P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-14 Olesen- 2057G GRBT050-Olesen-v6.cls July 8, 2005 1:24

Chapter 14

Serotonin and Other Biogenic Amines

Christian Waeber

Biogenic amines such as serotonin, norepinephrine, histamine, and dopamine are naturally occurring biologically active amines synthesized from three different amino acids. Histidine is the precursor of histamine; tryptophan is the precursor of serotonin (5-hydroxytryptamine or 5-HT); tyrosine is the precursor of dopamine, norepinephrine, and epinephrine as well as the trace amines tyramine and octopamine. In the central nervous system (CNS), biogenic amines control and modulate various functions, including cardiovascular homeostasis, circadian rhythms, emotional states, endocrine secretion, sexual behavior, and thermoregulation, as well as learning and memory.

Consistent with these pleiotropic effects, the etiology of several neural diseases, including migraine, has been linked to impaired biogenic amine signaling. As described in detail in Chapter 29, 5-HT is the neurotransmitter most frequently mentioned in relation with migraine. However, if the pharmacologic profiles of acute and prophylactic antimigraine drugs can be taken as an indication of which molecules play a role in migraine pathophysiology, biogenic amines other than 5-HT are likely be involved. For instance, β-adrenergic and dopamine receptor antagonists are commonly used to prevent or abort migraine attacks, and many prophylactic agents (e.g., flunarizine, amitriptyline, mirtazapine, pizotifen, cyproheptadine) have antihistaminic properties. In addition, high levels of circulating trace amines (tyramine, octopamine, and synephrine) have recently been reported in both migraine and cluster headache (17). This chapter discusses possible relationships between various biogenic amines and migraine, describes their synthetic pathways, and reviews some of their known mechanisms of action.

COMMON STRUCTURAL PROPERTIES OF BIOGENIC AMINE RECEPTORS

With the exception of 5-HT_3 receptors, all known biogenic amine receptors belong to the superfamily of rhodopsin-like G protein-coupled receptors (GPCRs) (56). Based on crystal structure data, hydropathy profile analyses, and phylogenetic comparisons, these receptors share the common motif of seven transmembrane (TM) domains. The membrane-spanning regions are linked by three extracellular loops that alternate with three intracellular loops. Activation of the receptors occurs by binding of specific biogenic amines to a binding pocket formed by the TM regions. Specific residues in different TM segments interact with functional groups of the biogenic amines. In particular, an aspartic acid residue in TM3, serine residues in TM5, and a phenylalanine residue in TM6 determine the ligand-binding properties of biogenic amine receptors. Ligand binding to its receptor induces a conformational change, initiating the activation of second messenger systems via specific G proteins. Residues in close vicinity to the plasma membrane in intracellular loops 2, 3, and 4 determine the specificity and efficacy of G-protein activation. Receptor-mediated signaling is turned off by phosphorylation of serine and threonine residues in the C-terminus and third intracellular loops, as it is known from rhodopsin (22).

5-HYDROXYTRYPTAMINE OR SEROTONIN

The initial step in the synthesis of 5-HT is the facilitated transport of L-tryptophan from blood into brain. Because other neutral amino acids, such as phenylalanine, leucine, and methionine, are transported by the same carrier, tryptophan entry into brain is related not only to its blood concentration but also to the concentrations of other neutral amino acids. Tryptophan hydroxylase catalyzes the tetrahydrobiopterin-dependent hydroxylation of tryptophan to 5-hydroxytryptophan, the first and rate-limiting step in the biosynthesis of 5-HT. The next step involves the decarboxylation of 5-hydroxytryptophan by L-aromatic amino acid decarboxylase (this enzyme is also present in catecholaminergic neurons, where it

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-14 Olesen- 2057G GRBT050-Olesen-v6.cls July 8, 2005 1:24

converts 3,4-dihydroxyphenylalanine to dopamine, see below).

The highest 5-HT concentrations are found in blood platelets and in the gastrointestinal tract (enterochromaffin cells of the mucosa contain more than 90% of the body's 5-HT). Lesser amounts are found in the brain and retina. Most serotonergic soma are located in morphologically diverse neurons clustered along the midline of the brainstem and reticular formation. Dahlstrom and Fuxe (16) have described nine groups of 5-HT-containing cell bodies, designated B1 through B9, which correspond for the most part with the raphe nuclei. Although there are only about 20,000 serotonergic neurons in the rat brain (around 300,000 in humans), the extensive axonal projection system arising from these neurons densely innervates nearly all regions of the CNS.

As with other biogenic amine transmitters, 5-HT is stored in vesicles and released by a Ca^{2+}-dependent exocytotic mechanism. The extent of 5-HT release depends on the firing rate of serotonergic neurons. Drugs that decrease the firing rate of serotonergic soma (e.g., 5-HT_{1A}-receptor agonists) decrease the release of 5-HT in the projection areas. Administration of 5-HT_{1B}-receptor agonists into areas receiving serotonergic innervation activates serotonergic autoreceptors in terminal fields and decreases 5-HT synthesis and release. However, in contrast to the activation of 5-HT_{1A} somatodendritic autoreceptors, these effects are not caused by decreases in the firing rate of serotonergic neurons.

Most of the released 5-HT is recaptured by an active reuptake mechanism via the serotonin transporter (SERT) located on serotonergic neurons. SERT exhibits about 50% homology with the transporters for norepinephrine and dopamine. The selectivity of monoamine reuptake inhibitors for these transporters varies greatly. For instance, tricyclic antidepressants such as desipramine are 25- to 150-fold more potent at inhibiting transport of norepinephrine than 5-HT. In contrast, selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, citalopram, sertraline, and paroxetine, are 15 to 75 times more potent at inhibiting the uptake of 5-HT than the uptake of norepinephrine. Various heterocyclic antidepressants (amitriptyline, imipramine, nortriptyline, clomipramine, doxepin, trazodone) are used in migraine prophylaxis, but the efficacy of tricyclic antidepressants in migraine does not seem to depend on their antidepressant action, and the strongest evidence of efficacy is for amitriptyline (2,62). Venlafaxine, a structurally novel bicyclic antidepressant that inhibits the reuptake of 5-HT and norepinephrine, has been shown to have a favorable efficacy and side effect profile when compared to amitriptyline (11). The use of the SSRIs (e.g., fluoxetine, sertraline, and paroxetine) has also been advocated in migraine prophylaxis, but data supporting the efficacy of these drugs are scant (15).

5-HT is primarily degraded by the enzyme monoamine oxidase (MAO), which occurs as two isoforms (MAO-A and MAO-B). MAO converts 5-HT to 5-hydroxyindole acetaldehyde, which in turn is metabolized by aldehyde dehydrogenase to produce 5-hydroxyindole acetic acid, the major excreted 5-HT metabolite. Both 5-HT and norepinephrine are metabolized preferentially by MAO-A. Inhibition of MAO-A activity has been linked to the antidepressant properties of a number of subtype selective (e.g., moclobemide) and nonselective (e.g., phenelzine) MAO inhibitors in clinical use. Interestingly, there is more MAO-A than MAO-B throughout rat brain, whereas human brain contains more MAO-B. Although serotonergic cell bodies contain predominantly MAO-B (for which 5-HT is not a preferred substrate), treatment of rats with clorgyline, a selective MAO-A inhibitor, raises the brain content of 5-HT and reduces the conversion of 5-HT to 5-hydroxyindole acetic acid. Thus, 5-HT may well be oxidized preferentially by MAO-A in vivo, as it is in vitro, even though serotonergic neurons do not contain much of this form of the enzyme.

With the exception of 5-HT_3 receptors, 5-HT receptors belong to the GPCR superfamily. With at least 14 distinct members, they are one of the most complex families of neurotransmitter receptors. Adding to this complexity, splice variants of various subtypes (5-HT_4, 5-HT_7) or RNA-edited isoforms (5-HT_{2C}) have been described (27). The 5-HT_1 receptor class is composed of five receptor subtypes (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F}), which, in humans, share 40 to 63% overall sequence identity and couple preferentially to Gi/o proteins, with resulting inhibition of cyclic adenosine monophosphate (cAMP) formation. The 5-HT_2 receptor class is composed of the 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors, which exhibit 46 to 50% overall sequence identity and couple preferentially to Gq/11 to increase the hydrolysis of inositol phosphates and elevate cytosolic [Ca^{2+}].

Based on their overall electrophysiologic features and sequence, 5-HT_3 receptors have been placed within the intrinsic ligand-gated ion channel receptor superfamily, together with nicotinic acetylcholine or $GABA_A$ receptors. 5-HT_3 receptors are found on both central and peripheral neurons, where they trigger rapid depolarization because of a transient inward current, subsequent to the opening of nonselective cation channels. A cDNA clone encoding a single subunit of the 5-HT_{3A} receptor was initially isolated from a neuron-derived cell line. Two splice variants were subsequently described in neuroblastoma–glioma cells and rat native tissues. A second subunit, 5-HT_{3B}, has been cloned. It appears that the heteromeric combination of 5-HT_{3A} and 5-HT_{3B} subunits is necessary to provide the full functional features of the 5-HT_3 receptor (61).

Although 5-HT_4, 5-HT_6, and 5-HT_7 receptors all couple preferentially to Gs and promote cAMP formation,

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-14 Olesen- 2057G GRBT050-Olesen-v6.cls July 8, 2005 1:24

they are classified as distinct receptor classes because of their limited (<35%) overall sequence identities (9,24). There have been no published reports to date concerning a physiologic functional response or specific binding to a 5-HT_5 recognition site. Two subtypes of the 5-HT_5 receptor (5-HT_{5A} and 5-HT_{5B}), sharing 70% overall sequence identity, have been found in rodents. The 5-HT_{5A} subtype has also been found in humans, but the human 5-HT_{5B} receptor gene does not encode a functional protein; there are stop codons in its coding sequence. In the rat, the recombinant 5-HT_{5A} receptor may be negatively coupled to adenylate cyclase activity (24).

Although most of the evidence for a direct role of 5-HT in the pathophysiology of migraine is circumstantial, there is a significant amount of literature linking this amine to migraine (see Chapter 29). For example, platelet 5-HT levels are reduced by 30% during attacks, and plasma concentrations are 60% lower; the biogenic amine-depleting drug reserpine causes a "typical headache" in migraineurs, probably by inducing 5-HT release from intracellular stores. Similarly, *m*-chlorophenylpiperazine (*m*-CPP), a major metabolite of the antidepressant trazodone, has been reported to cause migraine-like headaches in humans by activating 5-HT_{2B} or 5-HT_{2C} receptors. Perhaps the strongest evidence for a role of 5-HT in migraine is provided by the fact that some acute antimigraine drugs (ergot alkaloids, triptans) activate 5-HT_1 receptors (most probably the 5-HT_{1B}, 5-HT_{1F}, and/or 5-HT_{1F} subtypes), whereas various prophylactic agents (methysergide, pizotifen, cyproheptadine) are 5-HT_2 receptor antagonists (see Chapters 21, 50, 51, and 55).

DOPAMINE

Dopamine is a catecholamine neurotransmitter found predominately in the CNS. It is synthesized from tyrosine, which is converted to L-dihydroxyphenylalanine (L-DOPA) by the enzyme tyrosine hydroxylase. Dihydroxyphenylalanine is converted to dopamine by the cytoplasmic enzyme DOPA decarboxylase (or aromatic amino acid decarboxylase).

Five subtypes of dopamine receptor have been cloned. The D_1-like receptors (D_1 and D_5) are closely related. They couple to the G protein subunit $G_s\alpha$ and stimulate adenylyl cyclase activity. In contrast, D_2, D_3, and D_4 receptors (D_2-like) couple to $G_i\alpha$ and inhibit the formation of cAMP. The human D_2 gene consists of eight exons separated by seven introns (25). It undergoes alternative splicing to generate two molecularly distinct isoforms, D_2S and D_2L, that have distinct functions in vivo (39). D_2 receptor polymorphism has been hypothetically connected to a large number of neuropsychiatric disorders (65), but no conclusive link or association has been found. In a recent study, a large group of migraine patients with different D_2 genotypes showed similar clinical and psychological features (49). These results are at odds with a previous study showing that D_2 NcoI alleles significantly modify the clinical susceptibility to migraine with aura (47). In addition, NcoI C allele frequency has been reported to be significantly higher in individuals with migraine with aura, anxiety, or major depression than in individuals who have none of these disorders (46). This observation is unexpected, because the NcoI polymorphism involves a silent change at amino acid His^{313} and the expression of different alleles results in identical receptor molecules. Subsequent studies have in fact been unable to confirm the association between migraine with aura and D_2 NcoI alleles (20,33). In contrast to NcoI polymorphism, the -141C Ins/Del polymorphism in the D_2 receptor gene is functional and the -141C Ins allele frequency is significantly higher in schizophrenic patients than in control subjects (41). However, no association has been found between this polymorphism and migraine (36). Focusing on an isolated genetic population, Del Zompo et al. (19) found a disequilibrium in D_2 genotypes, but only in a subgroup of patients experiencing both nausea and yawning immediately before or during the pain phase of migraine (so-called dopaminergic migraineurs). A recent study assessed the association between polymorphism of other dopamine-related genes and susceptibility to migraine (38). No significant differences were found between control and migraine groups for the frequency of a 40-bp tandem repeat in the dopamine transporter gene and that of a dinucleotide repeat in the dopamine β-hydroxylase gene, but migraine without aura, and not migraine with aura, showed significant genetic association with D_4 receptor polymorphism. The precise role of D_2-like receptor gene polymorphism in migraine is therefore presently unclear. There is no evidence for allelic association between D_1-like (D_1, D_3, and D_5) dopamine receptor gene polymorphism and migraine with or without aura (55).

Various antidopaminergic drugs abort migraine attacks, and dopamine agonists may be useful for prophylaxis (6,58,59). Pharmacologic studies with dopaminergic agents like apomorphine suggest that migraineurs might present a dopaminergic hypersensitivity even between migraine attacks (8,14). Finally, patients with migraine show an increased density of D_2-like receptors on lymphocytes (5). Nevertheless, if dopamine and its receptors are indeed involved in migraine, its treatment, or both, the precise site of this action is unclear (44). The nervous and vascular systems are both likely to be involved in migraine pathophysiology, and both systems respond to dopamine. Dopamine is found in three major pathways in the CNS. A dopamine projection from the hypothalamus plays an important role in the regulation of prolactin release from the pituitary gland. Dopamine is also synthesized by neurons in the ventral tegmental area, which projects to the prefrontal cortex and the basal forebrain,

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-14 Olesen- 2057G GRBT050-Olesen-v6.cls July 8, 2005 1:24

including the nucleus accumbens. Another important dopamine pathway is from the substantia nigra pars compacta to the neostriatum. Dopamine or dopamine agonists have vasoactive effects on blood vessels in vitro and in vivo, producing vasoconstriction or vasodilatation, depending on the vascular bed and dose. Vasodilatation is seen in renal, mesenteric, coronary, and cerebral blood vessels, and, because it is inhibited by dopamine receptor antagonists, is probably mediated by specific dopamine receptors. In contrast, dopamine has vasoconstrictor effects in most vascular beds, including that of the brain, but it is believed to be mediated by α-adrenergic and 5-HT receptors.

NOREPINEPHRINE AND EPINEPHRINE

In the substantia nigra and some other brain regions, catecholamine synthesis proceeds only to dopamine, but in neurons of the locus coeruleus dopamine is further metabolized to norepinephrine by the enzyme dopamine-β-hydroxylase. After release, catecholamines can be taken up into neurons via the dopamine transporter, or metabolized by MAO (to 3,4,-dihydroxyphenylacetic acid) or catechol *O*-methyltransferase (to 3-methoxytyramine). These enzymes are major mechanisms for inactivation of catecholamines (and monoamines). Action by both enzymes results in the formation of homovanillic acid.

Adrenoceptors are located throughout the body on neuronal and non-neuronal tissues where they mediate a diverse range of responses to norepinephrine and epinephrine. The adrenoceptor family was first divided into α- and β-adrenoceptors based on pharmacologic studies in isolated tissue (3). α-Adrenoceptors located on peripheral sympathetic nerve terminals were later designated α_2-adrenoceptors and those located postsynaptically were designated α_1-adrenoceptors (31). Subsequent studies using pharmacologic and molecular biological techniques have further subdivided the α-adrenoceptor family; three subtypes within each group have now been cloned and pharmacologically characterized. The α_1-adrenoceptor subtypes have been classified as α_{1A}, α_{1B}, and α_{1D}-adrenoceptors; α_2-adrenoceptors have been classified as the α_{2A}-, α_{2B}-, and α_{2C}-adrenoceptors (rat, mouse, guinea pig, and cow α_{2A}-receptors exhibit a pharmacologic profile designated as α_{2D}).

β-Adrenoceptors are also heterogeneous and subdivided into three distinct subtypes based on functional, receptor binding, and genetic studies: β_1-, β_2-, and the atypical β_3-adrenoceptors. An additional subtype, identified in cardiac tissue as a putative, atypical subtype termed β_4, might be an affinity state of the β_1-adrenoceptor (30). β_1-Adrenoceptors predominate in the heart and on adipose tissue and display equal affinity for epinephrine and norepinephrine. In contrast, β_2-adrenoceptors are predominant on vascular, uterine, and airway smooth muscle and exhibit a higher affinity for norepinephrine than epinephrine. β-Adrenoceptor antagonists, either non–subtype selective or selective for the β_1-subtype, are widely used as antihypertensives, whereas β_2-adrenoceptor agonists are commonly used as bronchodilators. Selective β_3-adrenoceptor agonists are being developed for the treatment of type II diabetes and obesity.

Both α- and β-adrenoceptors are part of the large family of GPCR. α_1-Adrenoceptors mediate their functions through Gq/G11 proteins and phospholipase C, whereas α_2-adrenoceptors activate Go/Gi proteins and are negatively coupled to adenylate cyclase. In addition, there is evidence linking α_2-adrenoceptor to stimulation of Ca^{2+} influx and activation of K^+ channels, phospholipase A2, and Na^+/H^+ exchange (13). All three β-adrenoceptor subtypes are positively coupled to adenylate cyclase via activation of Gs δ proteins.

A wide variety of clinical signs and diagnostic tests suggest that dysfunction of the sympathetic nervous system exists in migraineurs (recently reviewed by Peroutka [45]). Furthermore, non–subtype-selective β-blockers (propranolol, nadolol, timolol) and β_1-selective blockers (atenolol, metoprolol) show efficacy as migraine preventing agents. In contrast, other β_1-selective (acebutolol) or nonselective β-adrenoceptor antagonists (alprenolol, oxprenolol, and pindolol) do not appear to be effective in migraine therapy (1). Some β-blockers interact with 5-HT_{1A} receptors in both animal and human brains (43), but no obvious correlation appears to exist between drug affinity at 5-HT_{1A} sites and potency of β-adrenergic agents in terms of migraine prevention. There are some indications that β-blockers exert their antimigraine effects on central catecholaminergic systems (52), suggesting that an action in the CNS might be responsible for the migraine prophylactic effect. However, although atenolol penetrates the CNS only poorly, it is an efficient antimigraine prophylactic agent. Thus, the mechanism of action of β-blockers in migraine still remains to be established, and no single property accounts for antimigraine prophylactic activity, suggesting either that a combination of characteristics is necessary or that various β-blockers act via different mechanisms. The only consistent feature of effective β-blockers is that only silent β-adrenergic antagonists (without partial agonist activity or without intrinsic sympathomimetic activity) are effective agents. Finally, it is worth mentioning that mirtazapine, an α_2-adrenergic receptor antagonist with a complex pharmacologic profile (18), has been reported to be effective in migraine prevention.

Isometheptene mucate is a mild vasoconstrictor used in combination with acetaminophen and a mild sedative for the treatment of moderate tension-type and migraine headaches. It has been suggested that isometheptene owes its therapeutic effect to a sympathomimetic action leading to cranial blood vessel constriction via α_{2A}- and α_{2C}-adrenoceptors (63). However, the contribution of

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-14 Olesen- 2057G GRBT050-Olesen-v6.cls July 8, 2005 1:24

vasoconstriction to the efficacy of acute antimigraine drugs is unclear (40,64). Because intravenous administration of the nonselective α_2-adrenoceptor agonist UK-14,304 blocks plasma protein extravasation within rat dura mater following unilateral electrical trigeminal ganglion stimulation (35), it is possible that prejunctional α_2-adrenoceptors on trigeminovascular afferents play a role in the efficacy of isometheptene or ergot derivatives (57).

HISTAMINE

Histamine biosynthesis is performed in one step by the enzyme L-histidine decarboxylase. Histamine degradation occurs mainly via two pathways: oxidation by diamine oxidase (DAO), leading to imidazole acetic acid, or methylation by histamine *N*-methyltransferase, producing tele-methylhistamine, which is further metabolized by MAO-B, producing tele-methylimidazole acetic acid. In the vertebrate CNS, histamine is almost exclusively methylated and only small amounts of DAO are detectable. Unlike the other amine transmitters, histaminergic nerve terminals do not exhibit a high-affinity uptake system for histamine (54).

In the mammalian brain, histamine is synthesized in a restricted population of neurons located in the tuberomammillary nucleus of the posterior hypothalamus. These neurons project diffusely to most cerebral areas and have been implicated in several brain functions (e.g., sleep/wakefulness, hormonal secretion, cardiovascular control, thermoregulation, food intake, and memory formation). In peripheral tissues, histamine is stored in mast cells, basophils, and enterochromaffin cells.

Histamine H_1, H_2, and H_3 receptors are all G-protein–coupled molecules and transduce extracellular signals via Gq, Gs, and Gi/o proteins, respectively (26). Generally, histamine modulates inflammatory and allergic responses via H_1 receptors, gastric acid secretion through H_2 receptors, and neurotransmitter release in the CNS via H_3 receptors. The expression pattern of the recently cloned H_4 subtype is highly suggestive of a role for this receptor in immune and inflammatory modulation. Unlike the H_1 and H_2 receptor genes, analysis of the H_3 receptor gene shows the presence of several introns and several H_3 receptor isoforms have been identified (34).

Plasma histamine levels have been shown to be significantly elevated in patients with migraine, both during headache and symptom-free periods (23,29). These elevated plasma histamine levels in migraine patients may be associated with increased spontaneous histamine release by leukocytes (29), or result from activation of dural mast cells, which might play a role in migraine pathogenesis (50). There is, however, little evidence for a direct correlation of plasma histamine levels and attack precipitation, other than the observation that histamine, when infused intravenously to migraineurs, causes an immediate headache during infusion and a delayed migraine headache that peaks approximately 5 hours after infusion (32). The intensity of the immediate headache is significantly attenuated and the delayed migraine completely abolished when patients are pretreated with the H_1 receptor antagonist, mepyramine. Histamine does not cross the blood–brain barrier (54) and it has been suggested that histamine acts on H_1 receptors located on the endothelium of cerebral arteries which, when activated, cause the formation of nitric oxide.

Several H_3 receptor agonists have been reported to inhibit neurogenic inflammation in various tissues, including the lungs and dura mater (34,35). These observations indicate a potential use of H_3-receptor agonists in inflammation, asthma, and migraine. Phase II clinical trials have so far resulted in negative outcomes in exercise-induced asthma (21) or migraine (53). Interestingly, in an open clinical trial, *N*-α-methylhistamine was reported to reduce headache intensity, frequency, and duration in 18 patients with migraine. At the highest dose tested, however, patients reported intense headaches, which were possibly caused by residual H_1-receptor agonistic effects (37).

TRACE AMINES

In addition to the classical biogenic amine neurotransmitters discussed, a series of less well-characterized amines derived from the metabolism of amino acids are also present in many tissues, especially in the brain. In mammals, these amines include tyramine, β-phenylethylamine, tryptamine, and octopamine. Tyramine, derived from the tyrosine through tyrosine decarboxylase enzyme activity, is metabolized by dopamine-β-hydroxylase into octopamine, and phenylethanolamine *N*-methyltransferase enzyme activity transforms octopamine into synephrine, the final biochemical step in the synthesis of trace amines.

Although the presence of trace amines in neural tissues has been known for many years (60), and alterations in the amount of trace amines in the nervous system are associated with pathologic conditions (48), the physiologic effects of trace amines are poorly understood. Tyramine and β-phenylethylamine act peripherally by promoting the efflux of catecholamines from sympathetic neurons and adrenals, which results in the indirect stimulation of adrenoceptors (7). In addition, trace amines can bind to classical amine receptors. For instance, because it shares structural and functional similarities with norepinephrine, octopamine has numerous effects on the adrenergic system (4), and tryptamine, very similar to 5-HT, has a high affinity for 5-HT_{1D}, 5-HT_{2B}, 5-HT_{2C}, and 5-HT_7 receptors (51).

The recent identification of GPCR activated by trace amines is an important advance in the understanding of the roles of these amines in the mammalian nervous

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-14 Olesen- 2057G GRBT050-Olesen-v6.cls July 8, 2005 1:24

system (10). The 15 members of these two distinct families of GPCR show a high degree of similarity with traditional G-protein–coupled biogenic amine receptors. One of these receptors (TA1) is activated by both β-phenylethylamine and tyramine with high affinity, leading to increased cAMP production. TA1 displays low affinity for tryptamine, octopamine, and dopamine. The related TA2 receptor appears to be specific for β-phenylethylamine and tryptamine. Both of these G-protein–coupled receptor families possess many of the structural hallmarks of the rhodopsin receptor superfamily (see above). Among these are several highly conserved stretches of residues in the predicted TM regions, as well as potential sites of regulatory phosphorylation in the C-terminal domain. Thus, these receptors are likely to couple to conventional signaling pathways as demonstrated for TA1 (10) and their signaling is likely to be regulated through mechanisms similar to those for other GPCR. Several of these new receptors are expressed within specific regions of the CNS, whereas others appear to be found in specific peripheral tissues such as the stomach, kidney, lung, and small intestine. In the CNS, the mRNA for the TA1 and TA2 receptor proteins can be found sparsely expressed in certain cells of the substantia nigra/ventral tegmental area, locus coeruleus, and dorsal raphe nucleus, areas where the cell bodies for the classic biogenic amines neurons are found.

Chocolate, cheese, citrus fruits, and other foods rich in trace amines are widely thought to trigger migraine attacks in susceptible individuals (42), but careful evaluation of the scientific evidence shows little support for this belief (28). Recently, plasma levels of octopamine and synephrine were found to be higher in migraine without aura patients than in controls. No significant difference in amine levels were found in migraine with aura, but plasma octopamine, synephrine, and tyramine levels were also found to be significantly higher in cluster headache patients, both in the remission and active phases (17). It is not clear whether these changes are causally related to migraine, or simply a result of other migraine-related alterations. Interestingly, a recently cloned trace amine receptor is activated by dihydroergotamine and lisuride (12). Although sumatriptan is inactive at these receptors, it will be interesting to determine whether the effectiveness of other antimigraine drugs is accounted for, at least partly, by trace amine receptors, and whether drugs specifically activating or blocking trace amine receptor show antimigraine efficacy.

REFERENCES

1. Ablad B, Dahlof C. Migraine and beta-blockade: modulation of sympathetic neurotransmission. *Cephalalgia*. 1986;6(Suppl 5):7–13.
2. Adly C, Straumanis J, Chesson A. Fluoxetine prophylaxis of migraine. *Headache*. 1992;32:101–104.
3. Ahlquist RA. Study of the adrenotropic receptors. *Am J Physiol*. 1948;153:586–600.
4. Axelrod J, Saavedra JM. Octopamine. *Nature*. 1977;265:501–504.
5. Barbanti P, Fabbrini G, Ricci A, et al. Migraine patients show an increased density of dopamine D3 and D4 receptors on lymphocytes. *Cephalalgia*. 2000;20:15–19.
6. Bigal ME, Bordini CA, Speciali JG. Intravenous chlorpromazine in the emergency department treatment of migraines: a randomized controlled trial. *J Emerg Med*. 2002;23:141–148.
7. Black JW, Jenkinson DH, Kenakin TP. Antagonism of an indirectly acting agonist: block by propranolol and sotalol of the action of tyramine on rat heart. *Eur J Pharmacol*. 1980;65:1–10.
8. Blin O, Azulay JP, Masson G, et al. Apomorphine-induced yawning in migraine patients: enhanced responsiveness. *Clin Neuropharmacol*. 1991;14:91–95.
9. Bockaert J, Claeysen S, Compan V, et al. 5-HT4 receptors. *Curr Drug Targets CNS Neurol Disord*. 2004;3:39–51.
10. Borowsky B, Adham N, Jones KA, et al. Trace amines: identification of a family of mammalian G protein-coupled receptors. *Proc Natl Acad Sci U S A*. 2001;98:8966–8971.
11. Bulut S, Berilgen MS, Baran A, et al. Venlafaxine versus amitriptyline in the prophylactic treatment of migraine: randomized, double-blind, crossover study. *Clin Neurol Neurosurg*. 2004;107:44–48.
12. Bunzow JR, Sonders MS, Arttamangkul S, et al. Amphetamine, 3,4-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace amine receptor. *Mol Pharmacol*. 2001;60:1181–1188.
13. Bylund DB. Pharmacological characteristics of alpha-2 adrenergic receptor subtypes. *Ann N Y Acad Sci*. 1995;763:1–7.
14. Cerbo R, Barbanti P, Buzzi MG, et al. Dopamine hypersensitivity in migraine: role of the apomorphine test. *Clin Neuropharmacol*. 1997;20:36–41.
15. Cutrer F, Waeber C, Moskowitz M. Headache. In: Enna S, Coyle J, eds. *Pharmacological management of neurological and psychiatric disorders*. New York: McGraw-Hill; 1998:525–568.
16. Dahlstrom A, Fuxe K. Evidence for the existence of monamine-containing neurons in the central nervous system. I. Demonstration of monamines in the cell bodies of brainstem neurons. *Acta Physiol Scand*. 1964;62:1–55.
17. D'Andrea G, Terrazzino S, Leon A, et al. Elevated levels of circulating trace amines in primary headaches. *Neurology*. 2004;62:1701–1705.
18. de Boer T. The pharmacologic profile of mirtazapine. *J Clin Psychiatry*. 1996;57(Suppl 4):19–25.
19. Del Zompo M, Cherchi A, Palmas MA, et al. Association between dopamine receptor genes and migraine without aura in a Sardinian sample. *Neurology*. 1998;51:781–786.
20. Dichgans M, Forderreuther S, Deiterich M, et al. The D2 receptor NcoI allele: absence of allelic association with migraine with aura. *Neurology*. 1998;51:928.
21. Fozard JR. BP-294 Ste Civile Bioprojet. *Curr Opin Investig Drugs*. 2000;1:86–89.
22. Gainetdinov RR, Premont RT, Bohn LM, et al. Desensitization of G protein-coupled receptors and neuronal functions. *Annu Rev Neurosci*. 2004;27:107–144.
23. Gazerani P, Pourpak Z, Ahmadiani A, et al. A correlation between migraine, histamine and immunoglobulin E. *Scand J Immunol*. 2003;57:286–290.
24. Glennon RA. Higher-end serotonin receptors: 5-HT(5), 5-HT(6), and 5-HT(7). *J Med Chem*. 2003;46:2795–2812.
25. Grandy DK, Marchionni MA, Makam H, et al. Cloning of the cDNA and gene for a human D2 dopamine receptor. *Proc Natl Acad Sci U S A*. 1989;86:9762–9766.
26. Hough LB. Genomics meets histamine receptors: new subtypes, new receptors. *Mol Pharmacol*. 2001;59:415–419.
27. Hoyer D, Hannon JP, Martin GR. Molecular, pharmacological and functional diversity of 5-HT receptors. *Pharmacol Biochem Behav*. 2002;71:533–554.
28. Jansen SC, van Dusseldorp M, Bottema KC, et al. Intolerance to dietary biogenic amines: a review. *Ann Allergy Asthma Immunol*. 2003;91:233–240; quiz 241–232, 296.
29. Kemper RH, Meijler WJ, Korf J, et al. Migraine and function of the immune system: a meta-analysis of clinical literature published between 1966 and 1999. *Cephalalgia*. 2001;21:549–557.
30. Konkar AA, Zhai Y, Granneman JG. beta1-adrenergic receptors mediate beta3-adrenergic-independent effects of CGP 12177 in brown adipose tissue. *Mol Pharmacol*. 2000;57:252–258.

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-14 Olesen- 2057G GRBT050-Olesen-v6.cls July 8, 2005 1:24

31. Langer SZ. Presynaptic regulation of catecholamine release. *Biochem Pharmacol*. 1974;23:1793–1800.
32. Lassen LH, Christiansen I, Iversen HK, et al. The effect of nitric oxide synthase inhibition on histamine induced headache and arterial dilatation in migraineurs. *Cephalalgia*. 2003;23:877–886.
33. Lea RA, Dohy A, Jordan K, et al. Evidence for allelic association of the dopamine beta-hydroxylase gene (DBH) with susceptibility to typical migraine. *Neurogenetics*. 2000;3:35–40.
34. Leurs R, Bakker RA, Timmerman H, et al. The histamine H3 receptor: from gene cloning to H3 receptor drugs. *Nat Rev Drug Discov*. 2005;4:107–120.
35. Matsubara T, Moskowitz MA, Huang Z. UK-14,304, R(-)-alpha-methyl-histamine and SMS 201-995 block plasma protein leakage within dura mater by prejunctional mechanisms. *Eur J Pharmacol*. 1992;224:145–150.
36. Maude S, Curtin J, Breen G, et al. The -141C Ins/Del polymorphism of the dopamine D2 receptor gene is not associated with either migraine or Parkinson's disease. *Psychiatr Genet*. 2001;11:49–52.
37. Millan-Guerrero RO, Pineda-Lucatero AG, Hernandez-Benjamin T, et al. Nalpha-methylhistamine safety and efficacy in migraine prophylaxis: phase I and phase II studies. *Headache*. 2003;43:389–394.
38. Mochi M, Cevoli S, Cortelli P, et al. A genetic association study of migraine with dopamine receptor 4, dopamine transporter and dopamine-beta-hydroxylase genes. *Neurol Sci*. 2003;23:301–305.
39. Monsma FJ Jr, McVittie LD, Gerfen CR, et al. Multiple D2 dopamine receptors produced by alternative RNA splicing. *Nature*. 1989;342:926–929.
40. Moskowitz MA. Neurogenic versus vascular mechanisms of sumatriptan and ergot alkaloids in migraine. *Trends Pharmacol Sci*. 1992;13:307–311.
41. Ohara K, Nagai M, Tani K, et al. Functional polymorphism of -141C Ins/Del in the dopamine D2 receptor gene promoter and schizophrenia. *Psychiatry Res*. 1998;81:117–123.
42. Peatfield RC, Glover V, Littlewood JT, et al. The prevalence of diet-induced migraine. *Cephalalgia*. 1984;4:179–183.
43. Peroutka SJ. The pharmacology of current anti-migraine drugs. *Headache*. 1990;30:5–11; discussion 24–18.
44. Peroutka SJ. Dopamine and migraine. *Neurology*. 1997;49:650–656.
45. Peroutka SJ. Migraine: a chronic sympathetic nervous system disorder. *Headache*. 2004;44:53–64.
46. Peroutka SJ, Price SC, Wilhoit TL, et al. Comorbid migraine with aura, anxiety, and depression is associated with dopamine D2 receptor (DRD2) NcoI alleles. *Mol Med*. 1998;4:14–21.
47. Peroutka SJ, Wilhoit T, Jones K. Clinical susceptibility to migraine with aura is modified by dopamine D2 receptor (DRD2) NcoI alleles. *Neurology*. 1997;49:201–206.
48. Premont RT, Gainetdinov RR, Caron MG. Following the trace of elusive amines. *Proc Natl Acad Sci U S A*. 2001;98:9474–9475.
49. Rebaudengo N, Rainero I, Parziale A, et al. Lack of interaction between a polymorphism in the dopamine D2 receptor gene and the clinical features of migraine. *Cephalalgia*. 2004;24:503–507.
50. Reuter U, Bolay H, Jansen-Olesen I, et al. Delayed inflammation in rat meninges: implications for migraine pathophysiology. *Brain*. 2001;124:2490–2502.
51. Roth B, Kroeze W, Patel S, Lopez E. The multiplicity of serotonin receptors: uselessly diverse molecules or an embarrassment of riches? *The Neuroscientist*. 2000;6:252–262.
52. Schoenen J, Maertens de Noordhout A, et al. Contingent negative variation and efficacy of beta-blocking agents in migraine. *Cephalalgia*. 1986;6:229–233.
53. Schwartz JC. The histamine H3 receptor: from molecular pharmacology to clinical applications. *2nd International Symposium on Molecular Medicine Abstracts*. 2002
54. Schwartz JC, Arrang JM, Garbarg M, et al. Histaminergic transmission in the mammalian brain. *Physiol Rev*. 1991;71:1–51.
55. Shepherd AG, Lea RA, Hutchins C, et al. Dopamine receptor genes and migraine with and without aura: an association study. *Headache*. 2002;42:346–351.
56. Shi L, Javitch JA. The binding site of aminergic G protein-coupled receptors: the transmembrane segments and second extracellular loop. *Annu Rev Pharmacol Toxicol*. 2002;42:437–467.
57. Silberstein SD, McCrory DC. Ergotamine and dihydroergotamine: history, pharmacology, and efficacy. *Headache*. 2003;43:144–166.
58. Silberstein SD, Young WB, Mendizabal JE, et al. Acute migraine treatment with droperidol: A randomized, double-blind, placebo-controlled trial. *Neurology*. 2003;60:315–321.
59. Somerville BW, Herrmann WM. Migraine prophylaxis with Lisuride hydrogen maleate—a double blind study of Lisuride versus placebo. *Headache*. 1978;18:75–79.
60. Usdin E, Sandler M. *Trace amines and the brain*. New York: Dekker; 1976.
61. van Hooft JA, Yakel JL. 5-HT3 receptors in the CNS: 3B or not 3B? *Trends Pharmacol Sci*. 2003;24:157–160.
62. Walker Z, Walker RW, Robertson MM, et al. Antidepressant treatment of chronic tension-type headache: a comparison between fluoxetine and desipramine. *Headache*. 1998;38:523–528.
63. Willems EW, Valdivia LF, Saxena PR, et al. Pharmacological profile of the mechanisms involved in the external carotid vascular effects of the antimigraine agent isometheptene in anaesthetised dogs. *Naunyn Schmiedebergs Arch Pharmacol*. 2001;364:27–32.
64. Williamson DJ, Hargreaves RJ. Neurogenic inflammation in the context of migraine. *Microsc Res Tech*. 2001;53:167–178.
65. Wong AH, Buckle CE, Van Tol HH. Polymorphisms in dopamine receptors: what do they tell us? *Eur J Pharmacol*. 2000;410:183–203.