascular diseases are still unclear.

An involvement of PKC is shown in Fujita’s studies, which is also consistent with earlier in vitro results in this context. As a matter of fact, PKC has even been claimed to be “the receptor” for rapid aldosterone effects. Taking this together, we should gratefully welcome such efforts to further elucidate the biological importance of rapid aldosterone actions in vivo, especially if aiming at disease models. As long as we do not have drugs that are specific for either genomic or nongenomic mineralocorticoid effects (as they exist for vitamin D and to a certain extent for estrogenic mechanisms to cardiovascular diseases are still unclear).

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References
