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INVITED COMMENTARY

Non-genomic steroid action—take a closer look, it's not rare! An invited commentary

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Not too long ago, one would have been smiled at or at least ignored by peers if claiming a steroid hormone to act rapidly. A steroid hormone had to act slowly through those intracellular receptors that had been discovered as a perfect fit for each particular steroid.

Why should nature provide more sophisiticated means for cellular responses to steroid hormones if a complex mechanism to explain them had already been identified? The dogma of genomic steroid action that involves those intracellular receptors serving as steroid-dependent transcription factors certainly had, and still has, its fascinating facets and ruled almost a generation's time of highly successful steroid research. The outstanding achievements of this story, however, confined non-conformist observations for a long time to a place in science that may be described as a fair of honest artifacts at its best, or a state of non-existence at its worst.

Things have changed over the past few years—for God's sake! Observations of non-genomic steroid effects are presently published at an increasing rate and, meanwhile, their thrust covers effects of almost all steroids in nearly all kinds of tissues and species.

Because of lack of the referees' confidence in the data presented, the author's early work on rapid aldosterone action (1) had been almost unpublishable, while a recent paper on non-genomic pH effects of aldosterone from the same source was rejected because of lacking originality (which means the story is now well accepted and confirmatory observations do not seem to be necessary any more). What made this dramatic change in the perception of steroid action happen?

Observations on non-genomic steroid action have been communicated from the very beginning of steroid research. To our knowledge, Hans Selye was the first to publish instant anesthetic effects of progesterone in rats as early as 1942 (2). Pietras and Szego, reporting on rapid estrogen action on myometrial calcium flux (3) more than three decades later, were then still pioneers in the analysis of non-genomic steroid action, which, among other features, is mainly identified by the rapid onset of effects being too swift for the involvement of time-consuming synthesis, processing and plasma membrane insertion of protein molecules. During the following one and a half decades, reports on further evidence for non-genomic steroid action were sparse, but in the early 1990s this field was boosted by several independent observations now supported and made available by modern technology such as fluorescence techniques and more sophisticated biochemical and molecular biology methodology. By then, numerous rapid effects of aldosterone (4), vitamin D_3 (5), corticosterone (6), neurosteroids (7) and literally steroids from all groups (including triiodothyronine) had been reported and explored systematically with regard to agonists, intracellular second messengers and effector systems. In a paper in this issue of European Journal of Endocrinology, Audy et al. closely follow those parent observations in their report on rapid effects of 17β-estradiol on calcium influx in human prostate cancer cells. The congruity of their data with those on non-genomic effects of the steroids mentioned above especially applies to the rapid time frame of the onset of the calcium signal occurring within seconds or a few minutes, to the dependence on extracellular calcium, to the inactivity of specific antagonists for the classical intracellular receptors and to the fact that coupling of the active steroid with albumin does not block its rapid action. These observations unequivocally represent the major landmark features of non-genomic steroid action and point to the involvement of a cell surface membrane receptor. For most of those effects described above, corresponding membrane binding sites that could transmit them as receptors, at least theoretically, have been detected by conventional binding assays (8). However, by this alone, a clear, causative relationship between receptor and effector is hard to obtain; filling the gap between the membrane binding site and the rapid effects by the analysis of the type and pharmacological features of second messengers involved appears to be a suitable means for establishing this relationship. Fairly complete pictures of receptor–second messenger–effector cascades may be given for a few example steroids, e.g. for aldosterone, which acts through IP3 and DAG, PLC, PKC, pH and calcium and probably tyrosine kinases, or for vitamin D_3, which is various cells appears to involve similar second messengers (for a review, see Ref. 9). However, the demonstration of such signalling cascades might not be enough to fully understand rapid steroid action; the story remains incomplete until the first member of the supposed family of membrane steroid receptors has been cloned and thus

is available for structural analysis and functional expression. So far, this has not been achieved with regard to any of the binding sites described above. In the author's laboratory a high-affinity membrane binding site for progesterone is being cloned at present (unpub. results). It is hoped that this is a steroid membrane receptor and might serve as a template for the cloning of the other members of the family within the near future.

The clinical dimension of non-genomic steroid effects is widely undetermined yet. There have been reports on human male infertility that might be related to a defective non-genomic progesterone action on spermatozoa (10). The rare condition of pseudohypoaldosteronism has been shown not to depend on a defective classical intracellular mineralocorticoid receptor, but rather on an abnormal non-genomic aldosterone response (11), and, recently, on mutations of the sodium channel (12). Those findings by Audy et al. may open new clinical strategies for fighting prostate cancer as a more detailed picture on steroid action evolves, whereby non-genomic and genomic actions of these hormones might be targeted differentially by antiproliferative therapy.

Modern molecular biology techniques will definitely shed more light on these complex actions of steroids, enabling us to fully utilize this enhanced knowledge for physiological understanding and clinical interventions.

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