Corticosteroid receptor antagonists: a current perspective

• Win Sutanto and E. Ronald de Kloet

Introduction
Corticosteroids, secreted by the adrenal cortex, are crucial for the functioning and homeostasis of bodily functions, both in the periphery and in the central nervous system (CNS). Thus aldosterone (Fig. 1) and deoxycorticosterone, the main mineralocorticoids, control sodium homeostasis while corticosterone (Fig. 1) and/or cortisol, the predominant glucocorticoids, depending upon the species, regulate stress-activated and circadian-driven neural metabolism and circuitry, i.e. they terminate the stress response and control the subsequent adaptive behaviour of the animal [1]. In the CNS, corticosteroid actions are mediated by two distinct intracellular (i.e. cytoplasmic or cytosolic) receptors currently referred to as the mineralocorticoid and glucocorticoid receptors. Mineralocorticoid receptors are also present in the kidney and they are physico-chemically identical to those in the hippocampus, the brain site most richly endowed with mineralocorticoid receptors. The kidney mineralocorticoid receptors, unlike those of the hippocampus, are aldosterone selective due to the presence of the metabolizing enzyme, 11β-hydroxysteroid dehydrogenase [2-3].

Mineralocorticoid and glucocorticoid receptors mediate biological responses to adrenal corticosteroids and synthetic ligands. The properties of mineralocorticoid and glucocorticoid receptors, and their role(s) in centrally and peripherally regulated functions have been the subject of several recent reviews [1-4]. With the knowledge that the interaction of corticosteroids with each receptor type is responsible for the differential action of the steroid, the search for corticosteroid analogues which bind specifically and with high affinity to either mineralocorticoid receptors or glucocorticoid receptors has been actively going on in the past decades. In spite of extensive research (e.g. in the search for 'pure' antiglucocorticoids, and likewise for antimineralocorticoids, hundreds of compounds have been synthesized and tested), a 'pure' antisteroid does not yet exist. In other words, a steroid may be specific for one receptor type and yet it still shows affinity for other receptor system(s) to a greater or lesser extent, resulting in multi-hormonal activities in the same molecule. In these cases, the clinical uses of these steroids become limited, especially for long-term therapy.

The aim of this overview is to highlight selected standard and novel ligands which bind to mineralocorticoid receptors or glucocorticoid receptors and/or show antimineralocorticoid or antiglucocorticoid activity. The pharmacological profiles of some of these compounds and the clinical implications these compounds may have, will also be discussed.

Mechanism of action of steroid hormone
It is generally accepted that, in accordance with the two-step theory of mechanism of steroid action, corticosterone and cortisol (as well as steroids such as progesterone) and their cognate synthetic antag-
onists (and agonists) enter the cell by passive diffusion (Fig. 2). They bind to their specific receptors with relatively high affinity. A given ligand may bind to one or more receptors (e.g. progesterone binds to mineralocorticoid, glucocorticoid and progesterone receptors), and a given receptor may interact with one or more ligands with equal or similar affinity (e.g. mineralocorticoid receptors in the brain bind corticosterone/cortisol, aldosterone, progesterone and an array of synthetic analogues with equal affinity [4 5]).

Anatomically, as depicted in Figure 2, a steroid receptor consists of a ligand-binding domain, which varies among receptors since it accommodates different hormones, a DNA-binding domain, which is highly conserved within most receptors and most species, and an N-terminal domain, which includes domains for transcriptional activation of target genes by the hormone–receptor complex (transcriptional activation function).

Following steroid–receptor interaction, the next crucial stage in the mechanism of action is the transformation (sometimes referred to as activation) of the receptor protein complex. The subsequent chain of events involves nuclear translocation and localization, binding to the hormone response elements, changes in chromatin structure and finally, activation (or inhibition) of the transcription of target genes, via interaction with transcription and transcription intermediary factors [9 10].

Pivotal in the steroid–receptor interaction is the involvement of two receptor-associated proteins (Fig. 2), namely, the heat shock protein (hsp 90, about 1% of the total protein in the cell) and the less abundant P59 (heat shock protein-binding immunophilin). The 90 kDa proteins belong to a class of highly conserved proteins which are crucial for cell viability. Hsp 90 associates with various cellular proteins such as steroid hormone receptors (i.e. with the ligand-binding domain of mineralocorticoid, glucocorticoid, progesterone, oestrogen and androgen receptors) and possibly maintains these proteins in a non-functional state. Association of receptors with hsp 90 results in the inability of these receptors to bind to the hormone response elements of their target genes, and thus transcription cannot be initiated. Steroid receptors, in the absence of hormone, form hetero-oligomeric complexes containing an hsp dimer and these are dissociated by hormone, allowing them to acquire DNA-binding capacity and transcriptional activity according to the correspond-

\[\text{Corticosterone}\]

\[\text{Aldosterone}\]

\[\text{Figure 1}\]

Steroid structures: corticosterone and aldosterone

Definition of an antisteroid and a steroid receptor ligand

The characteristic responses of steroid hormones require their binding to specific receptor proteins in target tissues. The pharmacological, or physiological, response(s) thus triggered (or induced) depends very much upon the interaction of the steroid–receptor complex with the nuclear chromatin. The precise details of such an interaction and the role played by the steroid in the process, which have been a puzzle for many years, are beginning to be unravelled with the advent of advanced and much more refined techniques in molecular and cellular endocrinology.

Definition of a mineralocorticoid receptor ligand and an antimineralocorticoid

By definition, mineralocorticoid receptor ligands are those compounds that bind specifically to mineralocorticoid receptors. In reality, not all of these compounds are classified as mineralocorticoids or antimineralocorticoids. Fulfilment of certain criteria makes a ligand a mineralocorticoid receptor binder. From X-ray crystallography studies, we now know that structural details within a steroid molecule will influence receptor affinity, activation, translocation, nuclear interaction and the resultant physiological response. The high-affinity binding to mineralocorticoid receptors appears to be correlated to a complementary fit between amino acid sequences on the receptor (or binding site) and a flat 4-ene-3-one A ring of the steroid [16].

Theoretically, aldosterone antagonists will bind to receptor site(s) normally occupied by aldosterone. Antagonists, however, may exert their effects by interfering with the synthesis or metabolism of a specific steroid, or any proteins essential to the expression of the physiological response of that particular steroid. Most binding data are obtained from in vitro studies; however, efficacy in vitro does not