



ACTH Antagonists

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Adrenocorticotropin (ACTH) acts via a highly selective receptor that is a member of the melanocortin receptor subfamily of type 1 G protein-coupled receptors. The ACTH receptor, also known as the melanocortin 2 receptor (MC2R), is unusual in that it is absolutely dependent on a small accessory protein, melanocortin receptor accessory protein (MRAP) for cell surface expression and function. ACTH is the only known naturally occurring agonist for this receptor. This lack of redundancy and high degree of ligand specificity suggests that antagonism of this receptor could provide a useful therapeutic aid and a potential investigational tool. Clinical situations in which this could be useful include (1) Cushing's disease and ectopic ACTH syndrome – especially while preparing for definitive treatment of a causative tumor, or in refractory cases, or (2) congenital adrenal hyperplasia – as an adjunct to glucocorticoid replacement. A case for antagonism in other clinical situations in which there is ACTH excess can also be made. In this article, we will explore the scientific and clinical case for an ACTH antagonist, and will review the evidence for existing and recently described peptides and modified peptides in this role.

Keywords: adrenocorticotropin hormone, receptor antagonism, Cushing's syndrome, congenital adrenal hyperplasia, high throughput screening, G protein-coupled receptor, receptor modelling, peptide hormone antagonists

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INTRODUCTION

The impact of receptor antagonism on modern medicine cannot be understated. Classical examples include the β -blockers in the treatment of hypertension and cardiovascular disease (1) and histamine H2 antagonism in the treatment of gastric hyperacidity (2). Even in the field of endocrinology, receptor antagonism of steroid hormones [e.g., tamoxifen (3), eplerenone (4), and flutamide (5)] and some peptide hormones [e.g., pegvisomant (6) and conivaptan (7)] has had major life-changing impact. The pituitary–adrenal axis is one endocrine axis that when disrupted can be associated with a wide range of pathologies, and yet, despite the fact that it comprises several unique and thus highly targetable components, receptor antagonism has received little attention as a therapeutic approach.

In this article, we will examine the possible benefits of development of an effective antagonist to a key component of this axis, the peptide hormone adrenocorticotropin (ACTH). The disorders in which clinical benefit might be attained will be considered. We will then consider the nature of the target – ACTH and the ACTH receptor complex, and certain unique features before discussing the history of ACTH antagonist research, ending with a description of the current state-of-the-art. Initially, a brief description of the pituitary–adrenal axis and its key components is necessary.

THE PITUITARY–ADRENAL AXIS

The corticotroph cells of the anterior pituitary gland are responsible for synthesis and secretion of the 39 residue peptide, ACTH (8). ACTH is derived from a larger precursor protein, pro-opiomelanocortin (POMC), by the action of a specific pro-hormone convertase enzyme (PC1 or PCSK1) (9). In other tissues – for example, the hypothalamus – this precursor is processed differently to produce α -MSH instead of ACTH (10). ACTH is synthesized and secreted by the pituitary in response to tonic control from the hypothalamus – principally in the form of two peptide hormones – corticotrophin-releasing hormone (CRH) and vasopressin (AVP), which in turn are regulated by multiple higher factors including stress (11).

Adrenocorticotropin has a short half-life in the circulation (12) and acts on a highly specific G protein-coupled receptor expressed almost uniquely in the adrenal cortex (13). This receptor, the MC2R is one of five members of the melanocortin receptor family – see **Table 1**. ACTH can activate all five of these receptors, although at physiological circulating levels, the sensitivity of the other receptors is such that they are not activated. Importantly, the naturally occurring agonists for these other receptors – α -MSH, γ -MSH, and possibly β -MSH – have no affinity for the MC2R (14, 15). Thus the MC2R is a highly sensitive and highly specific receptor for ACTH with a major, essential function of stimulating the fasciculata cells of the adrenal cortex to synthesize and secrete glucocorticoid. In addition, ACTH can stimulate zona glomerulosa cells to secrete mineralocorticoid and zona reticularis cells to secrete adrenal androgens.

Glucocorticoid (cortisol in man and most other species, corticosterone in rodents), secreted by the adrenal gland exert a plethora of physiological actions on virtually every cell in the organism. These actions are the result of interaction with the widely expressed glucocorticoid receptor – a nuclear hormone receptor. Glucocorticoid may also activate a second related receptor – the mineralocorticoid receptor – which is less widely expressed. However, the action of the 11 β -hydroxysteroid dehydrogenase type 2 enzyme inactivates glucocorticoid in mineralocorticoid receptor expressing tissues under normal circumstances leaving these receptors responsive to aldosterone (16). From an endocrine perspective, a key role of glucocorticoid is to feedback negatively on the pituitary and hypothalamus to inhibit ACTH secretion (17).

From this brief description, it can be seen that in theory, the MC2R should provide a perfect substrate for receptor targeting. This is a receptor with, effectively, a single function, expressed

in a highly tissue-restricted way and activated by a single, highly specific agonist. The question is – if it were possible to design the perfect antagonist – what clinical role might it play?

DISORDERS OF THE PITUITARY–ADRENAL AXIS

Disorders of this axis are, fortunately, uncommon and can be subdivided into disorders of hormone deficiency and excess. Glucocorticoid deficiency seems unlikely to benefit from MC2R antagonism, but in certain specific circumstances, there could be a valuable role for this therapeutic option as discussed later.

Glucocorticoid Excess

Glucocorticoid excess may result from primary adrenal disease – typically an adrenal adenoma or carcinoma – and is independent of ACTH. Indeed ACTH is normally suppressed by the actions of the negative feedback loop. More often, cortisol excess or Cushing's syndrome is the result of a pituitary adenoma secreting excess ACTH – known as Cushing's Disease – or less commonly a non-pituitary tumor that "ectopically" secretes ACTH. This group of disorders might theoretically provide a suitable target for an MC2R antagonist.

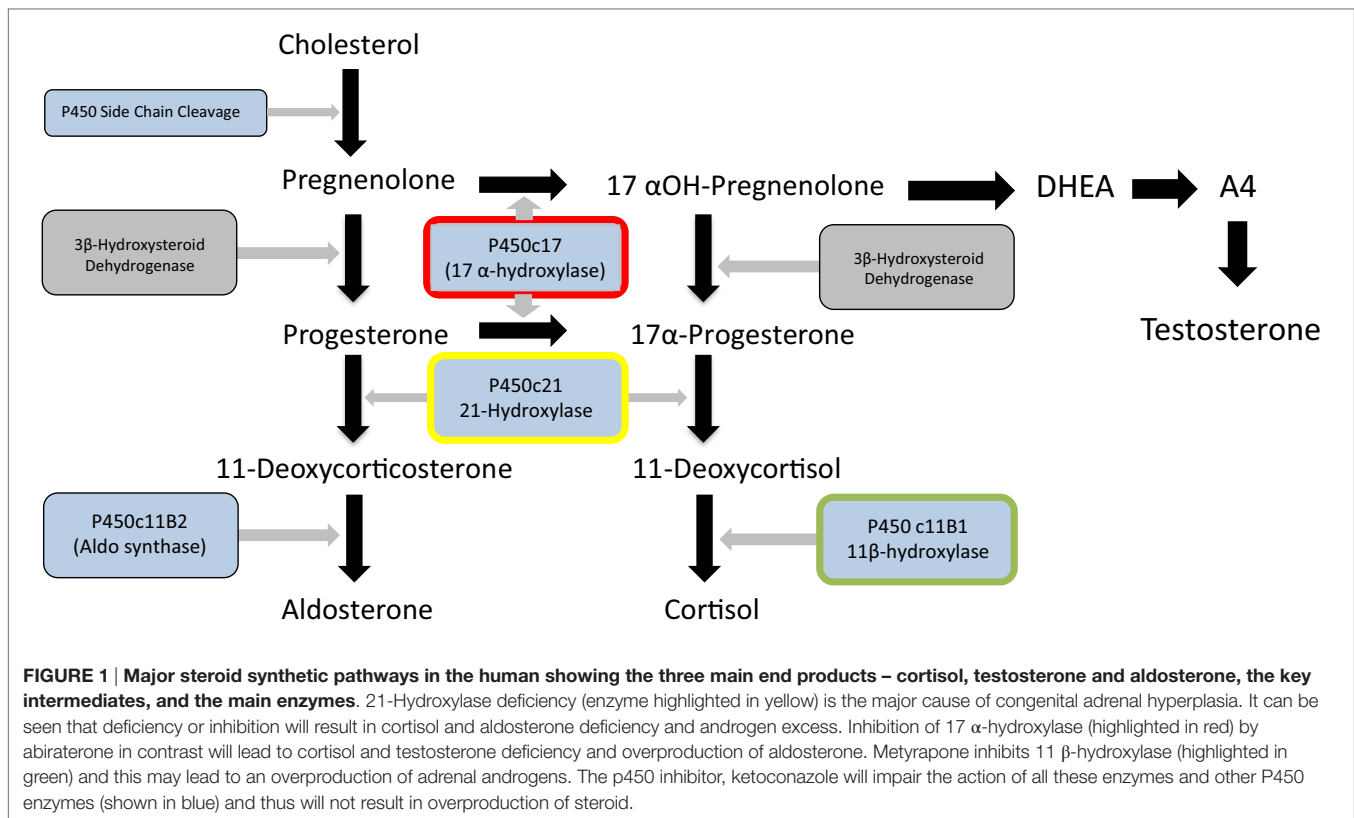
Cushing's Disease

Corticotroph adenomas are small, usually slow growing, benign tumors that normally come to clinical attention as a result of the effects of glucocorticoid excess, rather than because of the physical effects of an expanding tumor. Typically, Cushing's syndrome may take many years to develop. Consequently the diagnosis of the disorder and exclusion of other causes of Cushing's syndrome is a significant challenge. Once a diagnosis is conclusively made, the optimal treatment is surgical removal of the tumor – ideally preserving the remaining pituitary function. Surgery for Cushing's disease requires extensive experience and skill and is normally undertaken in specialist centers (18).

In some patients, the metabolic consequences of their untreated glucocorticoid excess are so significant that there would be risks in immediately proceeding to complex or prolonged surgery. The glucocorticoid synthesis blockers metyrapone and/or ketoconazole are frequently used in this situation to reduce steroid production (see **Figure 1**), and most patients tolerate and respond to this treatment reasonably well (19–21). However, an MC2R antagonist could be equally effective in this situation.

TABLE 1 | A summary of the main features of each of the melanocortin receptors in the human.

	Major sites of expression	Ligand preference	Function	Effect of deletion	Comments
MC1R	Melanocytes	α -MSH > ACTH > γ -MSH	Pigmentation of hair and skin	Red hair, pale skin	Agouti antagonizes
MC2R	Adrenal cortex	ACTH	Steroidogenesis adrenal growth	Adrenal failure	Absolute dependency on MRAP
MC3R	Brain, spinal cord	γ -MSH > α -MSH = ACTH	Complex, inhibits POMC neurones	Obesity	
MC4R	Brain, spinal cord	α -MSH > ACTH > γ -MSH	Appetite regulation	Obesity	Enhanced action with MRAP2 AGRP is natural antagonist
MC5R	Multiple tissues	α -MSH > ACTH > γ -MSH	Exocrine gland function	Defective water repulsion	



Following surgery, the glucocorticoid excess will come under rapid control in a minority of patients. More frequently, there will be a reduction in steroid over-secretion that may tail off over several weeks. In other cases, it may be necessary to re-explore the pituitary surgically, and this may result in pituitary clearance with a loss of other pituitary hormones (18). Control of glucocorticoid excess during this interim period will often necessitate the use of metyrapone and/or ketoconazole.

If further surgical measures are unsuccessful, endocrinologists may turn to the somatostatin receptor 5 agonist, pasireotide, which directly targets the corticotroph adenoma and provides partial or complete control of Cushing's in a proportion of cases (22). Other second-line options in this situation include pituitary radiotherapy or adrenalectomy. The former may take several years to normalize the glucocorticoid excess, necessitating metyrapone and/or ketoconazole during this time. An MC2R antagonist could be a possible alternative.

While glucocorticoid synthesis inhibitors are usually effective and reasonably well tolerated in these situations, there are some potential disadvantages to their prolonged use. Metyrapone blocks the 11β-hydroxylase enzyme, required for the last step of cortisol synthesis from 11-deoxycortisol. Consequently, as shown in **Figure 1**, steroid precursors are channeled through the androgen pathways resulting in increased secretion of adrenal androgens. In women, this may induce hirsutism and in pre-pubertal children both virilization and early puberty (23, 24). Ketoconazole, a cytochrome P450 inhibitor, inhibits several

steps of steroidogenesis and does not usually cause androgen excess. However, complications include potential rare but serious hepatotoxicity and multiple drug interactions. Consequently, although these treatments are effective and inexpensive, there could be a place for a highly specific MC2R antagonist in the management of Cushing's disease.

Ectopic ACTH Syndrome

The mechanisms of ectopic ACTH syndrome are essentially the same as those of Cushing's disease except that the underlying tumor is outside the pituitary gland. These rare tumors are often small carcinoid tumors that may occur anywhere in the lungs and gastrointestinal tract. Improvements in imaging over the last 10–20 years together with intravenous sampling for ACTH have made identification of the primary source far simpler. Once identified, and if surgical removal of the underlying tumor is possible, then this can be curative. As with Cushing's disease, it may be helpful to use a cortisol synthesis blocking drug while waiting for definitive treatment (18) and in cases where definitive treatment is not possible. Hence, for the same reasons described above, an MC2R antagonist may have a place in the clinical management of such conditions.

Small cell lung cancer makes up about 20% of all lung cancer and is a highly malignant neuroendocrine tumor of poor prognosis. This tumor is frequently associated with ectopic ACTH secretion, and the development of Cushing's syndrome in this disease may obviously worsen prognosis. Thus there may also be value in using an ACTH antagonist in this clinical situation.

Glucocorticoid Deficiency

The second group of disorders in which there may be a place for antagonizing ACTH action are those in which the physiological negative feedback of cortisol is reduced or lost, leading to a compensatory increase in ACTH secretion. In this situation, it is the stimulation of non-glucocorticoid adrenal steroidogenesis by ACTH, which requires control.

Congenital Adrenal Hyperplasia

The most prominent example of such a situation is that of congenital adrenal hyperplasia, caused in the majority of cases by mutations in both alleles of the *CYP21* gene encoding the 21-hydroxylase enzyme necessary for the penultimate step of cortisol synthesis (**Figure 1**) (25, 26). This is one of the commonest human autosomal recessive disorders occurring in about 1 in 15,000 live births. Reduced glucocorticoid feedback results in ACTH stimulation of adrenal androgen production. As a consequence, affected female children are likely to be virilized or have ambiguous genitalia at presentation. Life-long treatment with glucocorticoids will restore any cortisol deficiency and suppress ACTH secretion and subsequent androgen production (27). However, achieving the optimal dose and timings of hydrocortisone replacement to avoid the adverse effects of excessive glucocorticoid on growth and metabolism while maintaining adequate androgen suppression is challenging, resulting in poor health outcomes (28). Availability of an easily administered ACTH antagonist would be likely to facilitate treatment, allowing a “block and replace” approach in which the physician could focus on treatment of glucocorticoid replacement alone rather than androgen suppression.

Prostate Cancer Treatment

The use of the drug Abiratarone in the treatment of prostate cancer induces a form of acquired adrenal hyperplasia. Abiratarone is a potent inhibitor of the 17 α -hydroxylase and 17,20 lyase enzymes in the adrenal and is used to very effectively reduce the production of adrenal androgens in castration-resistant prostate cancer, with valuable benefits to prostate cancer treatment (29). Examination of adrenal steroid synthetic pathways (**Figure 1**) demonstrates that this inhibition is likely to channel steroid synthesis toward deoxycorticosterone synthesis and aldosterone production, leading to mineralocorticoid excess and glucocorticoid deficiency. The latter requires glucocorticoid replacement, but the fluid overload, hypertension, and hypokalemia resulting from aldosterone excess require treatment with a mineralocorticoid antagonist such as eplerenone (30). Use of an ACTH antagonist together with a replacement dose of hydrocortisone may be a preferred approach in this situation.

Investigation of Endocrine Disease

A further potential use of an ACTH antagonist is in the investigation of adrenal disorders. One of the key questions in the investigation of Cushing's syndrome is whether the cortisol excess is ACTH dependent. A number of tests have been used to determine this including the dexamethasone suppression test and the CRH stimulation test, combined with measurements of plasma ACTH and imaging studies. Hypoglycemic stress tests and metyrapone tests may also be required in complex cases (31). It is conceivable

that the use of a single dose ACTH antagonist test could provide a simple and clear solution to this question, although it is more likely that its use in combination with other investigations would be required in most cases.

THE TARGET

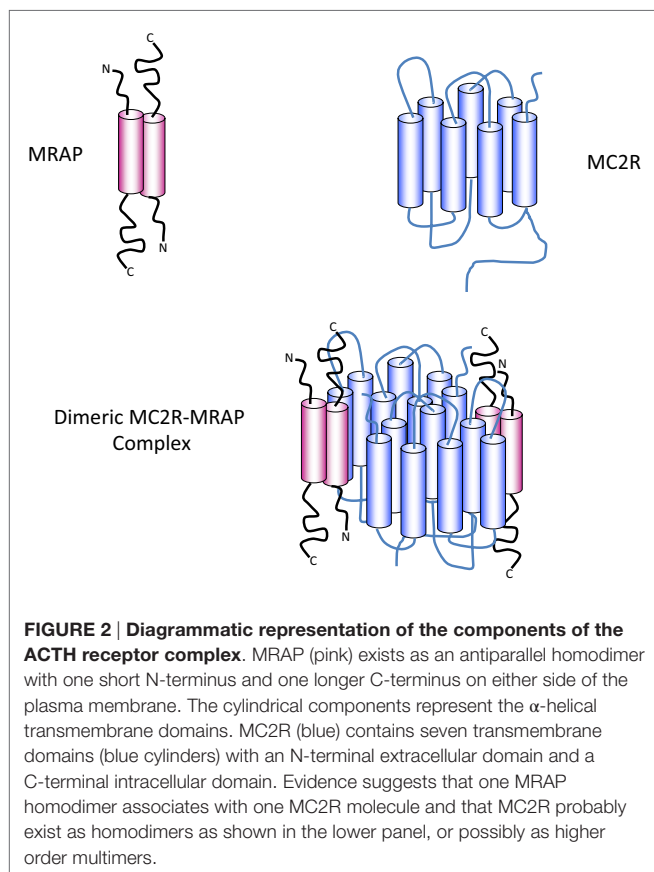
As discussed in the Section “Introduction,” the receptor for ACTH presents a remarkably attractive target for pharmacological manipulation. It is highly specific for a single peptide agonist – ACTH [1–39], and has no affinity or response to any other naturally occurring agonist. It is expressed in functional quantities only in the adrenal cortex, and thus the possibility of unwanted off-target effects of an antagonist is unlikely.

The key component of the ACTH receptor complex is the seven transmembrane domain MC2R – perhaps surprisingly, the smallest of all the G protein-coupled receptor (GPCR) family at only 289 residues in length (32). The MC2R cannot function alone as an ACTH receptor, which led to many difficulties in its characterization after initial cloning (33). The discovery that deficiency of a small, single transmembrane domain protein caused a clinical syndrome essentially identical to that caused by MC2R deficiency led to the identification of the melanocortin 2 receptor accessory protein (MRAP) as the MC2R co-receptor (34, 35).

Melanocortin receptor accessory protein is a highly unusual protein in that it naturally exists as an antiparallel homodimer and seems to be necessary for trafficking and cell surface expression of the MC2R, as well as binding of ACTH and hence signal transduction (36, 37). In common, with many other GPCRs, MC2R has the potential to homodimerise and the evidence suggests that it exists as a homodimer with two MRAP molecules, in an antiparallel homodimer formation, associated with each MC2R component (38) (**Figure 2**).

The nature of the ligand, ACTH is important in understanding receptor function (**Figure 3A**). The strongly conserved N-terminal 24 residues of ACTH are almost as efficient as the 39 residue naturally occurring peptide in activating this receptor. Further truncation of ACTH from the C-terminus is associated with gradual loss of activity until removal of the four basic residues (Lys–Lys–Arg–Arg) in positions 15–18, which inactivates this peptide at the ACTH receptor (39, 40). The first 13 residues are however active at all the other melanocortin receptors and thus it seems that this “tetrabasic” region acts as a “key” to unlock the MC2R–MRAP complex.

The evidence suggests that once the receptor is “unlocked,” the N-terminal region is an effective agonist for the receptor. As with all the melanocortin receptors, the His–Phe–Arg–Trp sequence (or HFRW sequence using the single letter amino acid code) at positions 6–9 and to some extent those residues flanking this induce the conformational changes required to activate the receptor. This HFRW sequence is fundamental to activation of all the melanocortin receptors and can be considered the “message” region of the peptide (40, 43, 44). Interestingly, a naturally occurring human mutation of Arg 8 in the HFRW sequence results in biologically inactive ACTH (45). The most N-terminal region (Ser–Tyr–Ser) has been reported to potentiate the action of the HFRW sequence (46).



Great strides have been made in recent years in understanding the three dimensional nature of GPCRs, based around a growing number of receptor crystal structures. No melanocortin receptor crystal structure has yet been reported, but increasingly sophisticated modeling exercises combined with receptor mutagenesis and substitution studies are providing information on how ligands interact with their receptor.

Pogozheva et al. studied the MC4R-binding site for NDP-MSH (a highly potent analog of α -MSH) and two small molecule agonists using a combination of alanine scanning mutagenesis of the receptor followed by functional analysis and *in silico* modeling. They concluded that the HFRW sequence of NDP-MSH was required to form a β -hairpin-like structure so that the phenyl ring of Phe 7 interacts with the indole ring of Trp 9 (**Figure 3B**). This allows interaction between His 6 of NDP-MSH and Glu 100 in transmembrane domain 2 (TM2) of MC4R, and Arg 8 of NDP-MSH and Asp 115 and 119 in TM3 of MC4R. The interacting aromatic residues of this sequence, Phe 7 and Trp 9 interact with the aromatic Phe at positions 261 and His 264 of MC4R in TM6 (41).

A relatively similar picture of NDP-MSH binding to the MC5R was constructed by Yang and colleagues using site-directed mutagenesis and structural modeling. They also suggested that Asp 115 and 119 in TMD 3 interact with Arg 8 of the HFRW sequence and that Phe 195 (in TMD 5) and Phe 254 (TMD 6) interact with Phe 7 and Trp 9 of HFRW. All of these residues are conserved in the MC2R (and other melanocortin

receptors), and it seems highly likely that these interactions are critical in determining the HFRW binding and activation of this receptor (42). Indeed, naturally occurring homozygous mutations of Asp 103 and 107 in MC2R, the equivalent conserved Asp residues in this receptor, lead to ACTH resistance/Familial Glucocorticoid Deficiency (47). This arrangement is shown in **Figure 3C**.

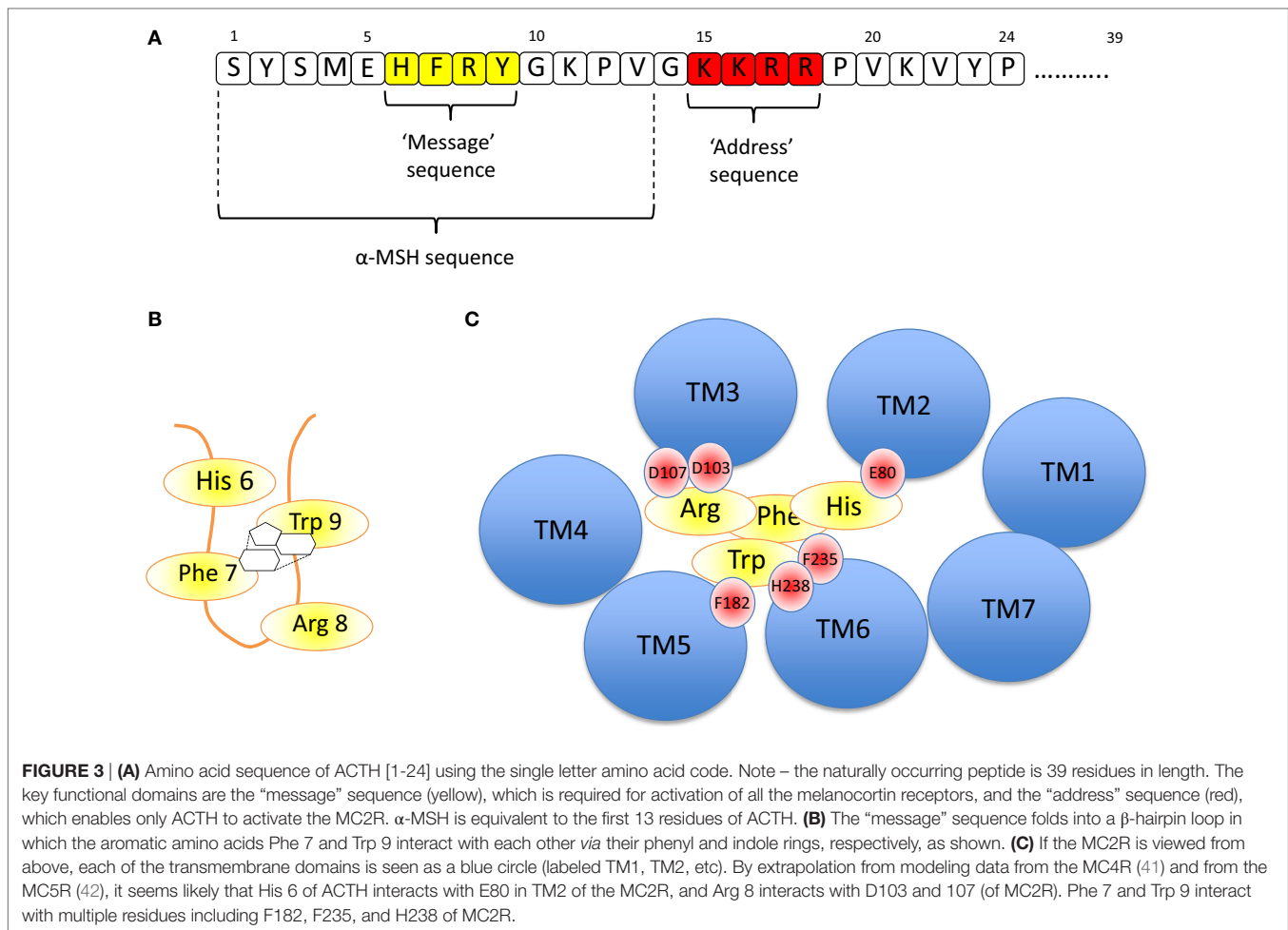
Using a receptor chimera approach in which regions of the MC4R were substituted into the MC2R, Fridmanis et al. suggested that one of the MRAP molecules binds to MC2R in the region of transmembrane domains 4 and 5 to create a binding pocket for the tetrabasic “address” sequence in ACTH. Following this interaction, a conformational shift in the receptor transmembrane domains takes place, which permits the formation of the HFRW-binding pocket (14). Although this remains speculative, it is an attractive hypothesis. It is notable that Malik et al. have shown that it is the N-terminal region of the MRAP molecule that is required on the extracellular surface of the cell for ACTH binding (48). Clearly complete understanding of this complex area will ultimately require determination of a crystal structure of the MC2R–MRAP–ACTH complex.

APPROACHES TO ANTAGONIZING ACTH

Given the extensive knowledge of the interaction of ACTH with its receptor gained over about 50 years one might anticipate that it would be a relatively straightforward matter to design an ACTH-like peptide with antagonist properties. The first attempts to do this resulted in peptides that retained the tetrabasic address region, but lacked the HFRW message sequence. This led to the development of ACTH [11–24] (49, 50) as a potential receptor antagonist. Li et al. isolated a naturally occurring peptide, ACTH [8–39], from human pituitary, which they showed to have ACTH antagonistic effects *in vitro*, and they called this corticotrophin-inhibiting peptide (CIP) (51). However, the data with each of these potential antagonists has been confusing with discrepant results for steroidogenesis and cAMP generation in some cases. For example, Szalay demonstrated that ACTH [11–24] stimulated steroidogenesis in dispersed zona glomerulosa and zona fasciculata cells (52), and Goverde and Smals (53) demonstrated some steroidogenesis with this peptide.

More recently, Kovalitskaia et al. investigated the binding of a wide range of ACTH fragments derived from an ACTH [11–24] parent peptide. They reported that the ACTH [15–18] tetrabasic fragment alone was an effective competitor for ACTH [11–24] in ligand-binding assays, and that it also failed to stimulate cAMP generation in adrenocortical membranes (54). Its use in competition with ACTH in cAMP generation or steroidogenesis has not been reported.

The consensus from most researchers seems to be that ACTH [11–24] is not an effective ACTH antagonist. This may be because the interaction between the tetrabasic region of ACTH converts the MC2R into a “primed receptor with an unoccupied HFRW-binding site, which may then be activated by the natural agonist.” Hoffman therefore used a different approach and developed an analog in which the Trp residue at position 9 of the HFRW message sequence was substituted with Phe or *N*-methyl Trp,



and showed inhibition of ACTH stimulated cAMP generation on bovine adrenal membranes (55).

Liang et al. has described a number of peptide analogs of ACTH based on alanine and histidine substitutions around the HFRW region and in the spacing between this and the tetrabasic region (56). In this work, they described the marked reduction in MC2R activation observed with some of these peptides and, in a US patent filed the preceding year, they reported potent ACTH antagonism with an ACTH [15–24] decapeptide (57).

In all of the above studies, the actions on adrenal tissues, slices, cells, or membranes have been studied, but little or no data on the selectivity of these peptide antagonists for the MC2R, or even melanocortin receptors in general have been obtained. It is usually highly desirable that any receptor active drug used therapeutically is selective for its target receptor and lacks off-target effects. The functions of the other melanocortin receptors and the effects of antagonizing or deleting them are summarized in **Table 1**, and it can be seen that a non-selective agent could induce a number of unwanted effects.

Bouw and colleagues reported an approach in which ACTH peptides that retain the intact tetrabasic region were substituted at various positions in the HFRW sequence and in some cases were cyclized in order to enhance stability. HEK293 cells stably expressing human MC2R and MRAP were used, and cAMP

production was measured with a luminescence assay. Several peptides exhibited significant antagonist actions among which GPS1573 – a variant of ACTH [7–18] with an N-terminal nor leucine – proline sequence and D-Phe and DD-Trp (in place of the L-Phe and L-Trp) in the HFRW sequence, and a cyclized variant of this – GPS1574 were most potent (IC₅₀s of 66 ± 23 nM and 260 ± 1 nM, respectively). These peptides retain some antagonist effect on the MC3R, MC4R and MC5R at approximately an order of magnitude less than that on the MC2R (58).

In work published in this issue, Nensey et al. report the actions of these same analogs on rat adrenal cells and show inhibitory effects in which the dose responses to ACTH [1–39] were shifted to the right by one log order or more. They also conducted *in vivo* experiments in young rats but were unable to show inhibition of the ACTH response even at 400-fold molar excess of antagonist in the case of GPS1573. GPS1574 was partially inhibitory at 30 min after ACTH injection (59).

In a recent study, presented in abstract form, researchers from Ipsen Bioscience Inc. reported the development of an ACTH-related peptide, IRC-274. This peptide was shown to inhibit ACTH binding to the human MC2R and MRAP expressed in HEK 293 cells with an IC₅₀ of 3 nM (60). cAMP generation in response to ACTH in this same model is inhibited with an IC₅₀ of 38 nM. Using an *in vivo* hypophysectomized rat model in which ACTH is

infused by osmotic minipump, significant inhibition of corticosterone production was observed. Using a second model in which mouse AtT20 pituitary corticotroph tumor cells were implanted into athymic nude mice, inhibition of corticosterone was again observed until the implanted tumors outgrew the inhibitory action of IRC-274. Interestingly, this antagonist exhibits a high degree of selectivity for the MC2R and has no significant actions on other melanocortin receptors. The sequence and structure of this peptide have not been revealed.

ALTERNATIVE APPROACHES

Small Molecules

From the above, it seems that after a rather long and chequered history some progress is now being made in developing a peptide ACTH antagonist that might ultimately be developed for use *in vivo*. The problems associated with peptide-based medication are well-known and include a short half-life in the circulation, the need to administer them by injection and the risk of inducing immunogenicity. In certain circumstances, the benefits of a peptide outweigh these potential disadvantages, and advances are being made in deriving preparations of peptides that may be taken orally or intranasally. However in many cases, there will be a need for a reliable long-term therapy as discussed earlier. Under these circumstances, it would be desirable to have an orally active agent, which would most likely be a small (non-peptide) molecule. Substantial efforts have been made to develop small molecules as agonists of the MC4 receptor with some limited success (61). With this objective in mind, we have undertaken a high throughput screen of about 200,000 small molecules using a cell-line expressing the human MC2R and MRAP, and this may provide a promising approach if a molecule with sufficient potency and selectivity can be identified.

Antibody-Based Approaches

Humanized monoclonal antibodies directed against key signaling molecules have proven to provide effective therapeutic solutions in inflammatory diseases and cancer. This approach has been used to target ACTH and the pituitary–adrenal axis by a number of investigators and one pharmaceutical company aims to begin human studies in the near future (62). While such antibodies may not necessarily provide a long-term therapeutic solution, they seem likely to have potential in shorter-term therapeutic situations, such as around the time of pituitary surgery for Cushing's disease.

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Corticostatins

Solomon and colleagues identified a novel lung and neutrophil peptide belonging to the defensin class of highly cationic antimicrobial peptides. They showed this peptide exhibited a number of functions including inhibition of ACTH binding and corticosterone secretion and named this corticostatin (63). It is also known as defensin α -4. These functions appear to be relatively non-specific, and little work has been published on this in recent years. We are not aware that this action of corticostatin has been explored for therapeutic purposes.

SUMMARY

We have reviewed the case for the development of an ACTH antagonist for therapeutic purposes. The conditions in which there is a potential clinical indication are relatively uncommon, and alternative therapies are well described in each case. However as a refinement to existing therapies or for the treatment of particularly difficult or complex cases, there would be a real clinical benefit. We have not considered a number of more common conditions, such as depressive illness or septic shock in which there might ultimately be a role for an ACTH antagonist, although these have been considered elsewhere (64).

The evidence suggests that progress is being made on more than one front in developing an antagonist. This has been delayed for many years by the absence of “clean” systems in which to test candidate peptides and compounds, owing to the problems in expressing the MC2R. This should no longer be a problem as a result of the identification of MRAP that enables cell surface expression of the MC2R. As a result there does seem to be a growing interest in this area and the next decade may witness exciting developments.

AUTHOR CONTRIBUTIONS

This work is part of the result of a 5-year project. Over this time, all authors have contributed information, ideas, and data to the work. The manuscript was primarily written by AC, with comment and editing from the other authors.

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