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β -phenylethylamine, a small molecule with a large impact

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Abstract

During a screen of bacterial nutrients as inhibitors of *Escherichia coli* O157:H7 biofilm, the Pr    research team made an intriguing observation: among 95 carbon and 95 nitrogen sources tested, β -phenylethylamine (PEA) performed best at reducing bacterial cell counts and biofilm amounts, when supplemented to liquid beef broth medium. This review article summarizes what is known about PEA.

After some starting information on the chemistry of the molecule, we focus on PEA as a neurotransmitter and then move on to its role in food processing. PEA is a trace amine whose molecular mechanism of action differs from biogenic amines, such as serotonin or dopamine. Especially low or high concentrations of PEA may be associated with specific psychological disorders. For those disorders that are characterized by low PEA levels (*e.g.* attention deficit hyperactivity disorder), PEA has been suggested as a 'safe' alternative to drugs, such as amphetamine or methylphenidate, which are accompanied by many undesirable side effects. On the food processing end, PEA can be detected in food either as a result of microbial metabolism or thermal processing. PEA's presence in food can be used as an indicator of bacterial contamination.

Keywords

neurotransmitter; antimicrobial

Introduction

β -phenylethylamine (PEA) is a small molecule that exhibits an array of intriguing and seemingly unrelated functions. The purpose of this review is to summarize general information about PEA, as well as detailing a selection of the functions, namely its role as a neurotransmitter and in food processing. General information is summarized in Chapter I, including the chemical properties of PEA (1.1), its natural occurrence and biological synthesis (1.2), and its chemical synthesis (1.3). Chapter II describes PEA's functions as a neurotransmitter and details its impact on attention deficit hyperactivity disorder (2.1), depression (2.2), and schizophrenia (2.3) as three examples of psychological disorders. A comparison of PEA's action to that of other trace and biogenic amines is provided (Illustration 3). Finally, Chapter III describes the role of PEA in food processing, starting with its occurrence in fermented food and meat as the result of microbial metabolism (3.1) and its occurrence in chocolate as the result of thermal processing (3.2). The article concludes with the recently described use of PEA as an antimicrobial to be used in the processing of beef meat (3.3).

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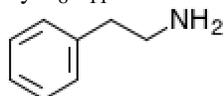
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Throughout this manuscript, we mention companies that sell PEA. We are not in any way affiliated with any of these and do not mean to discriminate. The list of companies is incomplete and exemplary.

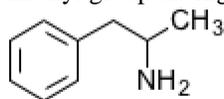
I. General Information

1.1 Chemical Properties of PEA

PEA is known under a variety of names including β -phenylethylamine, β -phenethylamine, and phenylethylamine. According to the International Union of Pure and Applied Chemistry (IUPAC), the proper name of PEA is 2-phenylethylamine. Its molecular formula is denoted by $C_8H_{11}N$:



The general information on and the chemical properties of PEA are summarized in Illustration 1. Briefly, PEA has a molecular weight of 121.17964 g/mol, a high solubility in ddH₂O (Cashin, 1972; Shannon et al., 1982), and a short half life (Shannon et al., 1982). These chemical characteristics impact PEA's biological functions. In particular, the lack of a methyl group distinguishes PEA from its structural relative amphetamine:



1.2 Natural Occurrence and Biological Synthesis of PEA

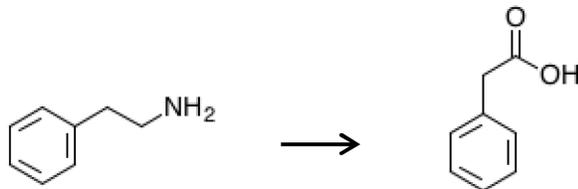
The occurrence of PEA and its derivatives has previously been reviewed (Bentley, 2006). PEA can be found in many algae (Güven et al., 2010), fungi and bacteria (Kim et al., 2012) as well as a variety of different plant species (Smith, 1977). PEA is the decarboxylation product of phenylalanine.



In several bacterial species, the above reaction is catalyzed by the enzyme tyrosine decarboxylase, which also converts tyrosine to another trace amine, tyramine (Marcobal et al., 2012; Pessione et al., 2009). Intriguingly, PEA synthesized by fungi and bacteria can also be found in food products (Onal et al., 2013), where it serves as an indicator of food quality and freshness. This includes the Korean natto (Kim et al., 2012) and commercial eggs (Figueiredo et al., 2013). Another food that contains PEA is chocolate, where it is not produced by bacteria, but during the thermal processing of cocoa (Granvogl et al., 2006). As one example of PEA in plants, PEA can be found in members of the family *Leguminosae*, which is the second-largest family of seed plants and is comprised of trees, shrubs, vines, herbs (such as clover), and vegetables (such as beans and peas). The various different species found within this family have been used as food, green manure, and for medicinal purposes (Sanchez-Blanco et al., 2012). A hypothesis was formulated that plant synthesized PEA may serve as a defense mechanism against insects and foraging animals (Smith, 1977).

PEA has also been found in the brains of humans and other mammals (Paterson et al., 1990; Philips et al., 1978), which is facilitated by its high solubility in plasma and its ability to cross the blood-brain barrier (Oldendorf, 1971). Like its α -methylated derivative, amphetamine, PEA has stimulant effects which lead to the release of so called biogenic

amines, including dopamine and serotonin (Bailey et al., 1987; Rothman & Baumann, 2006). Unlike amphetamine, PEA has difficulties maintaining high concentrations in the human body, due to its oxidative deamination to phenylacetic acid by the enzyme B monoamine oxidase (MAO) (Yang & Neff, 1973). Phenylacetic acid, has an effect that is similar to the activity of the natural endorphins, an effect that is known as a “runner’s high”.



Due to its impact on the levels of several ‘feel good hormones’ (see above), PEA has recently gained popularity as a nutritional supplement that is sold by numerous health stores to improve mood. Since it also decreases the amount of water intake, it aids weight loss efforts (Hoffman et al., 2006). Naturodoc describes PEA as “an immediate shot of happiness, pleasure, and emotional wellbeing” (<http://www.naturodoc.com>), Serenity Station describes the effects of PEA as “feeling happier, more alive and even having a better mood and attitude” (<http://www.serenity-station.com>). Altogether, PEA appears to have a number of positive effects on human health without the risks of its structural relatives.

1.3 Chemical Synthesis of PEA

Two different pathways that lead to the chemical synthesis of PEA have been established in the 40s and 50s of the past century. First, PEA is produced by reduction of a nitrile into an amine (Robinson & Snyder, 1955). Specifically, 1 kg of benzyl cyanide is mixed with 1 tablespoon of the Raney-Nickel catalyst in a calorimeter bomb. The formation of secondary amines in this reaction is reduced by the addition of ammonia. The reaction occurs at 13.9 Mpa and 130°C under hydrogen, the cooled down liquid is removed from the catalyst by filtration. This procedure has a yield of about 860 to 890 g of PEA, equaling 83 to 87%.

A second, simpler way of producing PEA is to reduce ω-nitrostyrene with lithium aluminum hydride in ether (Nystrom & Brown, 1948). The experimental procedure that employs the use of lithium aluminum in reduction reactions follows the mechanism used in a Grignard synthesis. ω-nitrostyrene is added to the previously prepared lithium aluminum hydride in ether while stirring. This results in an alcoholate precipitate, which thickens the solution requiring more ether to be added. Finally, using acid hydrolysis the metal alcoholate is decomposed and the product can be isolated and extracted from the ether.

Recent literature focuses on the biological synthesis of PEA, rather than the chemical one. 1-phenylethylamine can be synthesized by *Escherichia coli* overexpressing ω-transaminase (Cardenas-Fernandez et al., 2012). Likewise, the PEA biosynthetic enzyme from *Enterococcus faecium* can be expressed in *E. coli*, which leads to large amounts of L-phenylalanine and tyrosine decarboxylase activity (Marcobal et al., 2006). Intriguingly, PEA can serve as a substrate for the synthesis of other drugs, such as sulfonamides that are being used as antimicrobials (Rehman et al., 2012).

II. PEA as a Neurotransmitter

PEA is a member of the so called trace amines (reviewed by Premont et al., 2001). The expression ‘trace amine’ is used to refer to a group of amines that occur at much lower intra- and extra-cellular concentrations than the chemically and functionally related biogenic amines and neurotransmitters epinephrine, norepinephrine, serotonin, dopamine, and

histamine. The molecular mechanism of the trace amines involves binding to a novel G protein-coupled receptor, called TAAR (trace amine-associated receptor) (Borowsky et al., 2001; Bunzow et al., 2001), the most studied of which, TAAR1, can be activated by the drug amphetamine as well (Borowsky et al., 2001). The downstream events that follow the initial interaction of PEA and TAAR1 are not nearly as well understood as the receptors and their various ligands themselves (Zucchi et al., 2006), it is however believed that binding of PEA to TAAR1 results in an alteration of the monoamine transporter functions, which leads to inhibition of the re-uptake of dopamine, serotonin, and norepinephrine (Xie & Miller, 2008). Eventually, this will cause an increased concentration of these neurotransmitters at the synapses. A similar increase in the synaptic concentrations of dopamine can be accomplished by blocking the dopamine transporter directly. Methylphenidate is an example of a class of drugs that can perform this blockage (Gatley et al., 1999).

The chemical properties of the biogenic amines, trace amines, and structurally related drugs are summarized in Illustration 2. Illustration 3 is a graphic representation of the regulatory pathway from the trace amine PEA to the increased concentration of the biogenic amines and neurotransmitters dopamine and serotonin. The effects of the drugs amphetamine and methylphenidate are included. Chapter II summarizes the impact of PEA on three psychological disorders, attention deficit hyperactivity disorder, depression, and schizophrenia.

2.1 Attention deficit hyperactivity disorder

A common disease that an estimated 4-9% of young children suffer from is attention deficit hyperactive disorder (ADHD) (reviewed by (Cormier, 2008). ADHD is a chronic child hood disorder which is characterized by a number of behavioral symptoms, including a small attention span, increased frustration, distractibility, and often depression and anxiety (American Psychiatric Association, 2000). ADHD often is paralleled by co-existing psychiatric disorders and patients can have problems that are attributable to ADHD way into their adulthood (Brassett-Harknett & Butler, 2007). While diagnosis of ADHD is usually done by analysis of the symptoms (American Psychiatric Association, 2000), PEA was recently described as a biomarker for ADHD (Scassellati et al., 2012). This novel discovery will improve the confidence of the diagnostic efforts, possibly leading to reduced misdiagnosis and overmedication. Specifically, the urinary output of PEA was lower in a population of children suffering from ADHD, as compared to the healthy control population, an observation that was paralleled by reduced PEA levels in ADHD individuals (Baker et al., 1991; Kusaga, 2002). In a consecutive study (Kusaga et al., 2002), those of the children suffering with ADHD were treated with methylphenidate, also known as Ritalin. Patients whose symptoms improved in response to treatment with methylphenidate had a significantly higher PEA level than patients who did not experience such an improvement in their condition (Kusaga et al., 2002).

While this is encouraging by the first view, amphetamine and methylphenidate based drugs demonstrate many undesirable side effects, including mild headaches, nausea, insomnia, and constipation. Overdose, whether accidental or intentional, of any of the amphetamine of methylphenidate drugs has been associated with cardiovascular effects, which was attributed to increased levels of extracellular dopamine, norepinephrine, and serotonin (Spiller et al., 2013). While the connection between stimulant drugs as a treatment for ADHD and cardiovascular disease at this time still appears controversial (Olfson et al., 2012), naturopathic professionals have started to recommend PEA as a treatment for ADHD because of the assumed lack of side- and long-term effects (for an example, see <http://www.neuroconcepts.memberlodge.org/resources/Documents/Phenylethylamine>).

2.2 Depression

Depression is a very common, sometimes serious disease that affects a wide range of people. It is currently the second leading cause of disability in the age group of 15 to 44. By the year 2030, depression is predicted to be the primary cause of disability (World Health Association, 2008). While depression may be most common in the age group of 15 to 44, it can affect people of all ages and backgrounds. Among the characteristics of depression that were summarized in a review article (Voinov et al., 2013), women are 50% more likely to be affected by depression than men and depression can shorten a person's life by 25-30 years (Voinov et al., 2013).

Most medication that is currently available is about 80% effective for those suffering from depression (Voinov, 2013). Selective serotonin re-uptake inhibitors (SSRI) are the most popular antidepressant prescribed worldwide (Artigas, 2013). SSRI function by blocking the serotonin transporter and thus inhibiting the re-uptake of serotonin (Gutman & Owens, 2006; Peremans et al., 2006). This will result in an increase of the synaptic concentration of serotonin (see Illustration 3). However, SSRI act very slowly at the beginning of the treatment, while exhibiting a range of side effects upon long term use. These long-term side effects include insulin resistance (Chen et al., 2012), bone density loss (Haney et al., 2007), and some poorly understood effects on the offspring of mothers with maternal depression (Olivier et al., 2013). Overall, the question has been raised where to go from here (Artigas, 2013) and a need for the novel approaches to depression treatment is evident. The study by Xie and Miller (Xie & Miller, 2008), that had shown that PEA altered the serotonin transporter by interacting with TAAR, may point towards a safer alternative to SSRI treatment of depression in the form of PEA.

2.3 Schizophrenia

Schizophrenia is rare mental disorder that could potentially be related to PEA. About 1% of the world's population is affected by schizophrenia, which is characterized by problematic thinking and perception (Rossler et al., 2005). Typically, schizophrenia starts around adolescence and will stay with the patient for the rest of their life, though life expectancy can be largely reduced due to suicide. An additional complication is community attitude because many people perceive schizophrenic patients as potentially dangerous (Stuart & Arboleda-Florez, 2001).

There are different ideas on how one develops schizophrenia. One hypothesis proposes that dopamine contributes to the development of schizophrenia (Howes & Kapur, 2009). In agreement with this hypothesis, patients suffering from schizophrenia are hyper-sensitive to drugs (*e.g.* methylphenidate) that block the dopamine receptor (Lieberman et al., 1987). A new perspective is given by the TAAR1 receptor (Illustration 3). TAAR1 activation improves the symptoms that are associated with both schizophrenia and depression (in rodent and primate models), without causing the range of negative effects that result from direct blockage of the dopamine receptor (Revel et al., 2013).

Among other factors that may contribute to schizophrenia are inflammatory cytokines (Zakharyan & Boyajyan, 2013) and phospholipase (Koh, 2013). Altogether, schizophrenia may be the most complex of the here discussed psychological disorders and it is quite apparent that many factors contribute to its development.

III. PEA and other Amines in Food

PEA and other amines can be found in food as a result of two fundamentally different processes, metabolic activity of bacteria (3.1) or thermal processing of the food (3.2). In the cases of metabolic activity, amines can be used as a marker for contamination of food by the

respective bacteria. Most recently, it has been found that PEA can be added to food intentionally to reduce bacterial cell counts of *E. coli* O157:H7 (3.3).

3.1 PEA and other amines in food as a result of microbial contamination

Some foods that contain microorganisms can release high levels of amines, including the trace amines PEA, tyramine, and tryptamine, the biogenic amine histamine, and the polyamines putrescine and cadaverine (Shalaby, 1996). Such amines are formed by bacteria of the genera *Lactobacillus*, *Clostridium*, *Pseudomonas*, and *Enterobacteriaceae* that contain amino acid decarboxylases which remove an α -carboxyl group from the respective amino acid (Giraffa, 2003; Shalaby, 1996).

This increased concentration of amines is due to bacterial metabolic processes and is commonly associated with foods and food products made through the process of fermentation (Bunkova et al., 2013). A good example of this is the ‘cheese reaction’ which refers to high levels of tyramine as a result of elevated levels of tyrosine in cheese that has had increased storage times at temperatures higher than recommended by the producer. As mentioned earlier (Chapter 1.2), PEA can be a by-product of the tyrosine decarboxylase reaction because the same enzyme that is capable of converting tyrosine to tyramine can also metabolize phenylalanine to PEA (Marcobal et al., 2012). In individuals taking monoamine oxidase inhibiting drugs, the ‘cheese reaction’ can result in a hypertensive crisis (Boulton et al., 1970; Da et al., 1988; Deftereos et al., 2012).

A second group of food or food product that contains elevated levels of amines is meat and/or fish (Kulawik et al., 2013; Li et al., 2012; Liu et al., 2013), where amine production is part of the food spoilage reaction and can be used as an indicator of food freshness and quality. Specifically, bacteria from the families *Enterobacteriaceae* and *Pseudomonadaceae* can produce cadaverine and putrescine in spoiled turkey meat. It was suggested to use tyramine, putrescine, and cadaverin to quantify meat freshness (Fraqueza et al., 2012). In vegetables, high levels of tyramine were only seen in brine, unless the vegetables were contaminated prior to processing or the temperature and storage time were extreme (Moret et al., 2005).

Since elevated levels of amines are usually an indicator of food spoilage, it is possible use detection of amines as an indicator of food freshness. One such techniques is thin-layer chromatography to separate and identify amounts of tyramine and PEA (Garcia-Moruno et al., 2005).

3.2 PEA in chocolate as a result of thermal processing

The connection between “food and mood” has been recognized long time ago (Ottley, 2000). In particular, chocolate craving has been the focus of intense research (Durkin et al., 2012; Hormes & Timko, 2011; Werthmann et al., 2013). Lately, the combination of chocolate with coffee has been proposed as “a novel elixir for a long and happy life” (Dal Moro, 2013). Besides a number of other beneficial substances (*e.g.* antioxidants), chocolate also contains trace amounts of PEA (Ziegleder et al., 1992), a result of the thermal processing and fermentation of cocoa (Granvogl et al., 2006). Since we mentioned earlier that PEA is promoted to aid weight loss, one may conclude that if a person eats enough chocolate they will lose weight! Careful readers: in a study that attempted to determine the concentration of PEA in chocolate, the detection limit for PEA was 3 mg/kg of chocolate and the concentration of PEA in their chocolate samples was below this limit (Pastore et al., 2005). In contrast, the recommendation for PEA as a nutritional supplement is currently 500 mg/day (for an example, please, see <http://www.bodybuildingwarehouse.com>). This means

that the concentration of PEA in chocolate is not high enough to induce weight loss, so eating chocolate will still lead to weight gain.

One interesting controversy around chocolate and PEA is the question whether chocolate can cause migraine and whether this may be due to PEA. Of course, food in general can trigger migraine (Finocchi & Sivori, 2012). Also, individual studies point towards chocolate as one of those foods (Fukui et al., 2008), but other studies are in contrast with these findings (Marcus et al., 1997). The fact that other foods that contain PEA, tyramine, or histamine (*e.g.* cheese and wine) may also trigger migraine (Werthmann et al., 2013) raised the question whether dietary amines may be responsible for this response. This question is justified, considering that PEA causes the release of nor-epinephrine into the synaptic space, which consequently constricts the aorta and the coronary arteries (Broadley et al., 2009). However, results among various studies are inconclusive (Jansen et al., 2003) and the connection between chocolate and migraines remains a mystery.

3.3 PEA as an anti-microbial

In Chapter 3.1, we discussed contamination and food spoilage by bacteria. One such initially contaminated food can cross-contaminate additional food products through the food processing chain because of the bacteria's ability to attach to food contact surfaces and form biofilm (Giaouris et al., 2013). Recent research advances that are aimed at the prevention of biofilm formation include the manipulation of the bacteria's bacterial signal transduction pathways, including quorum sensing (Bassler, 2010) and two-component signaling (Lynnes et al., 2013b). One such environmental signal that bacteria can respond to is PEA, whose signal transduction pathway may include the flagellar and global regulator complex FlhD/FlhC (Stevenson et al., 2013). In our own research lab, PEA was found to be most inhibitory of the 95 carbon and 95 nitrogen sources screened for their effect on *E. coli* O157:H7 growth, bacterial cell counts, and biofilm amounts. Bacterial cell counts of *E. coli* O157:H7 were determined from beef meat pieces that were treated with different dilutions of PEA and subsequently inoculated with the bacteria; this resulted in a 90% reduction of bacterial cell counts when the beef was treated with a concentration of PEA at 150 mg/ml. This demonstrates how PEA could be good candidate as a beef treatment to reduce *E. coli* O157:H7 bacterial infections associated with contaminated meat (Lynnes et al., 2013a).

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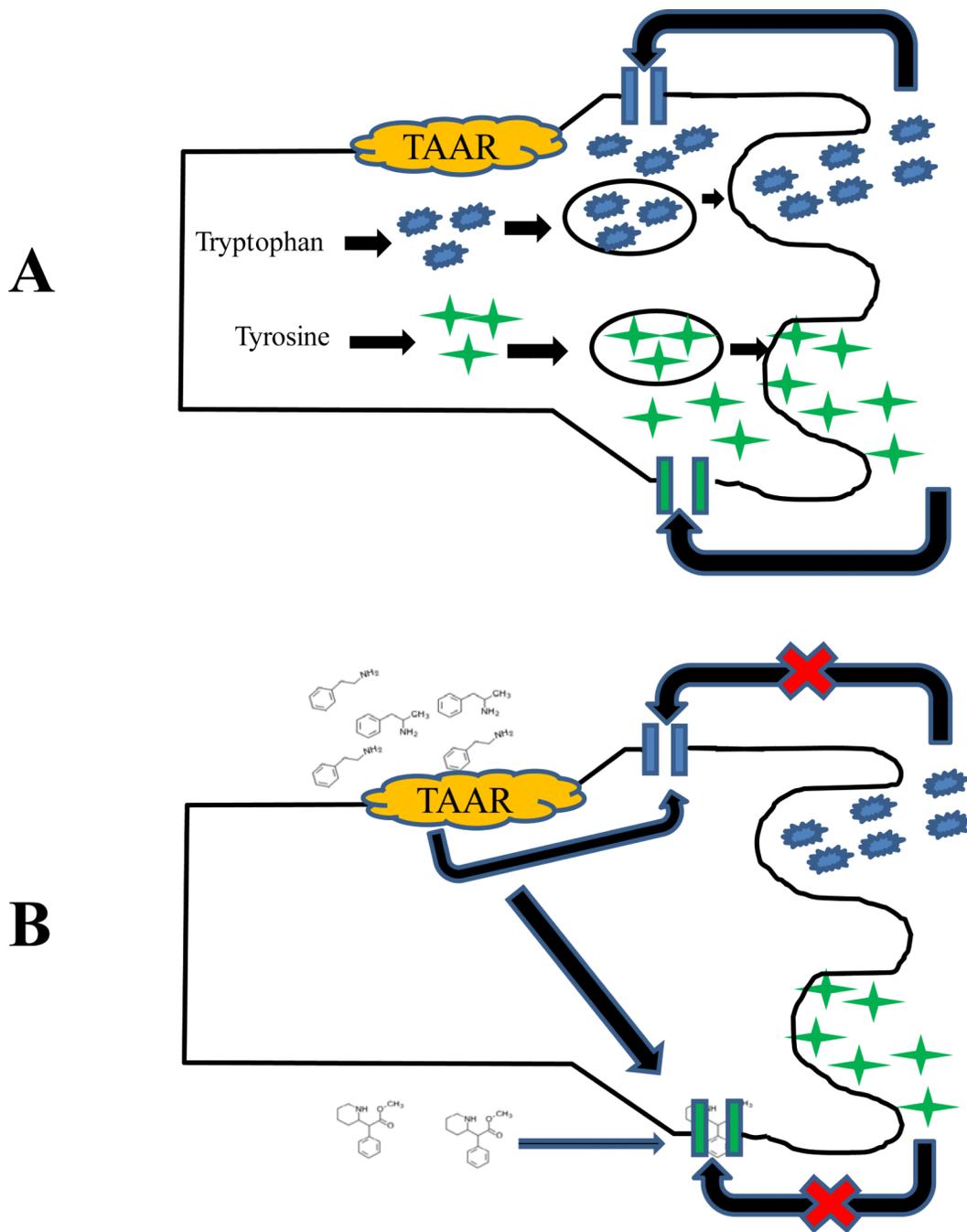


Illustration 3. Schematic of the inhibition of the dopamine and serotonin transporters by PEA, amphetamine, and methylphenidate

Panel A shows the normal action of release and re-uptake of the biogenic amines dopamine and serotonin. Panel B shows the modulation of the monoamine re-uptake transporters by PEA and amphetamine through TAAR, as well as the blockage of the dopamine transporter by methylphenidate.

Serotonin , dopamine , serotonin receptor , dopamine receptor  PEA , amphetamine , methylphenidate 

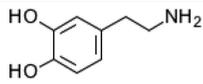
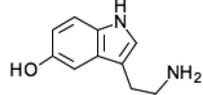
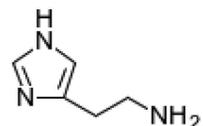
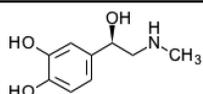
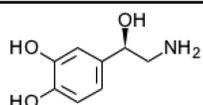
Illustration 1

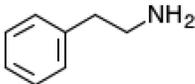
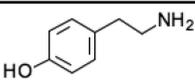
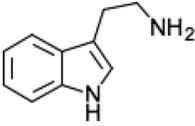
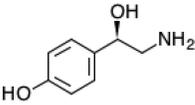
General information on and chemical properties of PEA

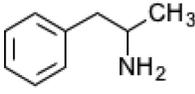
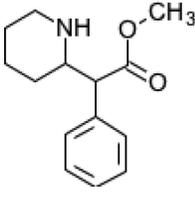
	Solvent independent properties	Solvent dependent properties			Reference
		In ddH ₂ O	In lipid	In Plasma	
Alternative names	phenylethylamine, β-phenylethylamine, 2-phenylethylamine, benzeneethanamine, phenethylamine, β-phenethylamine, 2-phenethylamine	NA	NA	NA	http://pubchem.ncbi.nlm.nih.gov
Molecular Formula	C ₈ H ₁₁ N	NA	NA	NA	http://pubchem.ncbi.nlm.nih.gov
Molecular weight	121.17964 g/mol	NA	NA	NA	http://pubchem.ncbi.nlm.nih.gov
Companies that sell PEA	Forest Health, Vitacost, Amazon, Walmart	NA	NA	NA	NA
Toxicity	Mouse LD ₅₀ (oral) 400 mg/kg	NA	NA	NA	MSDS, TCI America
Solubility	NA	High solubility	Low solubility	High solubility	MSDS, TCI (Cashin, 1972), (Shannon et al., 1982)
Half life	NA	NA	NA	~5-10min	(Shannon et al., 1982)

Illustration 2

Properties and functions of biogenic amines, trace amines and structurally related drugs

I. Biogenic Amines			
Name	Structure	Synthesized from:	Functions
Dopamine		L-Tyrosine	<u>CNS</u> : regulates movement <u>Blood vessels</u> : vasodilation
Serotonin		L-Tryptophan	<u>CNS</u> : mood, sleep, memory, and learning <u>Gut</u> : intestinal movement
Histamine		Histidine	<u>CNS</u> : sleep <u>Immune system</u> : inflammatory response (allergy)
Epinephrine (Adrenaline)		Tyrosine via dopamine and norepinephrine	<u>CNS</u> : stress response (fight or flight) <u>Blood vessels</u> : vasoconstriction
Nor-epinephrine (Nor-adrenaline)		Tyrosine via dopamine	<u>CNS</u> : heart contractions (heart rate), vascular tone (blood pressure)

II. Trace Amines			
Name	Structure	Synthesized from:	Protein Targets
β -phenylethylamine (PEA)		L-Phenylalanine	TAAR1
p-Tyramine		L-Tyrosine	TAAR1; dopamine receptor
Tryptamine		L-Tryptophan	5-hydroxytryptamine receptor; NFκB1; Cytochrome P450
Octopamine		Tyrosine via tyramine	TAAR1

III. Structurally related Drugs			
Name	Structure	Synthesized from:	Function
Amphetamine		Ephedrine	A stimulant of the central nervous system that mimics the effects of dopamine, epinephrine, and norepinephrine.
Methylphenidate		Piperidine derivative	A stimulant of the central nervous system that are used to treat attention deficit disorders and narcolepsy.