INTRODUCTION

Historically, the first approach to the concept of autopharmacology began with British physiologist and pharmacologist Henry Dale in the 1910s, discovered the role of acetylcholine in synaptic transmission, and later proved by Austrian physiologist Otto Loewi, to be the neurotransmitter involved in the proximal synapses of the autonomic nervous system (initially named Vagusstoff by Loewi, and later identified as acetylcholine). The same happened to another autonomic neurotransmitter, noradrenaline (Akzeleransstoff by Loewi), which later proved to be chemically similar to a long used pharmacological agent, adrenaline, a hormone secreted by the adrenal glands. Both scientists were awarded the 1936 Nobel Prize for Physiology or Medicine for their pioneering and important contributions [1].

Endogenous substances that could fall under the concept of autopharmacology are:
- Endorphins
- Dynorphin
- Bradykinin
- Prostaglandins
- Angiotensin
- Secretin
- Gastrin
- Cholecystokinin
- Histamine
- Cannabinoids
- Substance P

The main scientific criterion for an autopharmacological agent is the discovery of specific membrane receptors for it and, hopefully, its transduction and cell signaling mechanisms.

ENDOPHRIN

Endorphins (endogenous morphine) are endogenous opioid peptides that function as neurotransmitters. They are produced by the pituitary gland and the hypothalamus in vertebrates during exercise, excitement, pain, consumption of spicy food, love and orgasm, and they resemble the opiates in their abilities to produce analgesia and a feeling of well-being.

The term implies a pharmacological activity
(analogous to the activity of the corticosteroid category of biochemicals) as opposed to a specific chemical formulation. It consists of two parts: endo- and -orphin; these are short forms of the words endogenous and morphine, intended to mean a morphine-like substance originating from within the body.

The term endorphin rush has been adopted in popular speech to refer to feelings of exhilaration brought on by pain, danger, or other forms of stress, supposedly due to the influence of endorphins. When a nerve impulse reaches the spinal cord, endorphins that prevent nerve cells from releasing more pain signals are released. Immediately after injury, endorphins allow animals to feel a sense of power and control over themselves that allows them to persist with activity for an extended time [2].

History

Opioid neuropeptides were first discovered in 1974 by two independent groups of investigators: John Hughes and Hans Kosterlitz of Scotland isolated — from the brain of a pig — what some called enkephalins (from the Greek εγκέφαλος, cerebrum).

Around the same time, in the calf brain, Rabi Simantov and Solomon H. Snyder of the United States found what Eric Simon (who independently discovered opioid receptors in the brain) later termed endorphin by an abbreviation of endogenous morphine, meaning morphine produced naturally in the body. Importantly, recent studies have demonstrated that diverse animal and human tissues are in fact capable of producing morphine itself, which is not a peptide.

Mechanism of action

β-Endorphin is released into blood from the pituitary gland and into the spinal cord and brain from hypothalamic neurons. The β-endorphin that is released into the blood cannot enter the brain in large quantities because of the blood–brain barrier, so the physiological importance of the β-endorphin that can be measured in the blood is far from clear. β-Endorphin is a cleavage product of pro-opiomelanocortin (POMC), which is also the precursor hormone for adrenocorticotrophic hormone (ACTH). The behavioural effects of β-endorphin are exerted by its actions in the brain and spinal cord, and it is presumed that the hypothalamic neurons are the major source of β-endorphin at these sites. In situations where the level of ACTH is increased (e.g., Cushing’s syndrome), the level of endorphins also increases slightly [3].

β-Endorphin has the highest affinity for the μ1 opioid receptor, slightly lower affinity for the μ2 and δ opioid receptors, and low affinity for the κ1 opioid receptors. μ-Opioid receptors are the main receptor through which morphine acts. In the classical sense, μ opioid receptors are presynaptic, and inhibit neurotransmitter release; through this mechanism, they inhibit the release of the inhibitory neurotransmitter GABA, and disinhibit the dopamine pathways, causing more dopamine to be released. By hijacking this process, exogenous opioids cause inappropriate dopamine release, and lead to aberrant synaptic plasticity, which causes dependency. Opioid receptors have many other and more important roles in the brain and periphery however, modulating pain, cardiac, gastric and vascular function as well as possibly panic and satiation, and receptors are often found at postsynaptic locations as well as presynaptically.

Activity

Scientists sometimes debate whether specific activities release measurable levels of endorphins. Much of the current data comes from animal models which may not be relevant to humans. The studies that do involve humans often measure endorphin plasma levels, which do not necessarily correlate with levels in the central nervous system. Other studies use a blanket opioid antagonist (usually naloxone) to indirectly measure the release of endorphins by observing the changes that occur when any endorphin activity that might be present is blocked [4].

Runner's high

A publicized effect of endorphin production is the so-called runner's high, which is said to occur when strenuous exercise takes a person over a threshold that activates endorphin production. Endorphins are released during long, continuous workouts, when the level of intensity is between moderate and high, and breathing is difficult. This also corresponds with the time that muscles use up their stored glycogen. During a release of endorphins, the person may be exposed to bodily harm from strenuous bodily functions after going past his or her body's physical limit. This means that runners can keep running despite pain, continuously surpassing what they otherwise would consider to be their limit. Runner's high has also been known to create feelings of euphoria and happiness.

Runner's high has been suggested to have evolutionary roots based on the theory that it helped with the survival of early humans. Runner's high allows humans to run for vast lengths without pain. Most early humans hunted and gathered for their food. This required them to cover long distances hunting down their prey or foraging for their food. This could have caused them to develop conditions such as shin splints and stress fractures in their shin and feet bones. Without runner's high to negate the pain caused by running on bones with these conditions, early humans theoretically would not have been able to repeatedly cover these vast distances in search of their food and thus would have starved. Current African tribes make use of runner's high when conducting persistence hunting (a method in which tribesman hunt an animal and track it for miles, eventually killing the animal due to its vulnerability brought on by exhaustion) [5].
In 2008, researchers in Germany reported on the mechanisms that cause the runner's high. Using PET scans combined with recently available chemicals that reveal endorphins in the brain, they were able to compare runners' brains before and after a run.

It is also suggested by many that endorphins are some of the many chemicals that contribute to runner's high; other candidates include epinephrine, serotonin, and dopamine. Previous research on the role of endorphins in producing runner's high questioned the mechanisms at work, their data possibly demonstrated that the high comes from completing a challenge rather than as a result of exertion. Studies in the early 1980s cast doubt on the relationship between endorphins and the runner's high for several reasons: The first was that when an antagonist (pharmacological agent that blocks the action for the substance under study) was infused (e.g., naloxone) or ingested (naltrexone) the same changes in mood state occurred as when the person exercised with no blocker [6].

A study in 2003 by the Georgia Institute of Technology found that runner's high might be caused by the release of another naturally produced chemical, anandamide. The authors suggest that the body produces this chemical to deal with prolonged stress and pain from strenuous exercise, similar to the original theory involving endorphins. However, the release of anandamide was not reported with the cognitive effects of the runner's high; this suggests that anandamide release may not be significantly related to runner's high.

A study at the University of Arizona, published in April 2012, argues implicitly that endocannabinoids are, most likely, the causative agent in runner's high, while also arguing this to be a result of the evolutionary advantage endocannabinoids provide to endurance-based cursorial species. This largely refers to quadruped mammals, but also to biped hominids, such as humans. The study shows that both humans and dogs show significantly increased endocannabinoid signaling following high intensity running, but not low-intensity walking. The study does not, however, ever address the potential contribution of endorphins to runner's high. However, in other research that has focused on the blood–brain barrier, it has been shown that endorphin molecules are too large to pass freely, thus very unlikely to be the cause of the runner's high feeling of euphoria [7].

Depersonalization disorder

Endorphins are known to play a role in depersonalization disorder. The opioid antagonists naloxone and naltrexone have both been proven to be successful in treating depersonalization. To quote a 2001 naloxone study, In three of 14 patients, depersonalization symptoms disappeared entirely and seven patients showed a marked improvement. The therapeutic effect of naloxone provides evidence for the role of the endogenous opioid system in the pathogenesis of depersonalization.

Relaxation

In 2003, clinical researchers reported that profound relaxation in a float tank triggers the production of endorphins. This explains the pain relief experienced during float sessions.

Acupuncture

In 1999, clinical researchers reported that inserting acupuncture needles into specific body points triggers the production of endorphins. In another study, higher levels of endorphins were found in cerebrospinal fluid after patients underwent acupuncture. In addition, naloxone appeared to block acupuncture’s pain-relieving effects.

Pregnancy

A placental tissue of fetal origin — i.e., the syncytiotrophoblast — excretes beta-endorphins into the maternal blood system from the 3rd month of pregnancy. A recent study proposes an adaptive background for this phenomenon. The authors argue that fetuses make their mothers endorphin-dependent then manipulate them to increase nutrient allocation to the placenta. Their hypothesis predicts that: (1) anatomic position of endorphin production should mirror its presumed role in foetal-maternal conflict; (2) endorphin levels should co-vary positively with nutrient carrying capacity of maternal blood system; (3) postpartum psychological symptoms (such as postpartum blues, depression, and psychosis) in humans are side-effects of this mechanism that can be interpreted as endorphin-deprivation symptoms; (4) shortly after parturition, placentophagy could play an adaptive role in decreasing the negative side-effects of foetal manipulation; (5) later, breast-feeding-induced endorphin excretion of the maternal pituitary saves mother from further deprivation symptoms. These predictions appear to be supported by empirical data [8].

DYNORPHIN

Dynorphins are a class of opioid peptides that arise from the precursor protein prodynorphin. When prodynorphin is cleaved during processing by proprotein convertase 2 (PC2), multiple active peptides are released: dynorphin A, dynorphin B, and α/β-neo-endorphin. Depolarization of a neuron containing prodynorphin stimulates PC2 processing, which occurs within synaptic vesicle (biology) vesicles in the presynaptic terminal. Occasionally, prodynorphin is not fully processed, leading to the release of big dynorphin. This 32-amino acid molecule consists of both dynorphin A and dynorphin B. Dynorphin A, dynorphin B, and big dynorphin all contain a high proportion of basic amino acid residues, in particular lysine and arginine (29.4%, 23.1%, and 31.2% basic residues, respectively), as well as many hydrophobic residues (41.2%, 30.8%, and 34.4% hydrophobic residues, respectively). Although dynorphins are found widely distributed in the CNS, they have the highest concentrations...
in the hypothalamus, medulla, pons, midbrain, and spinal cord. Dynorphins are stored in large (80-120 nm diameter) dense-core vesicles that are considerably larger than vesicles storing neurotransmitters. These large dense-core vesicles differ from small synaptic vesicles in that a more intense and prolonged stimulus is needed to cause the large vesicles to release their contents into the synaptic cleft. Dense-core vesicle storage is characteristic of opioid peptides storage.

The first clues to the functionality of dynorphins came from Goldstein et al. in their work with opioid peptides. The group discovered an endogenous opioid peptide in the porcine pituitary that proved difficult to isolate. By sequencing the first 13 amino acids of the peptide, they created a synthetic version of the peptide with a similar potency to the natural peptide. Goldstein et al. applied the synthetic peptide to the guinea ileum longitudinal muscle and found it to be an extraordinarily potent opioid peptide. The peptide was called dynorphin (from the Greek dynamis=power) to describe its potency.

Dynorphins exert their effects primarily through the κ-opioid receptor (KOR), a G-protein-coupled receptor. Two subtypes of KORs have been identified: K1 and K2. Although KOR is the primary receptor for all dynorphins, the peptides do have some affinity for the μ-opioid receptor (MOR), δ-opioid receptor (DOR), N-methyl-D-aspartic acid (NMDA)-type glutamate receptor Different dynorphins show different receptor selectivities and potencies at receptors. Big dynorphin and dynorphin A have the same selectivity for human KOR, but dynorphin A is more selective for KOR over MOR and DOR than is big dynorphin. Big dynorphin is more potent at KORs than is dynorphin A. Both big dynorphin and dynorphin A are more potent and more selective than dynorphin B.

Production
Dynorphin is produced in many different parts of the brain, including the hypothalamus, the hippocampus and the spinal cord, and has many different physiological actions, depending upon its site of production. For example, dynorphin that is made in magnocellular vasopressin neurons of the supraoptic nucleus is important in the patterning of electrical activity. Dynorphin produced in magnocellular oxytocin neurons is a negative feedback inhibitor of oxytocin secretion. Dynorphin produced in the arcuate nucleus and in orexin neurons of the lateral hypothalamus affects the control of appetite [9].

Analgesia
Dynorphin has been shown to be a modulator of pain response. Han and Xie found that injecting dynorphin into the subarachnoid space of the rat spinal cord produced dose-dependent analgesia that was measured by tail-flick latency. Analgesia was partially eliminated by opioid antagonist naloxone.

Han and Xie found dynorphin to be 6-10 times more potent than morphine on a per mole basis. In addition, morphine tolerance did not reduce dynorphin-induced analgesia. Ren et al. demonstrated some of the complexities related to dynorphin induced analgesia. The authors found that combining subanalgic levels of morphine and dynorphin A1-13, a version of dynorphin A containing only the first 13 amino acids of the peptide, in the rat spinal cord had additive effects. However, when dynorphin A1-13 was injected into the intracerebroventricular (ICV) region of the brain, it had an antagonist effect on morphine-induced analgesia.

A study by Lai et al. found that dynorphin might actually stimulate pain. The group found that it acts on the bradykinin receptor as well as KOR. The N-terminal tyrosine of dynorphin A is necessary to activate opioid receptors such as KOR, but is unnecessary in binding to bradykinin receptors. Lai et al. studied the effects of dynorphin A2-13 that did not contain the N-terminal tyrosine. Based on the results of dynorphin A2-13, the authors proposed a mechanism in which dynorphin A activates bradykinin receptors and thus stimulates pain response. According to this mechanism, dynorphin activates bradykinin receptors, which triggers the release of calcium ions into the cell through voltage-sensitive channels in the cell membrane. Blocking bradykinin receptors in the lumbar region of the spinal cord reversed persistent pain. A multiple pathway system might help explain the conflicting effects of dynorphin in the CNS.

Svensson et al. provided another possible mechanism by which dynorphin might cause pain in the spinal cord. The authors found that administration of truncated dynorphin A2-17, which does not bind to opioid receptors, causes an increase in phosphorylated p38 mitogen-activated protein kinase (MAPK) in microglia in the dorsal horn of the spinal cord. Activated p38 has been previously linked to the NMDA-evoked prostaglandin release, which causes pain. Thus, dynorphin could also induce pain in the spinal cord through a non-opioid p38 pathway.

Other studies have identified a role for dynorphin and kappa opioid receptor stimulation in neuropathic pain. This same group also showed that the dynorphin-KOR system mediates astrocyte proliferation through the activation of p38 MAPK that was required for the effects of neuropathic pain on analgesic responses. Taken together, these reports suggest that dynorphin can elicit multiple effects on both Kappa opioid, and non-opioid pathways to modulate analgesic responses [10].

Addiction
Cocaine addiction results from complex molecular changes in the brain following multiple exposures to cocaine. Dynorphins have been shown to be an important part of this process. Although a single exposure to cocaine does not affect brain dynorphin levels, repeated exposures...
to the drug increases dynorphin concentrations in the striatum and substantia nigra in rats.

One proposed molecular mechanism for increased dynorphin levels involves transcriptional regulation by CREB (3', 5'-monophosphate response element binding protein). According to the model proposed by Carlezon et al., use of cocaine increases the expression of cAMP and cAMP-dependent protein kinase (PKA). PKA leads to the activation of CREB, which increases the expression of dynorphin in the nucleus accumbens and dorsal striatum, brain areas important in addiction. Dynorphin decreases dopamine release by binding to KORs on dopamine nerve terminals, which leads to drug tolerance and withdrawal symptoms.

**Cocaine**

Carlezon et al. performed several experiments to validate this model. They found that, when mice were injected with cocaine, they preferred to be in the place where they were injected (showed stronger place preference) significantly more than control mice (injected with saline) did. However, in mice overexpressing CREB under a constitutive promoter, place aversion was observed. This indicates that increasing CREB reverses the positive effects of cocaine. Northern blot analysis several days after CREB overexpression showed a marked increase in dynorphin mRNA in the nucleus accumbens.

Blocking KORs with an antagonist (norBNI) blocked the aversive effects caused by CREB overexpression. Thus, cocaine use ultimately appears to lead to an increase in the transcription of prodynorphin mRNA. Dynorphin inhibits dopamine release, which would counter the pleasurable effects of cocaine caused by the release of dopamine. There is also evidence suggesting that increased amounts of dynorphin can protect humans from cocaine addiction. According to research at Rockefeller University, the gene for dynorphin is present in two versions: a high output and a low output functional variation. The high output functional variation of the gene contains polymorphisms in the promoter regions that are speculated to cause it to produce more copies of dynorphin mRNA, which would give people carrying this variation a built-in defense system against drug addiction.

**Stress and depression**

Land et al. first described a mechanism of dysphoria in which corticotropin-releasing factor (CRF) provokes dynorphin release. While control mice displayed aversive behaviors in response to forced swim tests and foot shocks, mice lacking dynorphin did not show any such signs of aversion. They noted that injecting CRF led to aversive behaviors in mice with functional genes for dynorphin even in the absence of stress, but not in those with dynorphin gene deletions. Place aversion was eliminated when the receptor CRF2 was blocked with an antagonist.

Together these results led Land et al. to conclude that dysphoric elements of stress occur when CRF2 stimulates dynorphin release and activates KOR. The group further postulated that this pathway might be involved in drug seeking behavior. In support of this, it was shown previously that stress can reinstate cocaine-seeking behavior in mice through a CRF mechanism.

Dynorphin has also been shown to influence drug seeking behavior and is required for stress-induced, but not prime-induced, reinstatement of cocaine seeking. A downstream element of this pathway was later identified by Bruchas et al. The authors found that KOR activates p38, a member of the mitogen-activated protein kinase (MAPK) family, through phosphorylation. Activation of p38 is necessary to produce KOR-dependent behaviors. Because of its role in mediating dysphoria, dynorphin has also been investigated in relation to depression. Newton et al. studied the effects of CREB and dynorphin on learned helplessness (an animal model for depression) in mice. Overexpression of dominant negative CREB (mCREB) in transgenic mice had an antidepressant effect (in terms of behavior), whereas overexpressing wild-type CREB caused an increase in depression-like symptoms. As described previously, CREB increases transcription of prodynorphin, which gives rise to different dynorphin subtypes. Newton et al. supported this mechanism, as the mCREB was colocalized with decreased expression of prodynorphin. Also, direct antagonism of dynorphin caused antidepressant-like effects similar to those seen with mCREB expression. Thus, the CREB-dynorphin pathway regulates mood as well as cocaine rewards.

Shirayama et al. used several animal depression models in rats to describe the effects of dynorphins A and B in depression. The authors found that learned helplessness increases the levels of dynorphins A and B in the hippocampus and nucleus accumbens and that injecting KOR antagonist norBNI induces recovery from learned helplessness. Immobilization stress causes increases levels of both dynorphins A and B in the hippocampus and nucleus accumbens. Forced swim stress increases the levels of dynorphin A in the hippocampus. Shirayama et al. concluded that both dynorphins A and B were important in stress response. The authors proposed several mechanisms to account for the effects of the KOR antagonist norBNI on learned helplessness. First, increased dynorphin levels block the release of glutamate, a neurotransmitter involved in plasticity in the hippocampus, which would inhibit new learning.

Blocking dynorphin effects would allow glutamate to be released and restore functional plasticity in the hippocampus, reversing the phenomenon of learned helplessness. In addition, blocking dynorphin would enhance dopamine signaling and thus reduce depressive symptoms associated with stress. The authors suggest that KOR antagonists might have potential in treating depression in humans [12].
**Appetite and circadian rhythms**

Dynorphins are important in maintaining homeostasis through appetite control and circadian rhythms. Przewlocki et al. found that, during the day, dynorphins are naturally elevated in the neurointermediate lobe of the pituitary (NI pituitary) and depressed in the hypothalamus. This pattern is reversed at night. In addition, mice deprived of food and water, or of water alone, had increased levels of dynorphin in the hypothalamus during the day. Deprivation of water alone also decreased the dynorphin levels in the NI pituitary. These findings led Przewlocki et al. to conclude that dynorphins are essential in maintaining homeostasis.

Dynorphin has been implicated as an appetite stimulant. A number of studies in rats have shown that increasing the dynorphin levels stimulates eating. Opioid antagonists, such as naloxone, can reverse the effects of elevated dynorphin. This inhibition is especially strong in obese animals or animals that have access to particularly appealing food. Inui et al. found that administering dynorphin to dogs increased both their food and water intake. Dynorphin plays a role in the eating behavior of hibernating animals. Nizeilski et al. examined dynorphin levels in the ground squirrel, which undergoes periods of excessive eating and periods of starvation before winter. They found that dynorphin levels increased during the starvation periods. Berman et al. studied the levels of dynorphin during periods of food restriction. The group found that while food did not alter the expression of dynorphin B, it increases dynorphin A levels in several rat brain regions (hypothalamus, nucleus accumbens, and bed nucleus of the stria terminalis).

Recent research on dynorphin knockout mice did not find differences between knockout and control animals in food intake, but found that fat storage was reduced in male knockout mice. Fatty acids were oxidized more quickly in knockout animals. Studies have also shown that ingesting a high-fat diet increases the gene expression of dynorphin in the hypothalamus. Thus, dynorphin may cause overeating when a high-fat diet is available. The first to describe the role of opioid peptides in stress-related eating. In their study, mice had their tails pinched (causes stress), which induced eating. Stress-related eating was reduced by injecting naloxone, an opioid peptide antagonist.

Mandenoff et al. proposed that, although endogenous opioids are not necessary to maintain body weight and energy expenditure under predictable circumstances, they become activated under stressful conditions. They found that endogenous opioids, such as dynorphin, stimulate appetite and decrease energy expenditure. Taken together, the studies above suggest an important evolutionary mechanism in which more food is eaten, more nutrients are stored, and less energy is expended by an organism during times of stress [13].

**Temperature regulation**

In addition to their role in weight control, dynorphins have been found to regulate body temperature. Opioid peptides were first investigated in hyperthermia, where it was found that MOR agonists stimulate this response when injected into the periaqueductal gray (PAG) region of the brain. Xin et al. showed that delivery of dynorphin A1-17 (a KOR agonist) through microdialysis into the PAG region induced hypothermia in rats. The authors found that the severity of hypothermia was proportional to the dose of dynorphin A1-17 administered. Hypothermia could be prevented by administering KOR antagonist norBNI to the rat. Xin et al. hypothesized that while MOR agonists mediate hyperthermia, KOR agonists, such as dynorphin, mediate hypothermia.

Sharma and Alm found that subjecting rats to heat (38°C) caused dynorphins to be upregulated in the cerebral cortex, hippocampus, cerebellum, and the brain stem. Further, authors found that administration of nitric oxide synthase (NOS) inhibitors reduced dynorphin A1-17 levels in the brain and attenuated symptoms related to heat stress. Sharma and Alm concluded that hyperthermia increases dynorphin levels, which may cause damage and promote heat stress reaction. They further hypothesized that nitric oxide was part of this mechanism. Ansonoff et al. found that hypothermic effects are mediated through K1 (κ-opioid receptor 1), but not K2. The authors applied a KOR agonist to K1 knockout mice, which eliminated hypothermic response. Thus, K2 does not appear to have a role in the hypothermic mechanism [14].

**BRADYKININ**

Bradykinin is a peptide that causes blood vessels to dilate (enlarge), and therefore causes blood pressure to lower. A class of drugs called ACE inhibitors, which are used to lower blood pressure, increase bradykinin (by inhibiting its degradation) further lowering blood pressure. Bradykinin works on blood vessels through the release of prostacyclin, nitric oxide, and Endothelium-Derived Hyperpolarizing Factor. Bradykinin is a physiologically and pharmacologically active peptide of the kinin group of proteins, consisting of nine amino acids.

**Structure of Bradykinin**

The kinin-kallikrein system makes bradykinin by proteolytic cleavage of its kininogen precursor, high-molecular-weight kininogen (HMWK or HK), by the enzyme kallikrein.

**Metabolism**

In humans, bradykinin is broken down by three kininases: angiotensin-converting enzyme (ACE), aminopeptidase P (APP), and carboxypeptidase N (CPN), which cleave the 7-8, 1-2, and 8-9 positions, respectively.

**Physiological Role (Function)**

**Effects**
Bradykinin is a potent endothelium-dependent vasodilator, causes contraction of non-vascular smooth muscle, increases vascular permeability and also is involved in the mechanism of pain. Bradykinin also causes natriuresis, contributing to a drop in blood pressure. Bradykinin raises internal calcium levels in neocortical astrocytes causing them to release glutamate. Bradykinin is also thought to be the cause of the dry cough in some patients on angiotensin converting enzyme (ACE) inhibitor drugs. This refractory cough is a common cause for stopping ACE inhibitor therapy. In which case angiotensin II receptor antagonists are the next line of treatment.

Overactivation of bradykinin is thought to play a role in a rare disease called Hereditary Angioedema, formerly known as Hereditary Angio-Neurotic Edema. Initial secretion of bradykinin post-natally causes constriction and eventual atrophy of the ductus arteriosus, forming the ligamentum arteriosum between the pulmonary trunk and aortic arch.

Receptors

The B1 receptor (also called bradykinin receptor B1) is expressed only as a result of tissue injury, and is presumed to play a role in chronic pain. This receptor has been also described to play a role in inflammation. Most recently, it has been shown that the kinin B1 receptor recruits neutrophil via the chemokine CXCL5 production. Moreover, endothelial cells have been described as a potential source for this B1 receptor-CXCL5 pathway.

The B2 receptor is constitutively expressed and participates in bradykinin's vasodilatory role. The kinin B1 and B2 receptors belong to G protein coupled receptor (GPCR) family [15].

History

Bradykinin was discovered in 1948 by three Brazilian physiologists and pharmacologists working at the Instituto Biológico, in São Paulo, Brazil, led by Dr. Maurício Rocha e Silva. Together with colleagues Wilson Teixeira Beraldo and Gastão Rosenfeld, they discovered the powerful hypotensive effects of bradykinin in animal preparations. Bradykinin was detected in the blood plasma of animals after the addition of venom extracted from the Bothrops jararaca (Brazilian lancehead snake), brought by Rosenfeld from the Butantan Institute. The discovery was part of a continuing study on circulatory shock and proteolytic enzymes related to the toxicology of snake bites, started by Rocha e Silva as early as 1939. Bradykinin was to prove a new autopharmacological principle, i.e., a substance that is released in the body by a metabolic modification from precursors, which are pharmacologically active. According to B.J. Hagwood, Rocha e Silva's biographer, the discovery of bradykinin has led to a new understanding of many physiological and pathological phenomena including circulatory shock induced by venoms and toxins.

Therapeutic Implications

The practical importance of the discovery of bradykinin became apparent when one of his collaborators at the Medical School of Ribeirão Preto at the University of São Paulo, Dr. Sérgio Henrique Ferreira, discovered a bradykinin potentiating factor (BPF) in the bothropic venom which increases powerfully both the duration and magnitude of its effects on vasodilation and the consequent fall in blood pressure. On the basis of this finding, Squibb scientists developed the first of a new generation of highly-effective anti-hypertensive drugs, the so-called ACE inhibitors, such as captopril (trademarked Capoten).

Currently, bradykinin inhibitors (antagonists) are being developed as potential therapies for hereditary angioedema. Icatabant is one such inhibitor. Additional bradykinin inhibitors exist. It has long been known in animal studies that bromelain, a substance obtained from the stems and leaves of the pineapple plant, suppresses trauma-induced swelling caused by the release of bradykinin into the bloodstream and tissues. Other substances that act as bradykinin inhibitors include aloe and polyphenols, substances found in red wine and green tea.

PROSTAGLANDIN

A prostaglandin is any member of a group of lipid compounds that are derived enzymatically from fatty acids and have important functions in the animal body. Every prostaglandin contains 20 carbon atoms, including a 5-carbon ring. They are mediators and have a variety of strong physiological effects, such as regulating the contraction and relaxation of smooth muscle tissue. Prostaglandins are not endocrine hormones, but autocrine or paracrine, which are locally acting messenger molecules. They differ from hormones in that they are not produced at a discrete site but in many places throughout the human body. Also, their target cells are present in the immediate vicinity of the site of their secretion (of which there are many). The prostaglandins, together with the thromboxanes and prostacyclins, form the prostanoid class of fatty acid derivatives, a subclass of eicosanoids [16].

History and name

The name prostaglandin derives from the prostate gland. When prostaglandin was first isolated from seminal fluid in 1935 by the Swedish physiologist Ulf von Euler, and independently by M.W. Goldblatt, it was believed to be part of the prostatic secretions. (In fact, prostaglandins are produced by the seminal vesicles). It was later shown that many other tissues secrete prostaglandins for various functions. The first total syntheses of prostaglandin F2α and prostaglandin E2 were reported by E. J. Corey in 1969, an achievement for which he was awarded the Japan Prize in 1989.

In 1971, it was determined that aspirin-like drugs could inhibit the synthesis of prostaglandins. The biochemists Sune K. Bergström, Bengt I. Samuelsson and
John R. Vane jointly received the 1982 Nobel Prize in Physiology or Medicine for their research on prostaglandins.

**Biosynthesis of eicosanoids**

Prostaglandins are found in most tissues and organs. They are produced by almost all nucleated cells. They are autocrine and paracrine lipid mediators that act upon platelets, endothelium, uterine and mast cells. They are synthesized in the cell from the essential fatty acids (EFAs). An intermediate arachidonic acid is created from diacylglycerol via phospholipase-A2, then brought to either the cyclooxygenase pathway or the lipoxygenase pathway to form either prostaglandin and thromboxane or leukotriene respectively. The cyclooxygenase pathway produces thromboxane, prostacyclin and prostaglandin D, E and F. Alternatively, the lipoxygenase enzyme pathway is active in leukocytes and in macrophages and synthesizes leukotrienes.

**Release of prostaglandins from the cell**

Prostaglandins were originally believed to leave the cells via passive diffusion because of their high lipophilicity. The discovery of the prostaglandin transporter (PGT, SLCO2A1), which mediates the cellular uptake of prostaglandin, demonstrated that diffusion alone cannot explain the penetration of prostaglandin through the cellular membrane. The release of prostaglandin has now also been shown to be mediated by a specific transporter, namely the multidrug resistance protein 4 (MRP4, ABCC4), a member of the ATP-binding cassette transporter superfamily. Whether MRP4 is the only transporter releasing prostaglandins from the cells is still unclear [17].

**CYCLOOXYGENASES**

Prostaglandins are produced following the sequential oxidation of AA, DGLA or EPA by cyclooxygenases (COX-1 and COX-2) and terminal prostaglandin synthases. The classic dogma is as follows: COX-1 is responsible for the baseline levels of prostaglandins. COX-2 produces prostaglandins through stimulation. However, while COX-1 and COX-2 are both located in the blood vessels, stomach and the kidneys, prostaglandin levels are increased by COX-2 in scenarios of inflammation.

**Prostaglandin E synthase**

Prostaglandin E2 (PGE2) is generated from the action of prostaglandin E synthases on prostaglandin H2 (PGH2). Several prostaglandin E synthases have been identified. To date, microsomal prostaglandin E synthase-1 emerges as a key enzyme in the formation of PGE2.

**Other terminal prostaglandin synthases**

Terminal prostaglandin synthases have been identified that are responsible for the formation of other prostaglandins. For example, hematopoietic and lipocalin prostaglandin D synthases (hPGDS and IPGDS) are responsible for the formation of PGD2 from PGH2. Similarly, prostacyclin (PGI2) synthase (PGIS) converts PGH2 into PGI2. A thromboxane synthase (TxAS) has also been identified. Prostaglandin-F synthase (PGFS) catalyzes the formation of 9α, 11β-PGF2α,β from PGD2 and PGF2α from PGH2 in the presence of NADPH. This enzyme has recently been crystallized in complex with PGD2 and bimatoprost (a synthetic analogue of PGF2α).

**Function**

There are currently ten known prostaglandin receptors on various cell types. Prostaglandins ligate a sub-family of cell surface seven-transmembrane receptors, G-protein-coupled receptors. These receptors are termed DP1-2, EP1-4, FP, IP1-2, and TP, corresponding to the receptor that ligators the corresponding prostaglandin (e.g., DP1-2 receptors bind to PGD2). The diversity of receptors means that prostaglandins act on an array of cells and have a wide variety of effects such as:

- cause constriction or dilation in vascular smooth muscle cells
- cause aggregation or disaggregation of platelets
- sensitize spinal neurons to pain
- induce labor
- decrease intraocular pressure
- regulate inflammatory mediation
- regulate calcium movement
- control hormone regulation
- control cell growth
- acts on thermoregulatory center of hypothalamus to produce fever
- acts on mesangial cells in the glomerulus of the kidney to increase glomerular filtration rate
- acts on parietal cells in the stomach wall to inhibit acid secretion

Prostaglandins are potent but have a short half-life before being inactivated and excreted. Therefore, they send only paracrine (locally active) or autocrine (acting on the same cell from which it is synthesized) signals.

**Role in pharmacology**

Examples of prostaglandin antagonists are:

- NSAIDs (inhibit cyclooxygenase)
- Corticosteroids (inhibit phospholipase A2 production)
- COX-2 selective inhibitors or coxibs
- Cyclopentenone prostaglandins may play a role in inhibiting inflammation

**Clinical uses**

Synthetic prostaglandins are used:

- To induce childbirth (parturition) or abortion (PGE2 or PGF2, with or without mifepristone, a progesterone antagonist);
To prevent closure of patent ductus arteriosus in newborns with particular cyanotic heart defects (PGE1)
To prevent and treat peptic ulcers (PGE)
As a vasodilator in severe Raynaud's phenomenon or ischemia of a limb
In pulmonary hypertension
In treatment of glaucoma (as in bimatoprost ophthalmic solution, a synthetic prostamide analog with ocular hypotensive activity)
To treat erectile dysfunction or in penile rehabilitation following surgery (PGE1 as alprostadil).
To treat egg binding in small birds
As an ingredient in eyelash and eyebrow growth beauty products due to side effects associated with increased hair growth [18].

**ANGIOTENSIN**

Angiotensin is a peptide hormone that causes vasoconstriction and a subsequent increase in blood pressure. It is part of the renin-angiotensin system, which is a major target for drugs that lower blood pressure. Angiotensin also stimulates the release of aldosterone, another hormone, from the adrenal cortex. Aldosterone promotes sodium retention in the distal nephron, in the kidney, which also drives blood pressure up.

Angiotensin is an oligopeptide and is a hormone and a powerful dipsogen. It is derived from the precursor molecule angiotensinogen, a serum globulin produced in the liver. It plays an important role in the renin-angiotensin system. Angiotensin was independently isolated in Indianapolis and Argentina in the late 1930s (as 'angiotonin' and 'hypertensin', respectively) and subsequently characterised and synthesised by groups at the Cleveland Clinic and Ciba laboratories in Basel, Switzerland.

**Precursor, and types of angiotensin**

**Angiotensinogen**

Angiotensinogen is an α-2-globulin produced constitutively and released into the circulation mainly by the liver. It is a member of the serpin family, although it is not known to inhibit other enzymes, unlike most serpins. Plasma angiotensinogen levels are increased by plasma corticosteroid, estrogen, thyroid hormone, and angiotensin II levels. Angiotensinogen is also known as renin substrate. Human angiotensinogen is 452 amino acids long, but other species have angiotensinogen of varying sizes. The first 12 amino acids are the most important for activity.

**Angiotensin I**

**Renin-angiotensin-aldosterone system**

Angiotensin I is formed by the action of renin on angiotensinogen. Renin is produced in the kidneys in response to renal sympathetic activity, decreased intrarenal blood pressure (<90mmHg systolic blood pressure) at the juxtaglomerular cells, or decreased delivery of Na+ and Cl- to the macula densa. If less Na+ is sensed by the macula densa, renin release by juxtaglomerular cells is increased. Renin cleaves the peptide bond between the leucine (Leu) and valine (Val) residues on angiotensinogen, creating the ten-amino acid peptide (des-Asp) angiotensin I (CAS# 9041-90-1). Angiotensin I appears to have no biological activity and exists solely as a precursor to angiotensin 2.

**Angiotensin II**

Angiotensin I is converted to angiotensin II (AII) through removal of two C-terminal residues by the enzyme angiotensin-converting enzyme (ACE, or kinase), primarily through ACE within the kidney. ACE found in other tissues of the body has no physiological role (ACE has a high density in the lung, but activation here promotes no vasoconstriction, angiotensin II is below physiological levels of action). Angiotensin II acts as an endocrine, autocrine/paracrine, and intracrine hormone [19].

ACE is a target for inactivation by ACE inhibitor drugs, which decrease the rate of AII production. Angiotensin II increases blood pressure by stimulating the Gq protein in vascular smooth muscle cells (which in turn activates contraction by an IP3-dependent mechanism). ACE inhibitor drugs are major drugs against hypertension. Other cleavage products of ACE, seven or 9 amino acids long, are also known; they have differential affinity for angiotensin receptors, although their exact role is still unclear. The action of AII itself is targeted by angiotensin II receptor antagonists, which directly block angiotensin II AT1 receptors. Angiotensin II is degraded to angiotensin III by angiotensinases located in red blood cells and the vascular beds of most tissues. It has a half-life in circulation of around 30 seconds, whereas, in tissue, it may be as long as 15–30 minutes.

**Angiotensin III**

Angiotensin III has 40% of the pressor activity of angiotensin II, but 100% of the aldosterone-producing activity.

**Angiotensin IV**

Angiotensin IV is a hexapeptide that, like angiotensin III, has some lesser activity.

**Effects**

**Cardiovascular**

They are potent direct vasoconstrictors, constricting arteries and veins and increasing blood pressure. Angiotensin II has prothrombotic potential through adhesion and aggregation of platelets and production of PAI-1 and PAI-2. When cardiac cell growth is stimulated, a local (autocrine-paracrine) renin-angiotensin system is activated in the cardiac myocyte, which stimulates cardiac cell growth through protein kinase C. The same system can be activated in smooth muscle cells in conditions of
hypertension, atherosclerosis, or endothelial damage. Angiotensin II is the most important Gq stimulator of the heart during hypertrophy, compared to endothelin-1 and α1 adrenoreceptors.

**Neural**

Angiotensin II increases thirst sensation (dipsogen) through the subfornical organ of the brain, decreases the response of the baroreceptor reflex, and increases the desire for salt. It increases secretion of ADH in the posterior pituitary and secretion of ACTH in the anterior pituitary. It also potentiates the release of norepinephrine by direct action on postganglionic sympathetic fibers.

**Adrenal**

Angiotensin II acts on the adrenal cortex, causing it to release aldosterone, a hormone that causes the kidneys to retain sodium and lose potassium. Elevated plasma angiotensin II levels are responsible for the elevated aldosterone levels present during the luteal phase of the menstrual cycle.

**Renal**

Angiotensin II has a direct effect on the proximal tubules to increase Na+ reabsorption. It has a complex and variable effect on glomerular filtration and renal blood flow depending on the setting. Increases in systemic blood pressure will maintain renal perfusion pressure; however, constriction of the afferent and efferent glomerular arterioles will tend to restrict renal blood flow. The effect on the efferent arteriolar resistance is, however, markedly greater, in part due to its smaller basal diameter; this tends to increase glomerular capillary hydrostatic pressure and maintain glomerular filtration rate. A number of other mechanisms can affect renal blood flow and GFR. High concentrations of Angiotensin II can constrict the glomerular mesangium, reducing the area for glomerular filtration. Angiotensin II as a sensitizer to tubuloglomerular feedback, preventing an excessive rise in GFR. Angiotensin II causes the local release of prostaglandins, which, in turn, antagonize renal vasoconstriction. The net effect of these competing mechanisms on glomerular filtration will vary with the physiological and pharmacological environment.

**SECRETIN**

Secretin is a hormone that controls the secretions into the duodenum, and also separately, water homeostasis throughout the body. It is produced in the S cells of the duodenum in the crypts of Lieberkühn. Its effect is to regulate the pH of the duodenal contents via the control of gastric acid secretion and buffering with bicarbonate from the centroacinar cells of the pancreas as well as intercalated ducts. It is notable for being the first hormone to be identified. In humans, the secretin peptide is encoded by the SCT gene. It has recently been discovered to play a role in osmoregulation in the hypothalamus, pituitary, and kidney.

**Discovery**

In 1902, William Bayliss and Ernest Starling were studying how the nervous system controls the process of digestion. It was known that the pancreas secreted digestive juices in response to the passage of food (chyme) through the pyloric sphincter into the duodenum. They discovered (by cutting all the nerves to the pancreas in their experimental animals) that this process was not, in fact, governed by the nervous system. They determined that a substance secreted by the intestinal lining stimulates the pancreas after being transported via the bloodstream. They named this intestinal secretion secretin. Secretin was the first such chemical messenger identified. This type of substance is now called a hormone, a term coined by Bayliss in 1905.

**Structure**

Secretin is initially synthesized as a 120 amino acid precursor protein known as prosecretin. This precursor contains an N-terminal signal peptide, spacer, secretin itself (residues 28–54), and a 72-amino acid C-terminal peptide. The mature secretin peptide is a linear peptide hormone, which is composed of 27 amino acids and has a molecular weight of 3055. A helix is formed in the amino acids between positions 5 and 13. The amino acids sequences of secretin have some similarities to that of glucagon, vasoactive intestinal peptide (VIP), and gastric inhibitory peptide (GIP). Fourteen of 27 amino acids of secretin reside in the same positions as in glucagon, 7 the same as in VIP, and 10 the same as in GIP.

**Physiology**

**Stimulus**

Secretin is released into circulation and/or intestinal lumen in response to low duodenal pH that ranges between 2 and 4.5 depending on species. Also, the secretion of secretin is increased by the products of protein digestion bathing the mucosa of the upper small intestine. The acidity is due to hydrochloric acid in the chyme that enters the duodenum from the stomach via the pyloric sphincter. Secretin targets the pancreas, which causes the organ to secrete a bicarbonate-rich fluid that flows into the intestine. Bicarbonate ion is a base that neutralizes the acid, thus establishing a pH favorable to the action of other digestive enzymes in the small intestine and preventing acid burns. Other factors are also involved in the release of secretin such as bile salts and fatty acids, which result in additional bicarbonates being added to the small intestine. Secretin release is inhibited by H2 antagonists, which reduce gastric acid secretion. As a result, if the pH in the duodenum increases above 4.5, secretin cannot be released.

**Function**
Secretin increases watery bicarbonate solution from pancreatic and bile duct epithelium. Pancreatic centroacinar cells have secretin receptors in their plasma membrane. As secretin binds to these receptors, it stimulates adenylyl cyclase activity and converts ATP to cyclic AMP. Cyclic AMP acts as second messenger in intracellular signal transduction and leads to increase in release of watery carbonate. It is known to promote the normal growth and maintenance of the pancreas.

Secretin increases water and bicarbonate secretion from duodenal Brunner's glands in order to buffer the incoming protons of the acidic chyme. It also enhances the effects of cholecystokinin to induce the secretion of digestive enzymes and bile from pancreas and gallbladder, respectively. It counteracts blood glucose concentration spikes by triggering increased insulin release from pancreas, following oral glucose intake.

Although secretin releases gastrin from gastrinomas, it inhibits gastrin release from the normal stomach. It reduces acid secretion from the stomach by inhibiting gastrin release from G cells. This helps neutralize the pH of the digestive products entering the duodenum from the stomach, as digestive enzymes from the pancreas (e.g., pancreatic amylase and pancreatic lipase) function optimally at slightly basic pH. In addition, secretin stimulates pepsin secretion from chief cells, which can help break down proteins in food digestion. It also stimulates release of glucagon, pancreatic polypeptide and somatostatin.

**Uses**

Secretin has been widely used in medical field especially in pancreatic functioning test because it increases pancreatic secretions. Secretin is either injected or given through the tube that is inserted through nose, stomach then duodenum. This test can provide information about whether there are any abnormalities in pancreas which can be gastrinoma, pancreatitis or pancreatic cancer. Secretin has been proposed as a possible treatment for autism based on a hypothetical gut-brain connection, but as yet there is no evidence to support it as effective.

**Osmoregulation**

Secretin modulates water and electrolyte transport in pancreatic duct cells, liver cholangiocytes, and epididymis epithelial cells. It has also been recently been found to play a role in the vasopressin-independent regulation of renal water reabsorption. Secretin is found in the hypothalamus and neurohypophysis. During increased osmolality it is released from the posterior pituitary. In the hypothalamus, it activates vasopressin release. It has been suggested that abnormalities in such secretin release could explain the abnormalities underlying type D Syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH). In these individuals, vasopressin release and response are normal, although abnormal renal expression, translocation of aquaporin 2, or both are found. It has been suggested that Secretin as a neurosecretory hormone from the posterior pituitary, therefore, could be the long-sought vasopressin independent mechanism to solve the riddle that has puzzled clinicians and physiologists for decades [21,22].

**GASTRIN**

In humans, gastrin is a peptide hormone that stimulates secretion of gastric acid (HCl) by the parietal cells of the stomach and aids in gastric motility. It is released by G cells in the antrum of the stomach, duodenum, and the pancreas. It binds to cholecystokinin B receptors to stimulate the release of histamines in enterochromaffin-like cells, and it induces the insertion of K+/H+ ATPase pumps into the apical membrane of parietal cells (which in turn increases H+ release). Its release is stimulated by peptides in the lumen of the stomach.

**History**

Its existence was first suggested in 1905 by the British physiologist John Sydney Edkins, and gastrins were isolated in 1964 by Roderic Alfred Gregory and Tracy at the University of Liverpool. In 1964 the structure of Gastrin was determined.

**Physiology**

**Genetics**

The GAS gene is located on the long arm of the seventeenth chromosome (17q21).

**Synthesis**

Gastrin is a linear peptide hormone produced by G cells of the duodenum and in the pyloric antrum of the stomach. It is secreted into the bloodstream. Gastrin is found primarily in three forms:

- gastrin-34 (big gastrin)
- gastrin-17 (little gastrin)
- gastrin-14 (minigastrin)

Also, pentagastrin is an artificially synthesized, five amino acid sequence identical to the last five amino acid sequences at the C-terminus end of gastrin. The numbers refer to the amino acid count.

**Release**

Gastrin is released in response to certain stimuli. These include:

- stomach distension
- vagal stimulation (mediated by the neurocrine bombesin, or GRP in humans)
- the presence of partially digested proteins especially amino acids
- hypercalcemia

Gastrin release is inhibited by: The presence of acid (primarily the secreted HCl) in the stomach (a case of
negative feedback). Somatostatin also inhibits the release of gastrin, along with secretin, GIP (gastroinhibitory peptide), VIP (vasoactive intestinal peptide), glucagon and calcitonin.

**Function**

The presence of gastrin stimulates parietal cells of the stomach to secrete hydrochloric acid (HCl)/gastric acid. This is done both directly on the parietal cell and indirectly via binding onto CCK2/gastrin receptors on ECL cells in the stomach, which then responds by releasing histamine, which in turn acts in a paracrine manner on parietal cells stimulating them to secrete H+ ions. This is the major stimulus for acid secretion by parietal cells. Along with the above mentioned function, gastrin has been shown to have additional functions as well:

- Stimulates parietal cell maturation and fundal growth.
- Causes chief cells to secrete pepsinogen, the zymogen (inactive) form of the digestive enzyme pepsin.
- Increases antral muscle mobility and promotes stomach contractions.
- Strengthens antral muscle mobility and promotes stomach contractions.
- Plays a role in the relaxation of the ileocecal valve.
- Induces pancreatic secretions and gallbladder emptying.
- Impacts lower esophageal sphincter (LES) tone, causing it to relax. Taking this into consideration, high levels of gastrin may play a role in the development of some of the more common LES disorders such as acid reflux disease [23].

**Factors influencing secretion**

Gastric lumen:
- Stimulatory factors: dietary protein and amino acids (meat), hypercalcemia. (i.e. during the gastric phase)
- Inhibitory factor: acidity (pH below 3) - a negative feedback mechanism, exerted via the release of somatostatin from δ cells in the stomach, which inhibits gastrin and histamine release.

Paracrine:
- Stimulatory factor: bombesin
- Inhibitory factor: somatostatin - acts on somatostatin-2 receptors on G cells. In a paracrine manner via local diffusion in the intercellular spaces, but also systemically through its release into the local mucosal blood circulation; it inhibits acid secretion by acting on parietal cells.

Nervous:
- Stimulatory factors: Beta-adrenergic agents, cholinergic agents, gastrin-releasing peptide (GRP)
- Inhibitory factor: Enterogastric reflex

**Role in disease**

In the Zollinger-Ellison syndrome, gastrin is produced at excessive levels, often by a gastrinoma (gastrin-producing tumor, mostly benign) of the duodenum or the pancreas. To investigate for hypergastrinemia (high blood levels of gastrin), a pentagastrin test can be performed. In autoimmune gastritis, the immune system attacks the parietal cells leading to hypochlorhydria (low stomach acidity). This results in an elevated gastrin level in an attempt to compensate for increased pH in the stomach. Eventually, all the parietal cells are lost and achlorhydria results leading to a loss of negative feedback on gastrin secretion. Plasma gastrin concentration is elevated in virtually all individuals with mucolipidosis type IV (mean 1507 pg/mL; range 400-4100 pg/mL) secondary to a constitutive achlorhydria. This finding facilitates the diagnosis of patients with this neurogenic disorder [24].

**CHOLECYSTOKININ**

Cholecystokinin is a peptide hormone of the gastrointestinal system responsible for stimulating the digestion of fat and protein. Cholecystokinin, previously called pancreozymin, is synthesized by I-cells in the mucosal epithelium of the small intestine and secreted in the duodenum, the first segment of the small intestine, and causes the release of digestive enzymes and bile from the pancreas and gallbladder, respectively. It also acts as a hunger suppressant. Recent evidence has suggested that it also plays a major role in inducing drug tolerance to opioids like morphine and heroin, and is partly implicated in experiences of pain hypersensitivity during opioid withdrawal.

**Structure**

CCK is composed of varying numbers of amino acids depending on post-translational modification of the CCK gene product, preprocholecystokinin. Thus CCK is actually a family of hormones identified by number of amino acids, e.g., CCK58, CCK33, and CCK8. CCK58 assumes a helix-turn-helix configuration. Its existence was first suggested in 1905 by the British physiologist Joy Simcha Cohen. CCK is very similar in structure to gastrin, another of the gastrointestinal hormones. CCK and gastrin share the same five amino acids at their C-termini.

**Functions**

CCK mediates a number of physiological processes, including digestion and satiety. It is located in the small intestine, and detects the presence of fat in the chyme. CCK then tells the stomach to slow down the speed of digestion so the small intestine can effectively digest the fats.

Inhibitory factors: gastric inhibitory peptide (GIP), secretin, somatostatin, glucagon, calcitonin.
Digestion

Secretion of CCK by the duodenal and intestinal mucosa is stimulated by fat- or protein-rich chyme entering the duodenum. It then inhibits gastric emptying and gastric acid secretion and mediates digestion in the duodenum. It stimulates the acinar cells of the pancreas to release water and ions and stimulates the secretion of a juice rich in pancreatic digestive enzymes, hence the old name pancreozymin. Together these enzymes catalyze the digestion of fat, protein, and carbohydrates. Thus, as the levels of the substances that stimulated the release of CCK drop, the concentration of the hormone drops as well. The release of CCK is also inhibited by somatostatin. CCK also causes the increased production of hepatic bile, and stimulates the contraction of the gall bladder and the relaxation of the Sphincter of Oddi (Glisson's sphincter), resulting in the delivery of bile into the duodenal part of the small intestine. Bile salts form amphipathic micelles that emulsify fats, aiding in their digestion and absorption.

Neurobiology

As a neuropeptide, CCK mediates satiety by acting on the CCK receptors distributed widely throughout the central nervous system. In humans, it has been suggested that CCK administration causes nausea and anxiety, and induces a satiating effect. CCK-4 is routinely used to induce anxiety in humans though certainly different forms of CCK are being shown to have highly variable effects. The mechanism for this hunger suppression is thought to be a decrease in the rate of gastric emptying. CCK also has stimulatory effects on the vagus nerve, effects that can be inhibited by capsaicin. The stimulatory effects of CCK oppose those of ghrelin, which has been shown to inhibit the vagus nerve. The CCK tetrapeptide fragment CCK-4 (Trp-Met-Asp-Phe-NH2) reliably causes anxiety when administered to humans, and is commonly used in scientific research to induce panic attacks for the purpose of testing anxiolytic drugs. The effects of CCK vary between individuals. For example, in rats, CCK administration significantly reduces hunger in young males, but is slightly less effective in older subjects, and even slightly less effective in females. The hunger-suppressive effects of CCK also are reduced in obese rats [25,26].

Interactions

Cholecystokinin has been shown to interact with Cholecystokinin B receptor. CCK has also been shown to interact with calcineurin in the pancreas. Calcineurin will go on to activate the transcription factors NFAT 1–3, which will stimulate hypertrophy and growth of the pancreas. CCK can be stimulated by a diet high in protein, or by protease inhibitors. Cholecystokinin has been shown to interact with orexin neurons which control appetite and wakefulness (sleep). Cholecystokinin can have indirect effects on sleep regulation.

Cholecystokinin in the body cannot cross the blood brain barrier, but certain parts of the hypothalamus and brainstem aren't protected by the barrier [27].

HISTAMINE

Histamine is an organic nitrogen compound involved in local immune responses as well as regulating physiological function in the gut and acting as a neurotransmitter. Histamine triggers the inflammatory response. As part of an immune response to foreign pathogens, histamine is produced by basophils and by mast cells found in nearby connective tissues. Histamine increases the permeability of the capillaries to white blood cells and some proteins, to allow them to engage pathogens in the infected tissues.

Properties

Histamine forms colorless hygroscopic crystals that melt at 84°C, and are easily dissolved in water or ethanol, but not in ether. In aqueous solution histamine exists in two tautomeric forms, Nα-H-histamine and Nτ-H-histamine.

Tautomers of histamine

Histamine has two basic centres, namely the aliphatic amino group and whichever nitrogen atom of the imidazole ring does not already have a proton. Under physiological conditions, the aliphatic amino group (having a pKa around 9.4) will be protonated, whereas the second nitrogen of the imidazole ring (pKa ≈ 5.8) will not be protonated. Thus, histamine is normally protonated to a singly charged cation.

Synthesis and metabolism

Histamine is derived from the decarboxylation of the amino acid histidine, a reaction catalyzed by the enzyme L-histidine decarboxylase. It is a hydrophilic vasoactive amine. Conversion of histidine to histamine by histidin decarboxylase. Once formed, histamine is either stored or rapidly inactivated by its primary degradative enzymes, histamine-N-methyltransferase or diamine oxidase. In the central nervous system, histamine released into the synapses is primarily broken down by histamine-N-methyltransferase, while in other tissues both enzymes may play a role. Several other enzymes, including MAO-B and ALDH2, further process the immediate metabolites of histamine for excretion or recycling.

Bacteria also are capable of producing histamine using histidine decarboxylase enzymes unrelated to those found in animals. A non-infectious form of foodborne disease, scombroid poisoning, is due to histamine production by bacteria in spoiled food, particularly fish. Fermented foods and beverages naturally contain small quantities of histamine due to a similar conversion performed by fermenting bacteria or yeasts. Sake contains
histamine in the 20–40 mg/L range; wines contain it in the 2–10 mg/L range.

Storage and release

Mast cells
Most histamine in the body is generated in granules in mast cells or in white blood cells called basophils. Mast cells are especially numerous at sites of potential injury - the nose, mouth, and feet, internal body surfaces, and blood vessels. Non-mast cell histamine is found in several tissues, including the brain, where it functions as a neurotransmitter. Another important site of histamine storage and release is the enterochromaffin-like (ECL) cell of the stomach.

The most important pathophysiologic mechanism of mast cell and basophil histamine release is immunologic. These cells, if sensitized by IgE antibodies attached to their membranes, degranulate when exposed to the appropriate antigen. Certain amines and alkaloids, including such drugs as morphine, and curare alkaloids, can displace histamine in granules and cause its release. Antibiotics like polymyxin are also found to stimulate histamine release. Histamine release occurs when allergens bind to mast-cell-bound IgE antibodies. Reduction of IgE overproduction may lower the likelihood of allergens finding sufficient free IgE to trigger a mast-cell-release of histamine.

Mechanism of action
Histamine exerts its actions by combining with specific cellular histamine receptors. The four histamine receptors that have been discovered in humans and animals are designated H1 through H4, and are all G protein-coupled receptors (GPCR). Histamine receptors in insects, like Drosophila melanogaster, are histamine-gated chloride channels that function in inhibition of neurons. Histamine-gated chloride channels are implicated in neurotransmission of peripheral sensory information in insects, especially in photoreception/vision. Two receptors subtypes have been identified in Drosophila, HClA and HClB. There are no known GPCRs for histamine in insects.

Effects on nasal mucous membrane
Increased vascular permeability causes fluid to escape from capillaries into the tissues, which leads to the classic symptoms of an allergic reaction: a runny nose and watery eyes. Allergens can bind to IgE-loaded mast cells in the nasal cavity's mucous membranes. This can lead to three clinical responses:
- Sneezing due to histamine-associated sensory neural stimulation;
- Hyper-secretion from glandular tissue; and
- Nasal congestion due to vascular engorgement associated with vasodilation and increased capillary permeability.

Roles in the body

Sleep regulation
Histamine is released as a neurotransmitter. The cell bodies of histaminergic, the neurons which release histamine, are found in the posterior hypothalamus, in various tuberomammillary nuclei. From here, these neurons project throughout the brain, to the cortex through the medial forebrain bundle. Histaminergic action is known to modulate sleep. Classically, antihistamines (H1 histamine receptor antagonists) produce sleep. Likewise, destruction of histamine releasing neurons, or inhibition of histamine synthesis leads to an inability to maintain vigilance. Finally, H3 receptor antagonists increase wakefulness. It has been shown that histaminergic cells have the most wakefulness-related firing pattern of any neuronal type thus far recorded. They fire rapidly during waking, fire more slowly during periods of relaxation/tiredness and completely stop firing during REM and NREM (non-REM) sleep. Histaminergic cells can be recorded firing just before an animal shows signs of waking.

Suppressive effects
While histamine has stimulatory effects upon neurons, it also has suppressive ones that protect against the susceptibility to convulsion, drug sensitization, denervation supersensitivity, ischemic lesions and stress. It has also been suggested that histamine controls the mechanisms by which memories and learning are forgotten.

Erection and sexual function
Libido loss and erectile failure can occur following histamine (H2) antagonists such as cimetidine and ranitidine. The injection of histamine into the corpus cavernosum in men with psychogenic impotence produces full or partial erections in 74% of them. It has been suggested that H2 antagonists may cause sexual difficulties by reducing the uptake of testosterone.

Schizophrenia
Metabolites of histamine are increased in the cerebrospinal fluid of people with schizophrenia, while the efficiency of H(1) receptor binding sites is decreased. Many atypical antipsychotic medications have the effect of increasing histamine turnover.

Disorders
As an integral part of the immune system, histamine may be involved in immune system disorders and allergies. Mastocytosis is a rare disease in which there is a proliferation of mast cells that produce excess histamine. Histamine intolerance is a condition in which the body reacts to histamine in foods [28].

CANNABINOID
Cannabinoids are a class of diverse chemical compounds that activate cannabinoid receptors. These include the endocannabinoids (produced naturally in the
body by humans and animals), the phytocannabinoids (found in cannabis and some other plants), and synthetic cannabinoids (produced chemically by humans). The most notable cannabinoid is the phytocannabinoid Δ9-tetrahydrocannabinol (THC), the primary psychoactive compound of cannabis. However, there are known to exist numerous other cannabinoids with varied effects. Synthetic cannabinoids encompass a variety of distinct chemical classes: the classical cannabinoids structurally related to THC, the nonclassical cannabinoids (cannabinimetics) including the aminoalkylindoles, 1,5-diyrylpyrazoles, quinolines, and arylsulphonamides, as well as eicosanoids related to the endocannabinoids.

Cannabinoid receptors

Before the 1980s, it was often speculated that cannabinoids produced their physiological and behavioral effects via nonspecific interaction with cell membranes, instead of interacting with specific membrane-bound receptors. The discovery of the first cannabinoid receptors in the 1980s helped to resolve this debate. These receptors are common in animals, and have been found in mammals, birds, fish, and reptiles. At present, there are two known types of cannabinoid receptors, termed CB1 and CB2, with mounting evidence of more.

Cannabinoid receptor type 1

CB1 receptors are found primarily in the brain, to be specific in the basal ganglia and in the limbic system, including the hippocampus. They are also found in the cerebellum and in both male and female reproductive systems. CB1 receptors are absent in the medulla oblongata, the part of the brain stem responsible for respiratory and cardiovascular functions. Thus, there is not the risk of respiratory or cardiovascular failure that can be produced by some drugs. CB1 receptors appear to be responsible for the euphoric and anticonvulsive effects of cannabis.

Cannabinoid receptor type 2

CB2 receptors are predominantly found in the immune system, or immune-derived cells with the greatest density in the spleen. While found only in the peripheral nervous system, a report does indicate that CB2 is expressed by a subpopulation of microglia in the human cerebellum. CB2 receptors appear to be responsible for the anti-inflammatory and possibly other therapeutic effects of cannabis.

Phytocannabinoids (also called natural cannabinoids, herbal cannabinoids, and classical cannabinoids) are known to occur in several different plant species. These include Cannabis sativa, Cannabis indica, Echinacea purpurea, Echinacea angustifolia, Echinacea pallida, Acmella oleracea, Helichrysum umbracluligerum, and Radula marginata. The best known herbal cannabinoids are Δ9-tetrahydrocannabinol (THC) from Cannabis and the lipophilic alkamides (alkylamides) from Echinacea species. A significant number of cannabinoids are found in both Cannabis and Echinacea plants. In Cannabis, these cannabinoids are concentrated in a viscous resin produced in structures known as glandular trichomes. In Echinacea species, cannabinoids are found throughout the plant structure, but are most concentrated in the roots and stems. Tea (Camellia sinensis) catechins have an affinity for human cannabinoid receptors.

Health Effects of Cannabinoids

Phytocannabinoids are nearly insoluble in water but are soluble in lipids, alcohols, and other non-polar organic solvents. However, as phenols, they form more water-soluble phenolate salts under strongly alkaline conditions. All-natural cannabinoids are derived from their respective 2-carboxylic acids (2-COOH) by decarboxylation (catalyzed by heat, light, or alkaline conditions).

Types

At least 85 different cannabinoids have been isolated from the Cannabis plant. At least 25 different cannabinoids have been isolated from Echinacea species. To the right, the main classes of cannabinoids from Cannabis are shown. All classes derive from cannabigerol-type compounds and differ mainly in the way this precursor is cyclized. Tetrahydrocannabinol (THC), cannabidiol (CBD), cannabinol (CBN), and Dodeca-2E,4E,8Z,10E/Z-tetraenoic-acid-isobutylamides (from Echinacea species) are the most prevalent natural cannabinoids and have received the most study. Other common cannabinoids are listed below:

- CBG Cannabigerol
- CBC Cannabichromene
- CBL Cannabicyclol
- CBV Cannabivarin
- THCV Tetrahydrocannabivarin
- CBDV Cannabidiivarin
- CBCV Cannabichromevarin
- CBGV Cannabigerovarin
- CBGM Cannabigerol Monomethyl Ether Tetrahydrocannabinol

Tetrahydrocannabinol (THC) is the primary psychoactive component of the plant. It appears to ease moderate pain (analgesic) and to be neuroprotective. THC has approximately equal affinity for the CB1 and CB2 receptors. Delta-9-Tetrahydrocannabinol (Δ9-THC, THC) and delta-8-tetrahydrocannabinol (Δ8-THC), mimic the action of anandamide, a neurotransmitter produced naturally in the body. These two THC's produce the effects associated with cannabis by binding to the CB1 cannabinoid receptors in the brain.
Cannabidiol

Cannabidiol (CBD) is not particularly psychoactive in and of itself, and was thought not to affect the psychoactivity of THC. However, recent evidence shows that smokers of cannabis with a higher CBD/THC ratio were less likely to experience schizophrenia-like symptoms. This is supported by psychological tests, in which participants experience less intense psychotic-like effects when intravenous THC was co-administered with CBD (as measured with a PANSS test). Cannabidiol has little affinity for CB1 and CB2 receptors but acts as an indirect antagonist of cannabionid receptors. Recently it was found to be an antagonist at the putative new cannabinoid receptor, GPR55, a GPCR expressed in the caudate nucleus and putamen. Cannabidiol has also been shown to act as a 5-HT1A receptor agonist, an action that is involved in its antidepressant, anxiolytic, and neuroprotective effects. It appears to relieve convulsion, inflammation, anxiety, and nausea. CBD has a greater affinity for the CB2 receptor than for the CB1 receptor. CBD shares a precursor with THC and is the main cannabinoid in low-THC Cannabis strains. CBD apparently plays a role in preventing the short-term memory loss associated with THC in mammals.

Cannabinol

Cannabinol (CBN) is the primary product of THC degradation, and there is usually little of it in a fresh plant. CBN content increases as THC degrades in storage, and with exposure to light and air. It is only mildly psychoactive. Its affinity to the CB2 receptor is higher than for the CB1 receptor.

Cannabigerol

Cannabigerol (CBG) is non-psychotomimetic but still affects the overall effects of Cannabis. It acts as an α2-adrenergic receptor agonist, 5-HT1A receptor antagonist, and CB1 receptor antagonist. It also binds to the CB2 receptor.

Tetrahydrocannabivarin

Tetrahydrocannabivarin (THCV) is prevalent in certain central Asian and southern African strains of Cannabis. It is an antagonist of THC at CB1 receptors and attenuates the psychoactive effects of THC.

Cannabidivarin

Although cannabidivarin (CBDV) is usually a minor constituent of the cannabinoid profile, enhanced levels of CBDV have been reported in feral plants from the northwest Himalayas, and in hashish from Nepal.

Cannabichromene

Cannabichromene (CBC) is non-psychoactive and does not affect the psychoactivity of THC.

Double bond position

In addition, each of the compounds above may be in different forms depending on the position of the double bond in the alicyclic carbon ring. There is potential for confusion because there are different numbering systems used to describe the position of this double bond. Under the dibenzopyran numbering system widely used today, the major form of THC is called Δ9-THC, while the minor form is called Δ8-THC. Under the alternate terpene numbering system, these same compounds are called Δ1-THC and Δ6-THC, respectively.

Length

Most herbal cannabinoid compounds are 21-carbon compounds. However, some do not follow this rule, primarily because of variation in the length of the side-chain attached to the aromatic ring. In THC, CBD, and CBN, this side-chain is a pentyl (5-carbon) chain. In the most common homologue, the pentyl chain is replaced with a propyl (3-carbon) chain. Cannabinoids with the propyl side-chain are named using the suffix varin, and are designated, for example, THCV, CBDV, or CBNV.

Plant profile

Cannabis plants can exhibit wide variation in the quantity and type of cannabinoids they produce. The mixture of cannabinoids produced by a plant is known as the plant's cannabinoid profile. Selective breeding has been used to control the genetics of plants and modify the cannabinoid profile. For example, strains that are used as fiber (commonly called hemp) are bred such that they are low in psychoactive chemicals like THC. Strains used in medicine are often bred for high CBD content, and strains used for recreational purposes are usually bred for high THC content or for a specific chemical balance.

Quantitative analysis of a plant's cannabinoid profile is often determined by gas chromatography (GC), or more reliably by gas chromatography combined with mass spectrometry (GC/MS). Liquid chromatography (LC) techniques are also possible, and, unlike GC methods, can differentiate between the acid and neutral forms of the cannabinoids. There have been systematic attempts to monitor the cannabinoid profile of cannabis over time, but their accuracy is impeded by the illegal status of the plant in many countries.

Pharmacology

Cannabinoids can be administered by smoking, vaporizing, oral ingestion, transdermal patch, intravenous injection, sublingual absorption, or rectal suppository. Once in the body, most cannabinoids are metabolized in the liver, especially by cytochrome P450 mixed-function oxidases, mainly CYP 2C9. Thus supplementing with CYP 2C9 inhibitors leads to extended intoxication. Some is also stored in fat in addition to being metabolized in liver. Δ9-THC is metabolized to 11-hydroxy-Δ9-THC, which is then metabolized to 9-carboxy-THC. Some cannabis metabolites
can be detected in the body several weeks after administration. These metabolites are the chemicals recognized by common antibody-based drug tests; in the case of THC et al., these loads do not represent intoxication (compare to ethanol breath tests that measure instantaneous blood alcohol levels) but an integration of past consumption over an approximately month-long window.

**Plant synthesis**

Cannabinoid production starts when an enzyme causes geranyl pyrophosphate and olivetolic acid to combine and form CBG. Next, CBG is independently converted to either CBD or CBC by two separate synthase enzymes. CBD is then enzymatically cyclized to THC. For the propyl homologues (THCV, CBDV and CBNV), there is a similar pathway that is based on CBGV (recent studies show that THC is not cyclized from CBD but rather directly from CBG. no experiment thus far has turned up an enzyme that converts CBD into THC although it is still hypothesized).

**Separation**

Cannabinoids can be separated from the plant by extraction with organic solvents. Hydrocarbons and alcohols are often used as solvents. However, these solvents are flammable and many are toxic. Butane may be used, which evaporates extremely quickly. Supercritical solvent extraction with carbon dioxide is an alternative technique. Although this process requires high pressures (73 atmospheres or more), there is minimal risk of fire or toxicity, solvent removal is simple and efficient, and extract quality can be well controlled. Once extracted, cannabinoid blends can be separated into individual components using wiped film vacuum distillation or other distillation techniques. However, to produce high-purity cannabinoids, chemical synthesis or semisynthesis is generally required.

**History**

Cannabinoids were first discovered in the 1940s, when CBD and CBN were identified. The structure of THC was first determined in 1964. Due to molecular similarity and ease of synthetic conversion, CBD was originally believed to be a natural precursor to THC. However, it is now known that CBD and THC are produced independently in the cannabis plant from the precursor CBG.

**Endocannabinoids**

For more details on the roles and regulation of the endocannabinoids, see Endocannabinoid system. Anandamide, an endogenous ligand of CB1 and CB2. Endocannabinoids are substances produced from within the body that activate cannabinoid receptors. After the discovery of the first cannabinoid receptor in 1988, scientists began searching for an endogenous ligand for the receptor.

**Types of endocannabinoid ligands**

Arachidonoylthanolamine (Anandamide or AEA)

In 1992, in Raphael Mechoulam's lab, the first such compound was identified as arachidonoyl ethanolamine and named anandamide, a name derived from the Sanskrit word for bliss and -amide. Anandamide is derived from the essential fatty acid arachidonic acid. It has a pharmacology similar to THC, although its chemical structure is different. Anandamide binds to the central (CB1) and, to a lesser extent, peripheral (CB2) cannabinoid receptors, where it acts as a partial agonist. Anandamide is about as potent as THC at the CB1 receptor. Anandamide is found in nearly all tissues in a wide range of animals. Anandamide has also been found in plants, including small amounts in chocolate.

Two analogs of anandamide, 7,10,13,16-docosatetraenoylethanolamide and homo-γ-linolenoylthanolamine, have similar pharmacology. All of these are members of a family of signalling lipids called N-acyethanolamines, which also includes the noncannabimimetic palmitoylethanolamide and oleylethanolamide, which possess anti-inflammatory and orexigenic effects, respectively. Many N-acyethanolamines have also been identified in plant seeds and in mollusces.

**2-arachidonoyl glycerol (2-AG)**

Another endocannabinoid, 2-arachidonoyl glycerol, binds to both the CB1 and CB2 receptors with similar affinity, acting as a full agonist at both. 2-AG is present at significantly higher concentrations in the brain than anandamide, and there is some controversy over whether 2-AG rather than anandamide is chiefly responsible for endocannabinoid signalling in vivo. In particular, one in vitro study suggests that 2-AG is capable of stimulating higher G-protein activation than anandamide, although the physiological implications of this finding are not yet known.

**2-arachidonoyl glyceryl ether (noladin ether)**

In 2001, a third, ether-type endocannabinoid, 2-arachidonoyl glyceryl ether (noladin ether), was isolated from porcine brain. Prior to this discovery, it had been synthesized as a stable analog of 2-AG; indeed, some controversy remains over its classification as an endocannabinoid, as another group failed to detect the substance at any appreciable amount in the brains of several different mammalian species. It binds to the CB1 cannabinoid receptor (Ki = 21.2 nmol/L) and causes sedation, hypothermia, intestinal immobility, and mild antinociception in mice. It binds primarily to the CB1 receptor, and only weakly to the CB2 receptor.

**N-arachidonoyl-dopamine (NADA)**

Discovered in 2000, NADA preferentially binds to the CB1 receptor. Like anandamide, NADA is also an
agonist for the vanilloid receptor subtype 1 (TRPV1), a member of the vanilloid receptor family.

**Virodhamine (OAE)**

A fifth endocannabinoid, virodhamine, or O-arachidonoyl-ethanolamine (OAE), was discovered in June 2002. Although it is a full agonist at CB2 and a partial agonist at CB1, it behaves as a CB1 antagonist in vivo. In rats, virodhamine was found to be present at comparable or slightly lower concentrations than anandamide in the brain, but 2- to 9-fold higher concentrations peripherally.

**Function**

Endocannabinoids serve as intercellular 'lipid messengers', signaling molecules that are released from one cell and activating the cannabinoid receptors present on other nearby cells. Although in this intercellular signaling role they are similar to the well-known monoamine neurotransmitters, such as acetylcholine and dopamine, endocannabinoids differ in numerous ways from them. For instance, they use retrograde signaling. Furthermore, endocannabinoids are lipophilic molecules that are not very soluble in water. They are not stored in vesicles, and exist as integral constituents of the membrane bilayers that make up cells. They are believed to be synthesized 'on-demand' rather than made and stored for later use. The mechanisms and enzymes underlying the biosynthesis of endocannabinoids remain elusive and continue to be an area of active research. The endocannabinoid 2-AG has been found in bovine and human maternal milk.

**Synthetic and patented cannabinoids**

Historically, laboratory synthesis of cannabinoids were often based on the structure of herbal cannabinoids, and a large number of analogs have been produced and tested, especially in a group led by Roger Adams as early as 1941 and later in a group led by Raphael Mechoulam. Newer compounds are no longer related to natural cannabinoids or are based on the structure of the endogenous cannabinoids. Synthetic cannabinoids are particularly useful in experiments to determine the relationship between the structure and activity of cannabinoid compounds, by making systematic, incremental modifications of cannabinoid molecules. Medications containing natural or synthetic cannabinoids or cannabinoid analogs:

- Dronabinol (Marinol), is Δ9-tetrahydrocannabinol (THC), used as an appetite stimulant, anti-emetic, and analgesic
- Nabilone (Cesamet), a synthetic cannabinoid and an analog of Marinol. It is Schedule II unlike Marinol, which is Schedule III
- Sativex, a cannabinoid extract oral spray containing THC, CBD, and other cannabinoids used for neuropathic pain and spasticity in 22 countries including England, Canada and Spain. Sativex develops whole-plant cannabinoid medicines
- Rimonabant (SR141716), a selective cannabinoid (CB1) receptor inverse agonist used as an anti-obesity drug under the proprietary name Acomplia. It is also used for smoking cessation

Other notable synthetic cannabinoids include:

- JWH-018, a potent synthetic cannabinoid agonist discovered by Dr. John W. Huffman at Clemson University. It is being increasingly sold in legal smoke blends collectively known as spice. Several countries and states have moved to ban it legally.
- CP-55940, produced in 1974, this synthetic cannabinoid receptor agonist is many times more potent than THC.
- Dimethylheptylpipran
- HU-210, about 100 times as potent as THC
- HU-331 a potential anti-cancer drug derived from cannabidiol that specifically inhibits topoisomerase II.
- SR144528, a CB2 receptor antagonist
- WIN 55,212-2, a potent cannabinoid receptor agonist
- JWH-133, a potent selective CB2 receptor agonist
- Levonantradol (Nantrodolam), an anti-emetic and analgesic but not currently in use in medicine
- AM-2201, a potent cannabinoid receptor agonist [29,30].

**SUBSTANCE P**

In the field of neuroscience, substance P (SP) is a neuropeptide: an undecapeptide that functions as a neurotransmitter and as a neuromodulator. It belongs to the tachykinin neuropeptide family. Substance P and its closely related neuropeptide neurokinin A (NKA) are produced from a polyprotein precursor after differential splicing of the preprotachykinin A gene. The deduced amino acid sequence of substance P is as follows: Substance P is released from the terminals of specific sensory nerves, it is found in the brain and spinal cord, and is associated with inflammatory processes and pain.

**Discovery**

Substance P was originally discovered in 1931 by Ulf von Euler and John H. Gaddum as a tissue extract that caused intestinal contraction in vitro. Its tissue distribution and biologic actions were further investigated over the following decades. In 1983, NKA (previously known as substance K or neuromedin L) was isolated from porcine spinal cord and was also found to stimulate intestinal contraction.

**Receptor**

The endogenous receptor for substance P is neurokinin 1 receptor (NK1-receptor, NK1R). It belongs to the tachykinin receptor sub-family of GPCRs. Other neurokinin subtypes and neurokinin receptors that interact
with SP have also been reported. Amino acid residues that are responsible for the binding of SP and its antagonists are present in the extracellular loops and transmembrane regions of NK-1. Binding of SP to NK-1 results in internalization by the clathrin-dependent mechanism to the acidified endosomes where the complex disassociates. SP is subsequently degraded and NK-1 is re-expressed on the cell surface. Substance P and the NK1 receptor are widely distributed in the brain and are specifically found in brain regions that regulate emotion (hypothalamus, amygdala, and the periaqueductal gray). They are also found in close association with serotonin (5-HT) and neurons containing norepinephrine that are targeted by the currently used antidepressant drugs. The SP receptor promoter contains regions that are sensitive to cAMP, AP-1, AP-4, CEBPB and epidermal growth factor. Because these regions are related to complexed signal transduction pathways mediated by cytokines, it has been proposed that cytokines and neurotropic factors can induce NK-1. SP can also induce the cytokines that are capable of inducing NK-1 transcription factors.

Function

Substance P is an important element in pain perception. The sensory function of substance P is thought to be related to the transmission of pain information into the central nervous system. Substance P coexists with the excitatory neurotransmitter glutamate in primary afferents that respond to painful stimulation. Substance P has been associated with the regulation of mood disorders, anxiety, stress, reinforcement, neurogenesis, respiratory rhythm, neurotoxicity, nausea/emesis, pain and nociception. Substance P and other sensory neuropeptides can be released from the peripheral terminals of sensory nerve fibers in the skin, muscle and joints. It is proposed that this release is involved in neurogenic inflammation, which is a local inflammatory response to certain types of infection or injury. The regulatory function of SP also involves the regulation of its high-affinity receptor, NK-1. Substance P receptor antagonists may have important therapeutic applications in the treatment of a variety of stress-related illnesses, in addition to their potential as analgesics.

Vomiting

The vomiting center in the medulla contains high concentrations of substance P and its receptor, in addition to other neurotransmitters such as choline, histamine, dopamine, serotonin, and opioids. Their activation stimulates the vomiting reflex. Different emetic pathways exist, and substance P/NK1R appears to be within the final common pathway to regulate vomiting. Substance P antagonist (SPA) aprepitant is available in the market in the treatment of chemotherapy-induced nausea/emesis.

Pain

Substance P is involved in nociception, transmitting information about tissue damage from peripheral receptors to the central nervous system to be converted to the sensation of pain. It has been theorized that it plays a part in fibromyalgia. Capsaicin has been shown to reduce the levels of substance P, it is presumed, by reducing the number of C-fibre nerves or causing these nerves to be more tolerant. Thus, Capsaicin is clinically used as an analgesic and an inflammatory agent to reduce pain associated with arthritis and many types of neuralgia. A role of substance P and NKA in nociception is suggested by the reduction in response thresholds to noxious stimuli by central administration of K2 and K3 agonists. Based on recent studies, it was proposed that NK1, and possibly the NK2 receptor antagonists, could be developed as analgesic drugs. It has been studied that the mice carrying a disruption of the gene encoding SP/NKA show severely reduced nociceptive pain responses when the stimuli are moderate to intense. Pain behaviors induced by mechanical, thermal, and chemical stimulation of somatic and visceral tissues were reduced in the mutant mice lacking SP/NKA. However, it has been proposed that the importance of SP and NKA in animal's pain response apply only to a certain 'window' of pain intensities, and, when the intensity of the pain stimuli is further increased, the responses of the knockout mice is not severely different from the wild-type mice. Substance P increases glutamate activity (NMDA) in central nervous system, and it is associated with the development of brain edema and functional deficits after traumatic brain injury.

Cell growth

Substance P has been known to stimulate cell growth in culture, and it was shown that substance P could promote wound healing of non-healing ulcers in humans.

Diabetes

Substance P injected into pancreatic nerves has been shown to reverse diabetes in mice but effects to insulin secretion seem to be species dependent. In humans, substance P given intravenously seems to decrease insulin release and causes fluctuations in blood sugar levels.

Vasodilation

Substance P also has effects as a potent vasodilator. Substance P-induced vasodilatation is dependent on nitric oxide release. Substance P is involved in the axon reflex-mediated vasodilatation to local heating and wheal and flare reaction. It has been shown that vasodilatation to substance P is dependent on the NK1 receptor located on the endothelium. In contrast to other neuropeptides studied in human skin, substance P-induced vasodilatation has been found to decline during continuous infusion. This possibly suggests an internalization of neurokinin-1 (NK1). As is typical with many vasodilators, it also has bronchoconstrictive properties, administered
through the non-adrenergic, non-cholinergic nervous system (branch of the vagal system).

Clinical significance

Eczema

High levels of BDNF and substance P have been found associated with increased itching in eczema.

Gastrointestinal infection

Entamoeba histolytica is a single-celled parasitic protozoan that infects the lower gastrointestinal tract of humans. The symptoms of infection are diarrhea, constipation, and abdominal pain. This protozoan was found to secrete serotonin as well as substance P and neurotensin.

Denervation supersensitivity

When the innervation to substance P nerve terminals is lost, post-synaptic cells compensate for the loss of adequate neurotransmitter by increasing the expression of post-synaptic receptors. This, ultimately, leads to a condition known as Denervation Supersensitivity as the post-synaptic nerves will become hypersensitive to any invasion of substance P into the synaptic cleft.

REFERENCES


Deficiency

Naked mole rats lack cutaneous C fibers reactive to substance P (SP) and many small neurons that are normally SP-positive. Thus, these animals are insensitive to pain when painful stimuli are administered to the skin. New studies have shown that when the function of SP is genetically disrupted in mice, the animals demonstrated reduced responses to painful stimuli. Moreover, the response to capsaicin was absent or severely reduced in knockout mice [31,32].

CONCLUSION

A research area where autopharmacology principles assumed great importance was that of pain and inflammation, due to the great number of endogenous messengers, transmitters and modulators involved in their complex response at molecular and cellular level. The control and regulation mechanisms of the circulatory system and renal functions and their interactions (such as the renin/angiotensin system) are also greatly influenced by autopharmacological agents; an endogenous substance involved in hypotension in circulatory shock. Of course, all these systems are of extreme importance for clinical practice and for the discovery of new therapeutic drugs.


