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MINI-REVIEW

Ethanolamine: A Potential Promoiety with Additional Effects in the Brain

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Abstract: Ethanolamine is a bioactive molecule found in several cells, including those in the central nervous system (CNS). In the brain, ethanolamine and ethanolamine-related molecules have emerged as prodrug moieties that can promote drug movement across the blood-brain barrier. This improvement in the ability to target drugs to the brain may also mean that in the process ethanolamine concentrations in the brain are increased enough for ethanolamine to exert its own neurological actions. Ethanolamine and its associated products have various positive functions ranging from cell signaling to molecular storage, and alterations in their levels have been linked to neurodegenerative conditions such as Alzheimer's disease. This mini-review focuses on the effects of ethanolamine in the CNS and highlights the possible implications of these effects for drug design.

Keywords: Ethanolamine, brain, CNS, phospholipids, prodrug, synaptic, neuromodulator.

1. INTRODUCTION

Targeting drugs to the central nervous system (CNS) is difficult, mostly because of the presence of the blood-brain barrier; a physiological gatekeeper with selective permeability which protects the brain from potentially dangerous substances and maintains a stable environment for optimal neural performance [1, 2]. Depending on their structures, some drugs are small enough or lipophilic enough to pass through the blood-brain barrier via simple diffusion, whereas several others have to hitch a ride into the CNS tissues via carriers or transporters. For drugs whose structures do not facilitate either of these mechanisms, accessing the CNS can be slow or even non-existent, thereby impeding advancements in neurotherapeutics for many CNS disorders [3]. One way of overcoming this barrier is to complex the drug with a molecule such as ethanolamine to create a prodrug that is lipophilic and/or has designated carriers that allow it to cross the blood-brain barrier. After crossing the blood-brain barrier, this prodrug is hydrolyzed within the CNS to release the active drug.

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In recent years, ethanolamine and ethanolamine-related molecules (such as monomethylethanolamine and dimethylethanolamine) have emerged as prodrug moieties that promote movement across the blood-brain barrier. These chemicals have been complexed with drugs such as the non-steroidal anti-inflammatory drugs dexibuprofen [4, 5] and flurbiprofen [6] or the thyromimetic sobetirome [7, 8] to form ethanolamine derivatives. The drug complexes speed up and, in some cases, increase their movement into the CNS, thereby altering the plasma/ cerebrospinal fluid (CSF) ratios for the drugs. This process allows greater accumulation of the drug in the brain at lower doses, and reduces the dose needed for drug efficacy. A lower effective dose means that side effects associated with these drugs are kept to a minimum. The literature on these ethanolamine derivatives highlight ethanolamine's relative lack of toxicity as an advantage as a prodrug moiety [6]. Although this may be true, ethanolamine is not without effects in the CNS. Considering the hydrolysis half-life of some of these prodrugs is quite short in plasma (>12 min) but relatively long, in brain homogenates (>4hr) [5], its accumulation could, in turn, modulate brain function. This review builds on recent reviews [9, 10] to focus on the effects of ethanolamine in the brain in both health and disease and highlight the possible implications of these effects for drug design.

2. ETHANOLAMINE

Ethanolamine (NH_2-CH_2-CH_2-OH), known to some in academia and industry as a detergent and emulsifier, is a biogenic amine found throughout the body. The body is not capable of *de novo* synthesis of ethanolamine and so the amine must be sourced from the diet, either as free ethanolamine or as phosphatidylethanolamine (PE).

The exact details of the mechanisms by which ethanolamine, a hydrophilic molecule [11], enters cells remains elusive and may vary between cell types. In neuronal and glial cells isolated from the brains of chick embryos, uptake of ethanolamine from the culture medium appeared to be saturable, required a sodium ion gradient, and was inhibited by cotreatment with monomethyl- and dimethyl-ethanolamine and choline [12]. This may suggest the existence of a form of secondary active transport shared by ethanolamine-related molecules and choline. Similarly, in fibroblasts isolated from healthy adults and in isolated cells from the COS-7 cell line, the choline transporter like protein 1 (CTL-1) and, to a lesser extent, choline transporter like protein 2 (CTL-2) were shown to act as a shared transport mechanism for ethanolamine and choline. Interestingly, two patients with mutations in the gene coding for CTL-1 (SLC44A1) presented with neurodegeneration with brain iron accumulation and the effect of these mutations in fibroblasts was decreased SLC44A1 expression resulting in low membrane PE content [13]. Transport via CTL-1 is dependent upon a hydrogen ion gradient often created by the sodium-hydrogen ion exchanger, suggesting that ethanolamine is moved across the membrane via a secondary active transport mechanism using a hydrogen ion gradient. Li *et al.* [4] demonstrated that the novel ethanolamine derivatives of dexibuprofen were most likely transported into the brain via two different mechanisms; derivatives that incorporated primary and secondary amine modifications seemed to enter via simple passive diffusion, whereas those containing tertiary amine modifications could enter the brain via active transport mechanisms. Interestingly, although CTL-1 and CTL-2 are expressed in the brain microvascular endothelial cells that form part of the blood-brain barrier [14], neither seemed to be a candidate for the transport of the ethanolamine derivatives containing tertiary amine modifications.

Once inside cells, ethanolamine provides the building blocks for ethanolamine phospholipids (described below) as well as certain neurotransmitters, which are synthesized in the cells. Although the effects of exogenous ethanolamine on humans has not been assessed, animal studies demonstrate that exogenous ethanolamine has a half-life of 19 days and moves from the blood to the intracellular compartment, with minimal amounts remaining in the blood 24 hr after administration [15]. Furthermore, exogenous ethanolamine can increase both plasma and extracellular ethanolamine in the brain in a dose-dependent manner [16]. Exogenous ethanolamine also increases levels of ethanolamine phospholipids in brain tissue [16]. Baseline plasma ethanolamine levels seem to vary with age, with neonates having approximate plasma levels greater than 25 μM, whereas adults have less than 15 μM [17]. The increased ethanolamine in the blood of babies and the high ethanolamine content in breast milk [18] as well as the known ability of ethanolamine to act as a mitogen [19] may suggest a role for ethanolamine in growth and development.

3. ETHANOLAMINE PHOSPHOLIPIDS

Ethanolamine phospholipids are key components of biological membranes which play a role in many vital cell processes. In general, phospholipids are composed of a glycerol attached to two fatty acids and a polar head group. Ethanolamine forms part of the polar head group in two types of phospholipids; the diacyl-phospholipid phosphatidylethanolamine (PE), and the plasmalogen plasmenylethanolamine (PEP).

3.1. SYNTHESIS OF ETHANOLAMINE PHOSPHOLIPIDS

All cells are capable of synthesizing ethanolamine phospholipids for incorporation into their cell membrane. Ethanolamine diacyl-phospholipids are synthesized via three mechanisms: the Kennedy pathway; phosphatidylserine decarboxylation; and base exchange reactions. The Kennedy pathway, also known as the cytidine diphosphate (CDP): ethanolamine pathway, occurs in the cytoplasm and endoplasmic reticulum. In this pathway, ethanolamine in the cytoplasm is phosphorylated by ethanolamine kinase to form phosphoethanolamine. Next, cytidine triphosphate (CTP): ethanolaminephosphate cytidyltransferase (Pcyt) catalyses the reaction of CTP with phosphoethanolamine to form CDP ethanolamine. Finally, CDP ethanolamine then moves into the endoplasmic reticulum where it combines with diacylglycerol to form PE. The decarboxylation of phosphatidylserine occurs in the mitochondria to form PE and is catalysed by an enzyme only found in mitochondrial inner membranes called phosphatidylserine decarboxylase [20]. Base exchange reactions occur in the endoplasmic reticulum. These reactions involve the substitution of either choline or serine with ethanolamine or vice versa and are catalysed by phosphatidylserine-synthase-2 [21].

Synthesis of ethanolamine plasmalogens begins in the peroxisome with dihydroxyacetone phosphate and after a series of reactions 1-0-alkyl-2-hydroxy-sn-glycerophosphate is formed. This molecule then enters the endoplasmic reticulum where it is further modified and combined with phosphoethanolamine to form PEP [For detailed review, see 10, 22].

3.2. FUNCTIONS OF ETHANOLAMINE PHOSPHOLIPIDS

As a major component of cell and organelle membranes, phospholipids play a major role in limiting movement of substances into and out of cells and organelles. Cell- and organelle membranes are asymmetric with increased quantities of ethanolamine phospholipid on cytoplasmic and inner membranes, respectively. This asymmetry contributes to membrane curvature and cell signaling [As reviewed by 23]. As well as the effects imposed by their localisation within the membrane, ethanolamine phospholipids also exhibit effects related to their general structure. They are cone shaped, with a head group whose cross-sectional area is less than that of the

acyl chains, and therefore generally prefer to adopt non-bilayer structures [24]. This counterintuitive incorporation of a non-bilayer preferring lipid in a lipid bilayer creates curvature stress which is proposed to be used for events that require changes in membrane structure such as fusion and fission events [25-28].

The non-structural functions of ethanolamine phospholipids in general remained elusive for a long time. However, in recent years, plasmalogens, in particular, have been implicated in reactive oxygen species (ROS) scavenging. In plasmalogens, the first carbon of the glycerol molecule is attached to a fatty acid via a vinyl-ether bond, which is known to scavenge oxygen radicals [29], and as a result plasmalogens scavenge oxygen radicals significantly faster than other lipids [30]. In addition, cells lacking plasmalogens have increased sensitivity to chemical hypoxia induced by actinomycin A or cyanide compared to wild types [31]. However, these functions seem to be attributable to plasmalogens in general and not a function of the ethanolamine headgroup. Besides plasmalogens, experiments in yeast and mammalian cell culture have suggested that PE is involved in autophagy and it is proposed that it may be important in halting the aging process [32, 33].

Ethanolamine phospholipids play an important role in cell signaling by acting as a source of components for lipid-protein anchors and second messengers. Phosphatidylethanolamine provides ethanolamine for the synthesis of glycosylphosphatidylinositol which forms lipid anchors for membrane proteins [34]. It also acts as a store of signaling molecules, such as arachidonic acid [35] and the endogenous cannabinoid anandamide [36] .

4. ETHANOLAMINE AND ITS COMPOUNDS IN THE BRAIN

The resting levels of free ethanolamine in the brain are 12.03-53.1ug/ml equivalents [37] and approximately 8.43 (2.62-14.24) uM in the CSF [38]. The majority of phospholipids in the brain are ethanolamine phospholipids, which represent 55% of all phospholipids. Of the ethanolamine diacylphospholipids, those containing stearic acid, docosahexaenoic acid (DHA) and arachidonic acid are the most abundant. The ethanolamine plasmalogen content in the brain is composed mainly of stearic acid, arachidonic acid, DHA, vaccenic acid and oleic acid [39]. Ethanolamine phospholipids are also found in mitochondrial membranes and in the brain, these membranes are enriched in phosphatidylethanolamines and ethanolamine plasmalogens. Although the content of polyunsaturated fatty acids of ethanolamine phospholipids in the brain is high (65%), it is even higher in brain mitochondria (86%) and predominantly include arachidonic acid and DHA [40]. The ethanolamine phospholipid constitution differs among the different cell types in the brain [41] and between the white and gray matter [42]. The abundance of ethanolamine phospholipids in brain tissue therefore creates a platform for the possible modulation of physiological and pathological processes in the brain.

4.1. ETHANOLAMINE AS A NEUROMODULATOR?

Cellular depolarisation causes release of ethanolamine from mouse synaptosomes and synaptoneurosomes, and this release appears to be calcium dependent [43]. It was confirmed by various fractionation methods and solubility assays that the substance released at the synapses was indeed free ethanolamine, and not ethanolamine being released as part of phospholipids or as a substance linked to fatty acids (as in anandamide), or linked to a peptide or protein or as phosphoethanolamine, methylethanolamine, dimethylethanolamine, choline or acetylcholine [43]. These findings prompt key questions regarding the role of ethanolamine in the synaptic region; how is it released at the synapse and what is its function?

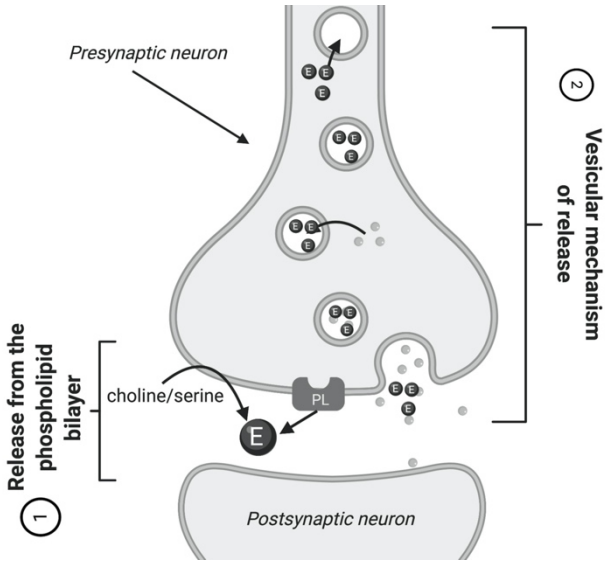


Figure 1: **Proposed mechanisms of ethanolamine release.** 1. Ethanolamine is proposed to be released directly from the ethanolamine phospholipids in the cell membrane either via base exchange reactions or via the action of phospholipases.2. Ethanolamine enters the vesicle and becomes protonated. This causes an increase in neurotransmitter uptake. so that ultimately both ethanolamine and neurotransmitter are released from the cell via exocytosis. E= ethanolamine, PL= phospholipase. This image was created with BioRender.com.

In terms of ethanolamine release at the synapse, it is possible that ethanolamine could be released directly from the synaptosomal plasma membrane. Two mechanisms are possible here, either through the base exchange reactions [44] that occur in these membranes or through the release of ethanolamine from phospholipids by a phospholipase. Perschak *et al.* [45] found that ethanolamine released at synapses is not mediated by base exchange reactions, however they could not rule out phospholipase-mediated release of ethanolamine. Furthermore, the calcium-dependent nature of ethanolamine release at synapses may suggest a vesicular mechanism of release [43]. In line with this, a third possible mechanism of release could involve the incorporation of free ethanolamine into synaptic vesicles followed by its release into the synaptic cleft. Evidence in favour of this mechanism suggests that ethanolamine enters synaptic vesicles where it becomes protonated, thereby increasing the membrane

potential of the vesicle and subsequently increasing uptake of neurotransmitters [46]. Ultimately, this leads to increased release of both ethanolamine and neurotransmitter in response to depolarisation. These findings become even more interesting when one considers that ethanolamine, independent of depolarisation or calcium levels, at concentrations from 0.31mM to 5mM, also increases vesicular release from synaptosomes [46]. Through both the increased loading of neurotransmitter into vesicles and the increased release of synaptic vesicles, ethanolamine levels have great potential to regulate synaptic activity.

Stimulus applied	Effect	Sample/model	Ref
Electrical	Ethanolamine release	Pigeon optic tectum	[49]
Ethanolamine	Potentiation of glutamate induced excitation and GABA inhibition	Pigeon optic nerve	[49]
Krebs incubation	Ethanolamine release	Rat brain homogenate	[50, 51]
Ethanolamine	GABA aminotransferase inhibition	Rat brain in vivo and in vitro	[52]
Electrical	Ethanolamine release	Rat cortico-pontine tract	[45]
Chemically induced depolarisation	Ethanolamine release (calcium-dependent)	Mouse brain synaptosomes & synaptoneurosomes	[43]
Ethanolamine	Aspartic acid release; Increased release of synaptic vesicles	Mouse brain synaptosomes	[46]
Chemical (L-serine)	Ethanolamine and phosphoethanolamine release	Rabbit hippocampus	[47]
Ethanolamine	Glutamate and aspartate release (NMDA receptor dependent)	Rabbit hippocampus	[47]
High potassium-induced depolarisation	Ethanolamine released	Trout saccular tissue	[53]
High potassium-induced depolarisation	No ethanolamine released	Rat substantia nigra	[54]
Ethanolamine	Acetylcholine release	Rat hippocampal slices	[55]
Ethanolamine	Acetylcholine synthesis	Human neuroblastoma L-AN-2 cells	[56]
Ethanolamine	Modulation of potassium channels and calcium transient	Neonatal rat cultured dorsal root ganglion neurons	[57]

Table **1** Ethanolamine as a neuromodulator.

While the calcium-induced release of ethanolamine in synaptic vesicles is reflective of neurotransmitter activity, in general, it seems to act as a neuromodulator at the synapse (Table **1**). Administration of ethanolamine (10mM) or Serine (10mM) via a microdialysis probe for 20 min to the brains of non-anaesthetized rabbits caused up to 3 times as much ethanolamine in the extracellular fluid (ECF). This in turn led to increased levels of glutamate and aspartate [47]. The release of aspartate was acute, disappearing upon removal of ethanolamine, and serine whereas the release of glutamate was sustained for 20 min after removal of the amino acids. The aspartate release appeared to be mediated by activation of NMDA receptors. It is unclear whether ethanolamine affects NMDA receptors as a coagonist or by altering the membrane structure around the receptor. Although ethanolamine in these studies was given at supraphysiological concentrations the concentration of ethanolamine in the ECF is similar to those found in some pathophysiological situations in the brain [48].

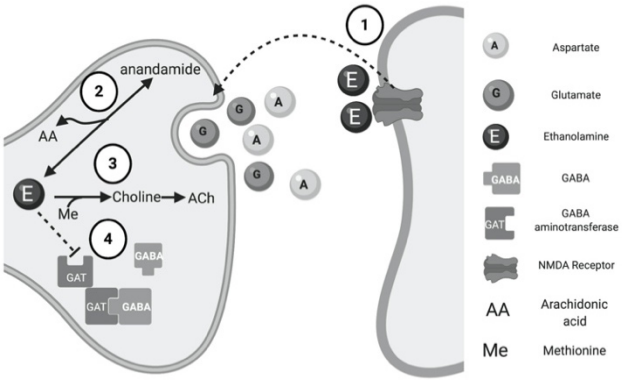


Figure 2: **Ethanolamine as a neuromodulator.** 1 Ethanolamine increases glutamate & aspartate release via NMDA receptors. 2. Ethanolamine is a byproduct of anandamide hydrolysis but in certain circumstances can combine with arachidonic acid to form anandamide. 3. Ethanolamine can be methylated to form choline which is necessary for acetylcholine formation. 4. Ethanolamine increases GABA by inhibiting its conversion by GABA aminotransferase. This image was created with BioRender.com.

4.2 ETHANOLAMINE AS A NEUROTRANSMITTER PRECURSOR?

Ethanolamine may also increase concentrations of the neurotransmitters acetylcholine and anandamide. Ethanolamine can increase synthesis of acetylcholine by two main mechanisms. Firstly, methylation of ethanolamine produces choline for the formation of acetylcholine [58], however it is debatable whether this pathway exists in the brain [59, 60]. Secondly, ethanolamine can displace choline from phospholipids through the base exchange reaction making it available for acetylcholine synthesis [21]. Recent data suggests that the novel ethanolamine derivative (FDES), used to treat traumatic brain injury, mediates part of its effects via increased acetylcholine synthesis [61].

Anandamide is usually formed in the brain by the breakdown of an n-acyl substituted derivative of PE called N-arachidonoyl-phosphatidylethanolamine (NAPE) [36]. This reaction is catalysed by an enzyme called NAPE-phospholipase D. Anandamide is metabolised by the enzyme

fatty acid amidohydrolase to form ethanolamine and arachidonic acid. It was discovered by Arreaza *et al.* [62] that this enzyme also catalyses the reverse reaction. However, the breakdown reaction dominates, except at high concentrations of ethanolamine and arachidonic acid [62]. Such high concentrations of ethanolamine do not occur under physiological conditions but may occur in some of the pathologies described later in this review.

Table **2** Changes in levels of ethanolamine and related compounds in brain disorders.

Brain disorder	Etn	P-Etn	PE	PEP	Sample	Ref
Alzheimer's disease	↓	↓			Human brain	[37]
				↓	Human brain	[67]
				↓	Human brain	[68]
			↓		Human brain & mouse models of AD	[42]
	↓	↔	↓		Human brain	[69]
Cerebral infarction	↑		↑		Rat brain	[48]
	↑				Rat/gerbil brain	[70]
Cavernous Angioma	↑				Human brain	[72]
Epilepsy	↑	↑			Rabbit ECF	[73]
		↑			Rabbit ECF	[75]
	↑				Human brain	[76]
Depression	↓		↔	↔	CSF	[64]
		↓			Human plasma	[77]
Bipolar disorder			↓	↓	Human plasma	[65]
Huntington's disease	↓	↓			Human brain	[37]
			↔		Human brain	[67]
Parkinson's disease			↓		Human Substantia Nigra	[78]
		↓			Human CSF	[79]

Etn = ethanolamine, P-Etn = phosphoethanolamine, PE = phosphatidylethanolamine, PEP = ethanolamine plasmalogen, ECF = Extracellular fluid, ↑ = increase, ↓ = decrease, ↔ = no change

5. ETHANOLAMINE IN NEUROLOGICAL DISORDERS

In the brain, ethanolamine and its derivatives have been implicated in the pathogenesis, diagnosis and treatment of several pathological processes, including depression [63, 64], bipolar disorder [65], Alzheimer's disease [37, 66-69], traumatic brain injury [61], stroke [47, 48, 70], and epilepsy [71-73] (Table **2**). In these conditions, the levels of ethanolamine and its compounds are affected to varying degrees. However, whether these changes are merely a byproduct of neurodegeneration with little effect on subsequent pathology or key pathophysiological changes, is an evolving topic, as highlighted in the main pathologies further outlined below.

5.1. ALZHEIMER'S DISEASE

Patients who suffer from Alzheimer's disease have 30-50% lower levels of ethanolamine in the brain [37, 69]. They also have lower levels of ethanolamine phospholipids [67-69] and this is evident even in the early stages of the disease [42]. In particular, a decreased ratio of plasmalogens to diacyl ethanolamine phospholipids seems to be a feature particular to Alzheimer's disease compared to other neurodegenerative diseases [67]. The relationship between plasmalogens and Alzheimer's disease has been reviewed in detail [74]. Of interest here is that the decrease in plasmalogen content of neural cells is not a mere side effect of neurodegeneration [67]. Plasmalogens seem to play an active role in protecting the brain against the progression of Alzheimer's disease by acting as scavengers of the reactive oxygen species [68]. Unfortunately, in doing this, the plasmalogens are broken down. Furthermore, damage to peroxisomes in Alzheimer's disease is thought to decrease synthesis of plasmalogens [68]. This increased breakdown of plasmalogens and decreased synthesis is likely to be what ultimately leads to decreased plasmalogen levels in the brain. While ethanolamine treatment may provide supplies for the synthesis of new plasmalogens, the lack of a functional synthetic pathway may limit its use.

5.2. DEPRESSION

In depression, the levels of free ethanolamine in the CSF are decreased [64]. Drug treatment does not seem to alter this change from normal physiology, however in remitted patients these levels seem to return to control levels [64]. In patients with bipolar disorder, levels of plasmalogens and PE are decreased in the blood of patients with type 1 bipolar disorder [65]. A small study focused on unmedicated patients with Major Depressive Disorder with a seasonal pattern found that, certain ethanolamine diacylphospholipids in the plasma were decreased in winter. However, this study had a very small sample size [77], and needs to be performed in a larger cohort. The relevance of these decreases in ethanolamine and its compounds is unknown. However, it is interesting to note that long term vagal stimulation which improves symptoms of depression for some patients [80, 81], has been shown to increase levels of ethanolamine in epileptic patients [71].

5.3. CEREBRAL ISCHEMIA

In rats exposed to occlusion of the middle cerebral artery, studies using nuclear magnetic resonance showed significantly increased ethanolamine levels in the ischemic hemisphere compared to the non-ischemic hemisphere [70].

Time course experiments in rabbits revealed that levels of both ethanolamine and ethanolamine-phosphate increase towards the end of cerebral ischemia and for 1-3 hours into reperfusion, reaching a level 3 times that of the initial level [48]. A study by Buratta *et al.* [47] suggests that ethanolamine release resulting from ischemia could lead to release of glutamate and aspartate through activation of NMDA receptors. However, if this were the case, one would expect a subsequent increase in glutamate and aspartate release around the peak ethanolamine release. Unfortunately, Hagberg *et al.* [48] demonstrate that glutamate and aspartate levels would have returned to baseline at that stage.

5.4 EPILEPSY

Post mortem studies have revealed increased ethanolamine levels in samples from epileptic brains [73, 76]. Similarly, dialysate studies in a rabbit model of folate induced epilepsy revealed increased phosphoethanolamine in the ECF but not total brain tissue in response to seizures [75]. Similar studies using kainic acid or bicuculline induced seizures also revealed increased levels of phosphoethanolamine, with kainic acid induced seizures also causing moderate increases in ethanolamine levels in the extracellular fluid [73]. Increased ethanolamine, amongst other amino acids, in conditions such as cavernous angiomas [72] have been suggested to stimulate seizures. This is contradicted by the finding that patients who had decreased seizure frequency in response to vagal stimulation, had further increases in ethanolamine and phosphoethanolamine in their CSF [71]. So, while ethanolamine is elevated in epileptic brains, it remains a mystery whether these changes are clinically relevant.

6. IMPLICATIONS FOR DRUG DEVELOPMENT

Including ethanolamine and ethanolamine-like molecules as a promoiety in several prodrugs has proven a valuable method of targeting of drugs to the brain. However, from the evidence discussed in this minireview, it seems that ethanolamine itself has many effects within the brain. Both positive and negative facets of these effects need to be considered in drug development. Taking advantage of potential positive effects of ethanolamine in Alzheimer's disease or traumatic brain injury may lead to the development of mutual prodrugs (prodrugs where the promoiety has positive effects of its own) that lead to improved outcomes for patients. However, ignoring the effects of ethanolamine in drug design may lead to unwanted side effects.

6.1. COULD ETHANOLAMINE BE USED IN NEUROLOGICAL TREATMENTS?

Various lines of evidence suggest that increased ethanolamine levels might be protective in certain pathologies. In epilepsy, vagal stimulation decreased seizure frequency for a subset of patients. In these patients ethanolamine levels were increased compared to non-responders [71]. Furthermore, treatment with dimethylethanolamine decreases epileptiform activity in acute human hippocampal slices *in vitro*. These effects seem to be mediated by modulation of synaptic excitability [82]. Both studies suggest a positive effect of ethanolamine or ethanolamine related molecules in epilepsy. Likewise, in the murine neuroblastoma cells ethanolamine formed from the breakdown of anandamide can protect at a concentration of 1-5μM against low serum induced apoptosis [83]. Meanwhile, in other organs cytoprotection initiated or mediated by ethanolamine has also been reported [84-86].

Suppression of the antiaging gene, Sirtuin 1 (SIRT1), has been implicated in several neurodegenerative disorders [87, 88]. It is suggested that SIRT1 becomes suppressed early in the aging process and so it serves as an ideal target for antiaging therapies. Although no research has focused on the relationship between ethanolamine and SIRT1 in the brain, evidence from other tissues seems to suggest a complex interplay. Skeletal muscle cells with a partial knockout of Pcyt had decreased levels of SIRT1. However, levels were restored when exogenous phosphoethanolamine was administered [89]. This seems to suggest that increased levels of PE are required for SIRT1 upregulation. This is interesting since both SIRT1 and PE related cell survival are both suggested to be mediated via increased autophagy [32, 33, 90].

Chronic diseases such as obesity and diabetes have been linked to drastic changes in diet and to the progression of neurological disorders [88]. It is therefore possible that significant changes in diet of a component like ethanolamine, which is associated with neurodegenerative diseases, may manifest as part of the same spectrum of diseases that result from these gene-environmental interactions. There is however currently no evidence linking such changes in systemic dietary factors and ethanolamine-related brain pathologies.

Mitochondrial dysfunction has been linked to both neurodegenerative and affective disorders. Both Alzheimer's and Parkinson's Disease have been linked to mitochondrial deficits [91], whereas the pathophysiology of affective illnesses has been proposed to include mitochondrial dysfunction [92]. Interestingly, exogenous ethanolamine can affect the mitochondria of the cell. Ethanolamine, given at concentrations up to5 mM induced mild uncoupling of mitochondria whereas at 10 mM ethanolamine completely inhibited mitochondrial respiration [93]. Whether such affects would be protective in the brain requires further research if ethanolamine therapy is to target mitochondrial dysfunction.

While decreased ethanolamine phospholipids seems to be detrimental in terms of decreased ROS scavenging capability [68] and regulation of autophagy [33], treatment with ethanolamine may not have beneficial effects in all pathologies. Decreases in ethanolamine phospholipids may be the result of either increased destruction of phospholipids, decreased synthesis of phospholipids or an imbalance between the two. If the initial pathology involves damage to the processes or structures involved in the synthesis of plasmalogens, then increasing ethanolamine concentrations may have no effect. Indeed, in models of Alzheimer's disease where peroxisomal damage has been suggested [68],

treatment with various plasmalogen compounds have had positive effects [94-96] but it is unknown whether ethanolamine alone has any effect. By contrast, animal studies demonstrate that ethanolamine, as a promoiety, had positive effects in the treatment of traumatic brain injury [61].

6.2 AN EFFECTIVE DOSE OF ETHANOLAMINE

Whether the concentration of ethanolamine released from prodrugs is large enough to have an effect will depend on several factors. In healthy subjects, the main determining factor should be the amount of ethanolamine released when the prodrug is hydrolyzed. However, in pathological situations like ischemia and epilepsy where ethanolamine levels are already increased, the ethanolamine released from the prodrug may have an additive effect. Furthermore, the contribution of dietary ethanolamine may also need to be considered.

At the upper limits, serious negative effects may be seen. Despite the fact that ethanolamine has a relatively low toxicity (i.p. LD50 in mice=1.050g/kg) [97], high concentrations have been associated with CNS depression and death. Weeks *et al.* [98] demonstrated that dogs and rats continuously exposed to ethanolamine vapors became lethargic and while the dogs recovered, the rats did not. Priddle et al [as cited in 99] demonstrated that low doses of ethanolamine caused CNS stimulation in dogs whereas high doses caused CNS depression. A focus on the changes in ethanolamine concentrations in response to prodrugs, in both health and pathology as well as the inclusion of control groups causing similar increases in ethanolamine, may lead to the identification of side effects relating to the ethanolamine moiety or indeed to the discovery of a new treatment for some of the pathologies outlined above.

CONCLUSION

Ethanolamine plays a critical role in brain physiology and pathophysiology as a precursor of ethanolamine plasmalogens and diacyl phospholipids. It is also evident that ethanolamine may play a non-phospholipid mediated role in synaptic transmission through increased neurotransmitter uptake and synaptic vesicle release, neuromodulation, and regulation of cell death and proliferation. Taking these effects into account when designing and assessing new ethanolamine-containing prodrugs may lead to more effective drugs, earlier identification of unwanted side effects and the serendipitous identification of new applications for a drug.

LIST OF ABBREVIATIONS

CNS	Central nervous system
CSF	Cerebrospinal fluid
CDP	Cytidine diphosphate
CTL-1	Choline transporter like protein-1
CTL-2	Choline transporter like protein-2
CTP	Cytidine triphosphate
DHA	Docosahexaenoic acid
ECF	Extracellular Fluid
Pcyt	CTP: ethanolaminephosphate cytidyltransferase
PE	Phosphatidylethanolamine
PEP	Plasmenylethanolamine
ROS	Reactive oxygen species
Sirt1	Sirtuin 1

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