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A REVIEW ON THERAPEUTIC UTILITY OF CRF1 RECEPTOR

GAHTORI A[*1], SATI A[2], SAINI K[2], PRABHAKAR M[3], SINGH V[1] AND BANSAL V[2]

1: Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Patel Nagar Dehradun, Uttarakhand, India

2: Department of Pharmacology, School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Patel Nagar Dehradun, Uttarakhand, India

3: Department of Pharmacy Practice, School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Patel Nagar Dehradun, Uttarakhand, India

***Corresponding Author: Ms. Milan Prabhakar: E Mail: milan.prabhakar112@gmail.com**

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ABSTRACT

The G protein-coupled receptor CRF1 plays a crucial part in the stress reaction and is mainly expressed in the brain. "Corticotropin-releasing factor" (CRF), which the brain secretes in reaction to stress, activates the receptor. When CRF binds to the CRF1 receptor, it causes the pituitary gland to produce adrenocorticotropic hormone (ACTH), which then causes the adrenal glands to generate stress hormones like cortisol. The CRF1 receptor regulates behaviours associated with depression, anxiety, and addiction in addition to stress reaction. Depression, anxiety, and post-traumatic stress disorder are just a few of the mental and stress-related conditions the brain experiences when the CRF1 receptor isn't functioning properly (PTSD). The CRF1 receptor has been thoroughly investigated for possible therapeutic uses in the therapy of stress-related illnesses as a potential pharmacological target. The impacts of CRF1 receptor antagonists (CRAs) are detected by anxiolytics and/or antidepressants in a number of animal stress models, and their possible therapeutic value in the management of "depression, anxiety, and other stress-related diseases is assessed". By inhibiting pituitary and possibly brain CRF1 receptors, CRAs lessen the HPA axis activation brought on by stresses, which may lessen the sickness brought on by prolonged stress. For the therapy of melancholy, anxiety, and PTSD, several CRF1 receptor antagonists have been created and are presently

undergoing clinical studies. The effectiveness of these substances is still being researched, though. This overview emphasises the CRF1 receptor's therapeutic value, which is an area of active study and holds great potential for the creation of innovative therapies for disorders linked to stress.

Keyword: Corticotrophin releasing factor type 1 (CRF-1), ACTH, Depression, Anxiety

INTRODUCTION-

Therapeutic Utility of CRF1 Receptor Antagonists in Anxiety

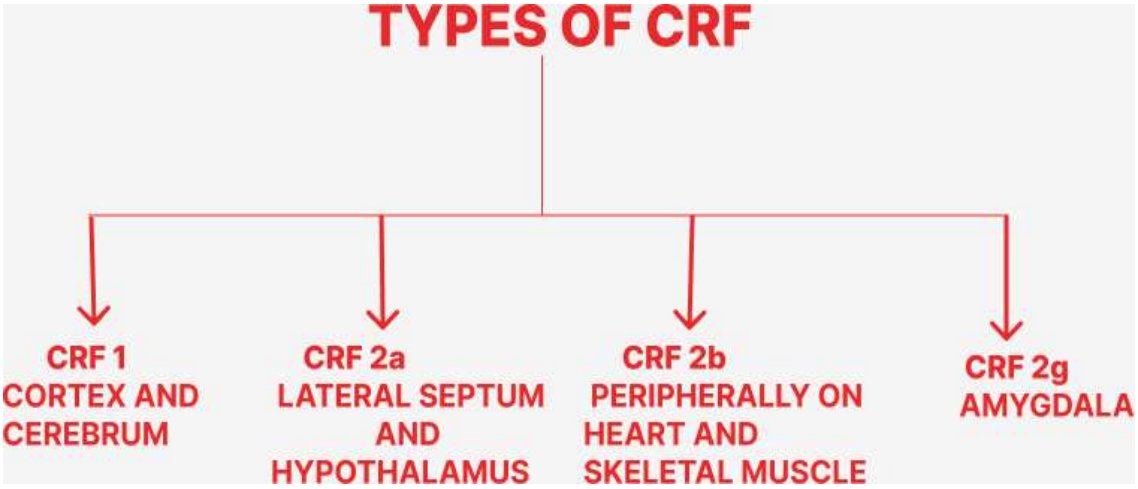
Corticotropin-releasing hormone, also known as corticotropin-releasing factor (CRF), synchronises the behavioral, endocrine, autonomic, and immunological responses to stress by regulating the hypothalamic-pituitary-adrenal axis **[1]**. A particular class of receptor antagonist known as a corticotropin-releasing hormone antagonist (CRH antagonist) inhibits **[2]**. As a result, among other things, CRH antagonists stop the cortisol and ACTH releases that stress causes. There is still a serious need for new pharmacological therapies for stress-related disorders including depression, anxiety, and others **[3]**. There are several unmet medical needs related to these illnesses. The disruption or dysfunction of a person's stress response system can lead to changed mood or emotional states and decreased typical stress coping systems, which may be a common factor in many disorders **[4]**. The 41 amino acid peptide corticotropin releasing factor (CRF) is essential for modulating the hypothalamic-pituitary-adrenal (HPA) axis response to stress. Innovative pharmacological approaches that target the CRF1 receptor are being researched for the treatment of anxiety **[5, 6]**.

In coordinating the behavioural, endocrine, autonomic, and immunological responses to anxiety and stress, corticotropin-releasing hormone (CRH), CRH-related peptides, and CRH receptors play key roles **[7]**. The corresponding peptides are implicated in the pathogenesis of several illnesses marked by dysregulated anxiety responses due to the extensive influence of the CRH system on physiological processes in both the brain and the periphery **[3]**. There is now a lot of research being done on the possible applications of CRH antagonists. Experimentally, the involvement of CRH-related peptides in disease processes, including anxiety and depression, sleep disorders, addictive behaviour, inflammatory disorders, acute and chronic neurodegeneration, and premature labour, has been clarified using selective antagonists **[3, 8]**.

The hypothalamic component regulating the hypothalamic-pituitary-adrenal (HPA) axis in response to anxiety has been named corticotropin-releasing hormone (CRH) **[9]**. Pituitary adrenocorticotropic hormone

(ACTH) is secreted when CRH is activated, which results in the synthesis of adrenal glucocorticoids **[10]**. Additionally, this 41-amino acid (aa) peptide functions as a neuromodulator, influencing multiple brain regions in the central nervous system (CNS) **[11, 12]**. The crucial functions CRH plays in coordinating the behavioural, endocrine, autonomic, and immunological responses to anxiety are now well known **[13]**.

CRH receptor subtypes –[14, 15]



The choroid plexus and cerebral arterioles of the brain express CRF-2b, however it is primarily expressed peripherally on the heart and skeletal muscle **[16]**. Numerous studies have demonstrated that the development of anxiety disorders and depression is influenced by the overactivity of the brain's CRF-CRF1 signalling system **[17]**. It has been suggested that CRH receptor antagonist therapy may be helpful for people who suffer from clinical illnesses such major depression and post-traumatic stress disorder that are causally associated to HPA hyperactivity **[18]**. Anti-CRH agents are thought to to reduce the rise in CRH caused by stress and inhibit the subsequent releases of ACTH and cortisol that happen after CRH activation **[19, 20]**. CRH receptor antagonists that can pass the blood-brain barrier are gaining more clinical attention for the treatment of depression, anxiety, and other disorders linked to HPA hyperactivity, such as the management of irritable bowel syndrome, which is aggravated by stress **[1, 2]**.

Corticotropin-releasing factor type 1 (CRF-1) antagonist

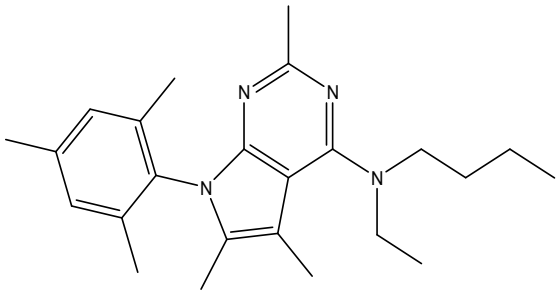
The corticotropin-releasing factor type 1 (CRF-1) antagonist is a class of drugs that block the activity of the CRF-1 receptor. The CRF-1 antagonist has been studied as a potential therapeutic target for a variety of neuropsychiatric disorders, such as anxiety, depression, and addiction. Research

indicates that CRF-1 is primarily involved in the neuroendocrine stress response **[22]**. CRF-1 receptors are located in the hypothalamus, amygdala, and other regions of the brain. In response to stress, CRF-1 is released, leading to hormone secretion from the hypothalamus-pituitary-adrenal (HPA) axis **[23]**. Chronic stress and over-activation of the HPA axis have been linked to several neuropsychiatric disorders, including addiction and depression **[24]**. By blocking CRF-1 activity, CRF-1 antagonists can potentially reduce stress-induced HPA axis activation and alleviate symptoms of related disorders. However, further studies are required to determine the long-term effectiveness and safety of these drugs in humans **[25, 26]**.

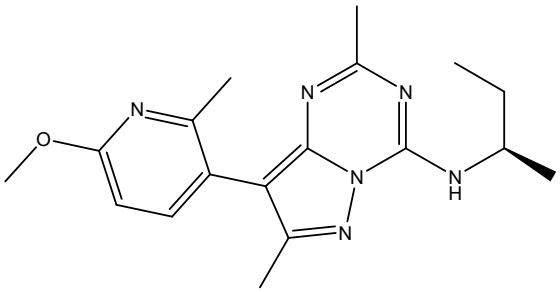
CRH receptor antagonists research in anxiety

Clinical research uses of peptide-based synthetic CRH receptor antagonists appear improbable at this time due to their inability to cross the blood-brain barrier, but non-peptidic selective CRH-R1 receptor antagonists have been studied and synthesised with varying degrees of effectiveness **[27]**. With just slight variations, the bulk of these antagonists have a common pharmacophore that is constant throughout most study tests **[28]**. Due to its increased significance in HPA hyperactivity, the majority of research into clinical CRF antagonists has concentrated on antagonists selective for the CRF-1 subtype, which is expressed in the brain and cerebrum **[29]**. The selective CRF-1 antagonist antalarmin and the more recent medication pexacerfont are two of the most well-known antagonists for this receptor that have been created and are frequently utilised in research. Pexacerfont did not significantly improve upon a placebo in a recent human experiment, which was disappointing **[30]**, in treating the symptoms of generalised anxiety disorder. However, more research is still required. Antalarmin has been shown to reduce the stress-induced CRF surge in CSF, decrease anxiety-related behaviours, and increase exploratory activity in monkeys; however, human trials are required to fully understand the clinical usefulness of antalarmin **[13]**. LWH-234, CP-154,526, NBI-27914, and R-121,919 are additional ligands for the CRF-1 receptor antagonist that are employed in studies. In both male and female patients who had experienced a major depressive episode, a small human clinical trial found that 30 days of treatment with the CRF1 antagonist R-121,919 was helpful in decreasing depression and anxiety scores, without any unfavourable side effects **[29, 31]**. There is a growing interest in studies looking at the treatment of anxiety disorders by combining the use of SSRIs and CRF-1 and CRF-2 antagonists **[30]**.

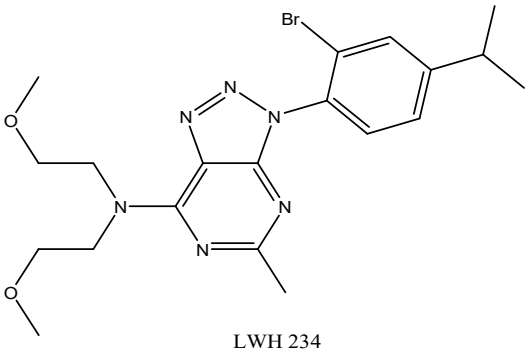
Chemical Structures of CRF-1 receptor antagonist with therapeutic utility in Depression and Anxiety



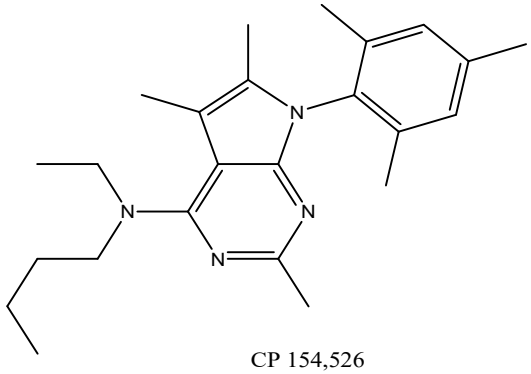
Antalarmin



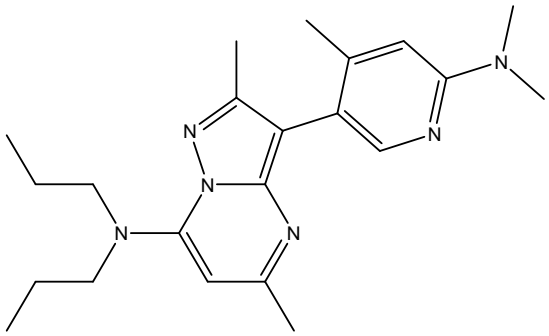
Pexacerfont



LWH 234



CP 154,526



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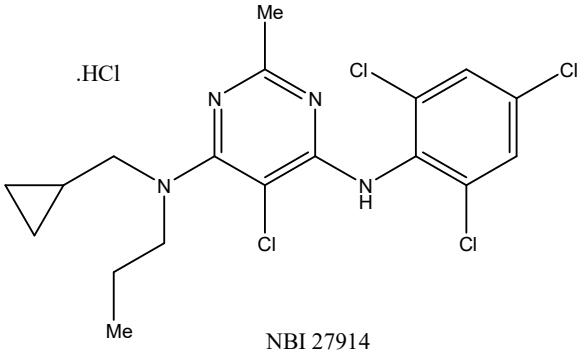

NBI 27914

Pexacerfont -

Bristol-Myers Squibb developed Pexacerfont **[32]** a CRF1 antagonist originally known as BMS-562,086. Long-term stress is one of the situations that causes the production of an endogenous peptide hormone known as corticotropin-releasing factor (CRF), also known as corticotropin-releasing hormone **[33]**. This causes the production of corticotropin (ACTH), another hormone linked to the body's response to stress **[34, 35]**. Chronic release of CRF and ACTH is thought to contribute directly or indirectly to many of the harmful physiological effects of chronic stress, such as excessive glucocorticoid

release, diabetes mellitus, osteoporosis, stomach ulcers, anxiety, and depression, as well as the emergence of high blood pressure and subsequent cardiovascular problems **[28, 36]**.

Pexacerfont, a newly developed CRF-1 antagonist, was undergoing clinical studies for the treatment of According to a clinical investigation with the identifier NCT00481325 titled "Study of Pexacerfont (BMS-562086) in the Treatment of Outpatients With Generalized Anxiety Disorder," it may also be beneficial for treating anxiety disorders **[37, 38]**. In a recent multicenter, randomised, double-blind, placebo-controlled study, pexacerfont (100 mg/day) did not outperform placebo on the primary end measure. (the mean change from baseline to end point in the Hamilton Anxiety Scale score) **[30, 39]**. These results suggest that CRF1 receptor blockade may not be an effective therapy for anxiety disorders in some human populations **[3, 40]**.

Alcohol Dependence: A Randomized Controlled Experimental Medicine Study with the CRH1 Antagonist Pexacerfont

Alcoholism (AD) is characterised by cycles of binge drinking followed by intervals of abstinence, resulting in long-lasting neuroadaptations that eventually encourage drug use. Relapse is a crucial part of this disease's progression, and it is commonly brought on by stress or drug-related triggers **[41, 42]**. As a result, one of the main objectives of AD drugs is to prevent relapse brought on by these stressors. Reintroducing drug seeking after extinction has been used to represent relapse in experimental animals **[43, 44]**.

Studies have indicated that the FDA-approved alcoholism drug naltrexone, an opioid antagonist, prevents cue-induced relapse but not stress-induced relapse **[45]**. Selective serotonin reuptake inhibitors or the alpha-1 adrenergic antagonist prazosin may have therapeutic benefits for some stress-related alcoholism sufferers, such as those with posttraumatic stress disorder (PTSD) **[46]**. However, there are presently no authorised alcoholic drugs that reliably prevent stress-induced relapse **[13]**.

Such drugs may increase response rates in alcoholism treatment, either through methods that customise care for individual characteristics,or through synergistic effects with already available treatments **[47]**.

Preclinical research has discovered a number of pathways that may shield against stress related relapse in alcoholism **[13, 48]**. Of these, it is generally believed that antagonists of the corticotropin-releasing hormone (CRH) 1 receptor show great potential. Specifically, expanded CRH1 receptors in the history of AD results in an upregulation of the amygdala. [47]

Antalarmin

A drug called antalarmin blocks CRF-1. Corticotropin releasing factor (CRF), also known as corticotropin releasing hormone, is an endogenous peptide hormone that is released in response to a range of situations, including chronic stress and drug addiction **[49]**. This causes the release of corticotropin (ACTH), another hormone linked to the body's response to stress **[50]**. It is believed that the chronic release of CRF and ACTH is what causes many of the harmful physiological effects of chronic stress, such as excessive glucocorticoid release, stomach ulcers, anxiety, and depression, as well as the development of high blood pressure and subsequent cardiovascular problems **[4, 26]**. A non-peptide drug called antalarmin works by inhibiting the CRF-1 receptor, which reduces the amount of ACTH released in response to protracted stress **[51, 52]**.

This has been demonstrated to reduce behavioural responses to stressful situations in animals and it is hypothesised that antalarmin itself, or more likely newer CRF antagonist drugs still in development, may be helpful for reducing the negative health effects of chronic stress in humans in addition to having potential applications in the treatment of conditions like anxiety, depression, and drug addiction **[24, 53]**.

The efficiency of standard antidepressant drugs has not yet been matched by any of the CRF antagonists studied, despite some promising early findings **[54]**. But when antalarmin and an SSRI antidepressant were combined, the results were more encouraging, suggesting a chance for a synergistic impact. Antalarmin as a prospective therapy has also yielded good findings for anxiety **[55]**, stress-related hypertension and anxiety itself **[13, 56]**.

Chronic antalarmin use showed anti-inflammatory properties as well, and it has been suggested that it may help manage inflammatory diseases like arthritis **[57]**, stress induced gastrointestinal ulcers and irritable bowel syndrome among others **[58]**.

Antalarmin and other CRF-1 antagonists have shown promise in the treatment of drug addiction issues, including varying degrees of opiate use a significant decrease in ethanol self-administration in ethanol-dependent rodents **[53]**, a decrease in ethanol self-administration in humans **[55]**. Antalarmin did reduce dose escalation with continued use in studies on cocaine dependent rats, indicating that it might stabilise cocaine usage and prevent it from growing over time, though not reliably decrease it **[59]**. The usage of cocaine was only slightly reduced in studies on cocaine-dependent monkeys, and these reductions were not statistically significant **[60, 29]**.

Drugs & Combinations	Drug Action	Uses	References
Pexacerfont	CRF 1 Antagonist	In treatment of Out Patient with Generalised Anxiety Disorder	Coric *et al*, [30], Handbook of stress, vol. 2 [61]
Antalarmin	Block CRF 1	For rendering negative health effects of chronic Stress in human also in anxiety and drug addition	Webster *et al*, Zoumakis *et al* [51], [28]
Antalarmin + SSRI	Synergistic Impact	Stress related and anxiety disorder	Habib *et al*, Zorilla *et al*[13], [62]
Antalarmin + CRF 1 Antagonist	Synergistic Impact	Decrease ethanol administration	Giguere V *et al* , Vaughan *et al*[63], [64]

Evidence for hyperactivation of CRF1 pathways in anxiety-

AUTHORS	FINDINGS
Nemeroff CB *et al* and Report of Targets & 2007 [65],[66]	Increased drive of the pituitary limb of the HPA axis via the CRF1 receptor.
Report of significance of Psychoneuroendocrinology [67]	Dexamethasone decrease the reduction of HPA axis activity indicate MDD patient have lessened feedback mechanism.
Hatzinger *et al* [68]	Intravenous injection of CRF-1 receptor reduced stimulant of ACTH.
C.B. Nemeroff *et al*[69]	MDD is characterised by hyperactivated brain CRF with two circuit set- depressed. patient have increased level of CRF in CSF.
Research Report of New Vistas in Neuropsychiatry[70]	CRF 1 down regulate in post-morteum suicide victim.
Merali *et al* [71]	By repeatedly activating CRF1 receptors in the brain, chronically elevated CRF production may desensitise them.
C.B. Nemeroff *et al* [72]	Greater CRF staining in dorsal raphe 5HT cells and NE cells of the locus coeruleus. According to results from post-mortem studies on the brains of suicidal people who were despondent.
Meraki *et al* [73]	Administration of the 2-adrenergic antagonist yohimbine increases NE activity, and administration of a "5HT-depleting" diet decreases 5HT activity, both of which result in decreased 5HT activity and elevated CRF levels in the CSF in humans. This is a "classic reuptake inhibitor antidepressant" that has been shown to target the pathway of CRF.
Belanoff *et al*, Schatberg *et al* [74], [75]	CRF-1 pathway is hyperactivated in the population of melancholy individuals.Patients with depression who also experience psychotic symptoms have significantly enhanced HPA axis activity and raised plasma cortisol levels.
P.W. Gold *et al*[76], [77]	High amounts of CSF,CRF, and NE as well as indications of HPA axis dysregulation have all been connected to severe melancholic sadness.
Heim *et al*, Report of Psychiatry & 2004 [78]),[79]	Adult depressives who have had trauma in their early years are also known to have significant HPA axis dysfunction
Bradley *et al* [80]	Depression has been related to CRF1 gene variations.CRA is beneficial for specific subpopulations of depressed people who show the most CRF1 pathway dysfunction and/or who may have a specific genetic makeup and a history of exposure to stressors.
Kasckow *et al*, C. Nemeroff *et al* , Report of Targets and 2007, Report of Targets & 2006 [81] , [82] , [66], [83]	There is more evidence for the hyperactivation of the CRF1 pathway in anxiety disorders, and this evidence varies according to the subtype. not working adequately.Two further indications of PTSD are HPA axis (low circulating cortisol but increased stress-induced release, for illustration).
Kasckow *et al*, Reul *et al*[81][84] , [83]	NE levels are high in PTSD, and it has been demonstrated that pharmacological stimulation with yohimbine causes PTSD symptoms, HPA axis activation, and increases in CRF and NE in the CSF.
Rivier *et al* [85]	"G-protein-coupled receptors" with two different subtypes, CRH1 and CRH2, (GPGR). Both receptors are variably expressed in the brain and bind not only CRH but also stresscopin-related peptide (also known as UCN II), urocortin I (UCN I), and stresscopin. (UCN III). UCN II and III have a limited affinity for CRH1 receptors and primarily link to CRH2 receptors, whereas UCN I binds to both CRH1 and CRH2 receptors equally.
Heinrichs *et al*[86]	Anxiety, sleeplessness, reduced hunger, decreased erotic desire, psychomotor agitation, and other stress-related symptoms are all explained by CRH. These findings were reached after studying either rats whose behaviour was changed by CRH injection or mice whose brains were overexpressed with CRH.
G. W. Smith *et al*, Timpl *et al*[87], [88]	Antisense sensors reduced stress-induced anxiety-like behaviour in addition to CRH. Concerns about the selectivity of effects from central peptide injections or antisense probes, which confirmed the

	critical role of CRH1 receptors, led to the genetic engineering of rodents mutants with the CRH1 receptor deleted.
Muller *et al*[89]	**A functional CRH1 receptor reduction that was limited to the limbic system was created in a mouse mutant in which CRH1 receptors were selectively eliminated.**
Muller *et al* [90]	**This finding was significant because inappropriate regulation of stress hormones must be taken into account as a possible confounder in mutants with nonfunctional CRH1 receptors in the peripheral, particularly the pituitary, because these hormones can result in abnormal behaviour.**
Research & 1999 report Research& 1999[91]	**In addition to confirming that CRH1 receptors in the brain are responsible for anxiety-like behavior, this mouse model supported the hypothesis that inhibiting CRH1 receptor activity may offer a novel hypothesis-driven pharmacological strategy for treating stress-related disorders like depression and anxiety.**
Reul & Holsboer *et al* [84]	**Despite the extraction and determination of corticotrophin releasing hormone (CRH) from the ovine hypothalamus, the name of the hypothalamic releasing factor responsible for regulating pituitary adrenocorticotropin hormone (ACTH) secretion has remained a riddle.**
G. W. Smith *et al*[87]	**Axonal endings in the external zone of the median eminence, which are produced by parvocellular neurons of the hypothalamic paraventricular nucleus, release the CRH peptide into the pituitary portal circulation.**
G. W. Smith *et al*, Wynn *et al* [92] , [93]	**Research is being done on CRH, a neuropeptide that not only regulates the synthesis of ACTH but also mimics the effects of stress on behaviour and the stimulation of the autonomic nervous system in the brain.**
Aguilera *et al*, Giguere *et al*, Report of stimulation of CAMP [94]) , ([63]	**Early research conducted after the discovery of CRH demonstrated that the adenylyl cyclase/cAMP signalling pathway's plasma membrane receptor is the method by which CRH performs its effects.**
P. C. Wynn *et al* [95]	**Rat pituitary membranes were used for binding assays with radioiodinated Tyr-o-CRH to identify specific CRH receptors.**
De Souza *et al*, Rivier *et al*, Schilling *et al*, P. Wynn. *et al*[96],[85] , ([97] , [93]	**The topographic distribution of CRH receptors in the pituitary and other tissues in several species, as well as their complete characterization as CRH binding characteristics, were disclosed by radioligand binding to membranes, autoradiographic techniques, and cytochemical approaches. Through later studies utilising radioligand binding to membranes, autoradiographic methods, and cytochemical techniques, the complete characterization of CRH binding characteristics and the topographic distribution of CRH receptors in the pituitary and other tissues in several species were accomplished.**
G. Smith *et al*, P. Wynn *et al* [92] , [93]	**The molecular structure of human and rat receptors in the pituitary, brain, and other organs has been clarified as a result of the cloning of the human pituitary CRH receptor.**
Eckart *et al*, Perrin & Vale *et al*[98], [99]	**The full characterization of CRH binding properties and the topographic distribution of CRH receptors in the pituitary and other organs in different species were made possible by subsequent study using radioligand binding to membranes, autoradiography, and cytochemical techniques.**
Report of neuroendocrinology & 1994[100]	**Controlling the number of CRHR1 receptors in the cell membrane may significantly affect how CRH-responsive cells are, as has been demonstrated for other systems. The amount of CRH receptors in the pituitary varies greatly with changes in HPA axis activity.**
Eckart al, Nikodemova *et al*, Perrin and Vale *et al* [98],[101], [99]	**Since the original characterization of CRH binding two decades ago, our knowledge of the mechanisms that regulate CRH receptors has greatly increased.Recent studies have demonstrated that receptor synthesis, post-translational processing, and targeting to the membrane, as well as the rate of receptor desensitisation and internalisation following interaction with the ligand, all have an impact on the amount of biologically active CRHR1 on the cell membrane, as reflected in CRH binding and signalling responses. The altered activity of the hypothalamic-pituitary-adrenal (HPA) axis and changes in CRHR1 in the pituitary are examined in this paper. The spread of CRH receptor classes in different tissues is also briefly discussed.**

CONCLUSION -

By modifying behavioral, autonomic, and endocrine reactions, the hypothalamic peptide corticotropin-releasing hormone (CRH) and its receptors play a crucial part in stress adaptation. Through antagonistic CRF1 receptors, CNS diseases that may be caused by incorrect CRF hyperactivation can be treated. CRF1 networks play a significant role in the stress response system, which is essential for an organism's existence. The development of CRF1 antagonists for the pharmacotherapy of pathological anxiety is supported by the pathophysiologically significant brain CRF hyperactivation in anxiety disorders and the

extensive preclinical evidence demonstrating an anxiolytic-like effect of decreasing CRF1 receptor neurotransmission. It is hopeful that selective CRF1 antagonists will be less likely to trigger CRF1 receptor-mediated negative effects than competitive CRF peptide analogues in unstressed circumstances in rodent models of activity, anxiety, behavioural arousal, energy balance, and abuse risk.

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