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The influence of different excipients on Valproic acid tablets in neurological disorder treatment

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Abstract
Valproic acid is widely used in treating neurological disorders such as epilepsy, bipolar disorder, and migraine, yet its exact mechanisms of action remain unclear. In this review, we aim to comprehensively outline the multifaceted mechanisms underlying Valproic acid's therapeutic effects. VPA modulates neurotransmitter systems, including gamma-aminobutyric acid (GABA), glutamate, and dopamine, influencing synaptic transmission and neuronal excitability. It enhances GABAergic transmission by inhibiting GABA degradation enzymes, promoting GABA release, and inhibiting reuptake, thereby contributing to its antiepileptic and mood-stabilizing effects. Valproic acid also reduces glutamatergic transmission by inhibiting N-methyl-D-aspartate receptors, thus attenuating glutamate-induced excitotoxicity. Moreover, Valproic acid affects dopaminergic neurotransmission by enhancing dopamine release and inhibiting reuptake, aiding mood stabilization. Another critical mechanism involves Valproic acid's modulation of voltage-gated ion channels, particularly sodium and calcium. Valproic acid reduces neuronal excitability and hyperactivity by inhibiting these channels, which is particularly beneficial in epilepsy treatment. Additionally, Valproic acid inhibits histone deacetylase, increasing histone acetylation and enhancing gene transcription. This epigenetic modulation upregulates neuroprotection, synaptic plasticity, and neurotransmission genes. Furthermore, Valproic acid exhibits neuroprotective properties by attenuating excitotoxicity, oxidative stress, and apoptosis, protecting against neuronal damage. Excipients in tablet formulations play a pivotal role in modifying Valproic acid’s mechanisms of action. Sustained-release formulations are essential for maintaining stable plasma concentrations, while enteric coatings protect against gastric degradation, enhancing bioavailability. Excipients can also enhance solubility and improve drug delivery. For instance, surfactants and solubilizers can enhance Valproic acid’s dissolution, while disintegrants promote rapid disintegration for faster drug release, which is crucial for acute conditions like seizures. Understanding how different excipients affect Valproic acid’s mechanisms provides insights into optimizing therapy and developing novel treatments for neurological disorders.

Keywords: Valproic acid, neurotransmitters; GABA

1. Introductions
Valproic acid (VPA) has long been recognized as a cornerstone in the treatment of various neurological disorders, playing a vital role in managing conditions such as epilepsy, bipolar disorder, and migraine. Despite its extensive clinical use, the precise mechanisms by which VPA exerts its therapeutic effects remain incompletely understood [1]. This knowledge gap presents challenges in optimizing VPA therapy and developing novel treatments for neurological conditions. In this comprehensive review, we aim to elucidate the multifaceted mechanisms underlying the therapeutic actions of VPA, focusing on its modulation of neurotransmitter systems, ion channels, gene expression, and neuroprotective properties [2]. VPA profoundly affects neurotransmitter systems within the brain, impacting synaptic transmission and neuronal excitability. Among these, gamma-aminobutyric acid (GABA) transmission is a primary target. GABA is the principal inhibitory neurotransmitter in the central nervous system, crucial for maintaining the balance between excitatory and inhibitory signals. VPA enhances GABAergic transmission through various mechanisms [3]. Firstly, it inhibits the enzyme GABA transaminase, which is responsible for GABA degradation and increases GABA levels in the brain. Additionally, VPA inhibits the reuptake of GABA into presynaptic neurons and enhances GABA release, thereby augmenting inhibitory signaling. These actions contribute significantly to VPA's antiepileptic and mood-stabilizing effects. Moreover, VPA modulates glutamatergic and dopaminergic neurotransmission, further

influencing neuronal activity and synaptic function [4]. Glutamate, the major excitatory neurotransmitter, plays a crucial role in neuronal excitability and synaptic plasticity. Dysregulation of glutamatergic signaling has been implicated in various neurological disorders, including epilepsy and neurodegenerative diseases. VPA reduces glutamatergic transmission by inhibiting the activity of N-methyl-D-aspartate (NMDA) receptors, thereby attenuating glutamate-induced excitotoxicity. This neuroprotective action is particularly relevant in conditions where excessive glutamate release contributes to neuronal damage [5].

Similarly, VPA affects dopaminergic neurotransmission, which plays a central role in mood regulation and reward processing. By enhancing dopamine release and inhibiting dopamine reuptake, VPA modulates dopaminergic signaling, contributing to its mood-stabilizing effects in bipolar disorder [6]. These combined effects on neurotransmitter systems underscore the diverse therapeutic actions of VPA in neurological disorders. Another critical VPA action mechanism involves its modulation of voltage-gated ion channels, particularly sodium and calcium channels. Voltage-gated sodium channels are integral to action potential generation and propagation in neurons. By inhibiting sodium channels, VPA reduces neuronal excitability and hyperactivity, which is beneficial in treating epilepsy [7]. Additionally, VPA inhibits L-type calcium channels, which play essential roles in neurotransmitter release and synaptic plasticity. Modulation of these channels by VPA regulates synaptic transmission and neuronal excitability, further contributing to its antiepileptic and mood-stabilizing effects. In addition to its direct effects on neurotransmitter systems and ion channels, VPA profoundly affects gene expression through epigenetic modifications. Epigenetic regulation refers to heritable changes in gene expression that occur without alterations in the DNA sequence [8]. VPA primarily inhibits histone deacetylases (HDACs), enzymes that remove acetyl groups from histone proteins, leading to chromatin condensation and transcriptional repression. By inhibiting HDACs, VPA increases histone acetylation, resulting in a more relaxed chromatin structure and enhanced gene transcription. This epigenetic modulation leads to the upregulation of genes involved in various neuroprotective processes, including neuronal survival, synaptic plasticity, and neuroprotection [9]. For example, VPA increases the expression of genes encoding neurotrophic factors such as brain-derived neurotrophic factor (BDNF), which plays a crucial role in neuronal survival, synaptic function, and neurogenesis. Moreover, VPA regulates the expression of genes involved in neurotransmitter synthesis, ion channel function, and synaptic transmission, further contributing to its therapeutic effects in neurological disorders [10].

Beyond its effects on neurotransmitter systems and gene expression, VPA exhibits neuroprotective properties through various mechanisms. Excitotoxicity, oxidative stress, and apoptosis are common pathways leading to neuronal injury and death in neurological disorders, and VPA has been shown to attenuate these processes. VPA protects against excitotoxic neuronal damage by inhibiting NMDA receptors and reducing calcium influx into neurons [11]. Furthermore, VPA enhances antioxidant defenses, scavenging free radicals, and inhibits apoptotic pathways, promoting neuronal survival and reducing neuronal death. In tablet formulation, sustained-release formulations are essential to maintain stable plasma concentrations of VPA over time, minimizing fluctuations and reducing the risk of breakthrough seizures or mood swings. Excipients can enhance solubility and bioavailability, improving absorption and pharmacokinetics. Enteric coatings can protect VPA from gastric degradation, reducing gastrointestinal side effects [12].

2. Role of VPA in Neurotransmitter Systems

Valproic acid (VPA) is a widely used medication known for its efficacy in treating various neurological disorders, including epilepsy, bipolar disorder, and migraine. Its therapeutic effects are attributed to its modulation of several neurotransmitter systems in the brain, which influence synaptic transmission and neuronal excitability. One of the primary neurotransmitter systems targeted by VPA is the gamma-aminobutyric acid (GABA) system [13]. GABA is the major inhibitory neurotransmitter in the brain, crucial for maintaining the balance between excitatory and inhibitory signals. Alterations in GABA function have been implicated in various neurological disorders. VPA enhances GABAergic transmission through multiple mechanisms. Firstly, it inhibits the enzyme GABA transaminase, responsible for the degradation of GABA, leading to increased GABA levels in the brain [14]. This elevation in GABA levels enhances inhibitory signaling, contributing to VPA's antiepileptic and mood-stabilizing effects. Additionally, VPA inhibits the reuptake of GABA into presynaptic neurons and enhances GABA release, further augmenting GABAergic signaling. These combined actions on GABAergic transmission help stabilize neuronal activity, reducing seizure activity and mood swings associated with bipolar disorder [15].

In addition to its effects on GABA, VPA also modulates the glutamatergic and dopaminergic systems. Glutamate is the major excitatory neurotransmitter in the brain, playing a crucial role in neuronal excitability and synaptic plasticity. Dysregulation of glutamatergic signaling has been implicated in epilepsy and neurodegenerative disorders [16]. VPA has been shown to reduce glutamatergic transmission by inhibiting the activity of N-methyl-D-aspartate (NMDA) receptors, thereby attenuating glutamate-induced excitotoxicity. By blocking these receptors, VPA prevents excessive glutamate signaling, which can lead to neuronal damage and cell death. This neuroprotective action is particularly relevant in conditions where glutamate excitotoxicity contributes to neuronal injury [17].

Furthermore, VPA regulates dopaminergic neurotransmission, which plays a central role in mood regulation and reward processing. Dysregulation of the dopaminergic system has been implicated in various psychiatric disorders, including bipolar disorder [18]. VPA enhances dopamine release and inhibits dopamine reuptake, leading to increased dopaminergic signaling. This modulation of dopaminergic neurotransmission may contribute to VPA's mood-stabilizing effects in bipolar disorder, helping to alleviate symptoms of mania and depression. Beyond its effects on neurotransmitter systems, VPA influences gene expression through epigenetic modifications. Epigenetic regulation refers to changes in gene expression that occur without alterations in the DNA sequence [19]. VPA primarily inhibits histone deacetylases (HDACs), enzymes responsible for removing acetyl groups from histone proteins. By inhibiting HDACs, VPA increases

histone acetylation, resulting in a more relaxed chromatin structure and enhanced gene transcription. This epigenetic modulation leads to the upregulation of genes involved in various neuroprotective processes, including neuronal survival, synaptic plasticity, and neuroprotection [20]. For example, VPA increases the expression of genes encoding neurotrophic factors such as brain-derived neurotrophic factor (BDNF), which promotes neuronal survival and synaptic function. Moreover, VPA exhibits neuroprotective properties by attenuating excitotoxicity, oxidative stress, and apoptosis. Excitotoxicity refers to the process of neuronal damage and cell death caused by excessive stimulation of glutamate receptors, particularly NMDA receptors. VPA inhibits NMDA receptors, preventing excessive calcium influx into neurons and reducing excitotoxic damage [21]. Additionally, VPA enhances antioxidant defenses, scavenging free radicals and protecting neurons from oxidative damage. It also inhibits apoptotic pathways, regulating the expression of pro- and anti-apoptotic genes, promoting neuronal survival and reducing cell death. These neuroprotective effects contribute to VPA's efficacy in preventing neuronal injury and degeneration in various neurological disorders [22].

2.1 Mechanism of Action of Valproic Acid through Ion-channel

Valproic acid (VPA) exerts its therapeutic effects in neurological disorders through various mechanisms, one of which involves the modulation of voltage-gated ion channels, particularly sodium and calcium channels. These channels play crucial roles in regulating neuronal excitability, action potential generation, and synaptic transmission. Voltage-gated sodium channels are essential for initiating and propagating action potentials in neurons [23]. These channels open in response to depolarization, allowing the influx of sodium ions, which triggers action potential firing. By inhibiting sodium channels, VPA reduces neuronal excitability and hyperactivity. This action is particularly relevant in the treatment of epilepsy, where excessive neuronal firing and synchronization can lead to seizures. VPA's ability to dampen neuronal excitability by blocking sodium channels helps to prevent abnormal electrical activity and seizure propagation [24].

Furthermore, VPA inhibits L-type calcium channels, another class of voltage-gated ion channels crucial for neurotransmitter release and synaptic plasticity. Calcium influx through these channels regulates various cellular processes, including neurotransmitter release, synaptic strength, and synaptic plasticity [25]. VPA modulates synaptic transmission and synaptic plasticity by blocking calcium influx into neurons, contributing to its antiepileptic and mood-stabilizing effects. In epilepsy, aberrant synaptic transmission and neuronal hyperexcitability contribute to seizure generation and propagation [26]. By inhibiting L-type calcium channels, VPA reduces calcium influx into presynaptic terminals, thereby decreasing neurotransmitter release. This reduction in neurotransmitter release dampens synaptic transmission and neuronal excitability, helping to prevent the spread of abnormal electrical activity associated with seizures [27].

Moreover, VPA's modulation of L-type calcium channels influences synaptic plasticity, the ability of synapses to strengthen or weaken over time in response to activity. Synaptic plasticity is essential for learning and memory, and alterations in synaptic plasticity have been implicated in various neurological disorders, including epilepsy and mood disorders [28]. By blocking L-type calcium channels, VPA alters calcium-dependent signaling pathways involved in synaptic plasticity. This modulation can affect long-term changes in synaptic strength and neuronal connectivity, contributing to VPA's ability to stabilize mood and prevent mood swings in conditions like bipolar disorder [29]. Additionally, VPA's effects on calcium channels may have neuroprotective properties. Excessive calcium influx into neurons can trigger various neurotoxic processes, including excitotoxicity and apoptosis, leading to neuronal injury and cell death. VPA mitigates these neurotoxic effects by reducing calcium influx through L-type channels, protecting neurons from damage and promoting neuronal survival [30].

3. Factors affecting the excipient used to formulate Valproic acids with respect to their mechanism of action

Excipients are inactive substances added to pharmaceutical formulations to enhance the stability, bioavailability, and overall performance of active pharmaceutical ingredients (APIs) like valproic acid (VPA). These excipients play a crucial role in modifying the pharmacokinetics, pharmacodynamics, and therapeutic effects of VPA in various neurological disorders [31]. Here's an in-depth exploration of how different excipients in VPA tablets modify its mechanism of action:

3.1 Binder (e.g., Povidone)

Binders are essential components in tablet formulations as they provide cohesion to the tablet matrix. Povidone, a commonly used binder, forms a strong bond between particles, ensuring tablet integrity during compression and subsequent handling. While the binder itself does not directly influence VPA's mechanism of action, it plays a critical role in ensuring consistent tablet structure and dissolution [32]. Tablets must disintegrate and release the drug uniformly to facilitate absorption. The presence of an effective binder like povidone ensures that the tablet maintains its structural integrity throughout its shelf life and during ingestion, leading to predictable dissolution and absorption of VPA. In antiepileptic therapy, maintaining steady plasma concentrations of VPA is crucial for controlling seizures. The binder ensures that the tablet disintegrates and releases VPA consistently, allowing for reliable absorption. This helps in maintaining therapeutic blood levels of VPA, thereby optimizing its antiepileptic effects [33].

3.2 Lubricant (e.g., Magnesium stearate)

Lubricants are added to tablet formulations to reduce friction between the tablet's surface and the equipment used during tablet compression [34]. Magnesium stearate, one of the most commonly used lubricants, improves tablet flowability and ejection from the tablet press, ensuring uniform tablet dimensions and preventing capping or sticking. While lubricants do not directly affect VPA's mechanism of action, they indirectly influence its therapeutic effects by ensuring consistent tablet quality and dissolution [35]. By reducing friction, magnesium stearate facilitates the smooth and uniform compression of tablet ingredients, leading to tablets with consistent drug content and dissolution profiles. Consistent tablet structure and dissolution are crucial for achieving predictable drug release

and absorption [36]. In the context of VPA therapy, uniform tablet dimensions and dissolution contribute to the maintenance of steady plasma concentrations, which is essential for optimizing its therapeutic effects in neurological disorders [37].

3.3 Disintegrant (e.g., Crospovidone)

Disintegrants are added to tablet formulations to facilitate the breakup of tablets into smaller particles when exposed to aqueous fluids, thereby enhancing tablet disintegration and drug dissolution. Crospovidone, a commonly used disintegrant, promotes rapid disintegration of tablets in the gastrointestinal tract, allowing for faster drug release and absorption [38]. Crospovidone's mechanism of action involves swelling and rapid hydration upon contact with aqueous fluids, leading to the breakup of the tablet into smaller particles. This enhances the surface area available for dissolution, thereby accelerating drug release. In the context of VPA therapy, rapid tablet disintegration and drug release are beneficial, especially for patients requiring quick onset of action, such as those experiencing acute seizures. By promoting faster drug absorption, crospovidone helps in achieving therapeutic blood levels of VPA more rapidly, thereby optimizing its antiepileptic effects [39].

3.4 Filler (e.g., Microcrystalline cellulose)

Fillers, also known as diluents, are added to tablet formulations to increase the bulk of the tablet and provide uniformity in tablet weight and size. Microcrystalline cellulose, a commonly used filler, acts as an inert carrier for VPA and other tablet ingredients, ensuring even drug distribution throughout the tablet matrix [40]. While fillers do not directly affect VPA's mechanism of action, they play a crucial role in achieving consistent tablet quality and dissolution. Microcrystalline cellulose provides structural integrity to the tablet and ensures uniform distribution of VPA, facilitating its dissolution and absorption in the gastrointestinal tract [41]. Consistent tablet weight and size are essential for accurate dosing and reliable drug release. In the context of VPA therapy, uniform distribution of the drug ensures consistent drug release and absorption, leading to predictable plasma concentrations and optimized therapeutic effects in neurological disorders [42].

3.5 Glidant (e.g., Colloidal silicon dioxide)

Glidants are added to tablet formulations to improve powder flow properties by reducing interparticle friction. Colloidal silicon dioxide, a commonly used glidant, enhances the flowability of tablet ingredients during manufacturing, ensuring uniform mixing and compression [43]. Colloidal silicon dioxide's mechanism of action involves forming a thin layer on the surface of particles, reducing friction between them and improving powder flow. This ensures uniform distribution of tablet ingredients and prevents the formation of aggregates, leading to tablets with consistent drug content and dissolution profiles. In the context of VPA therapy, uniform mixing and compression of tablet ingredients are essential for achieving consistent tablet quality and dissolution [44]. By improving powder flow, colloidal silicon dioxide contributes to the uniform distribution of VPA in the tablet matrix, ensuring predictable drug release and absorption in the gastrointestinal tract.

3.6 Coating Material (optional, e.g., Hydroxypropyl methylcellulose)

Coatings are applied to tablets for various purposes, including protection from environmental factors, taste masking, and modified drug release. Hydroxypropyl methylcellulose (HPMC), a commonly used coating material, can be used to modify the release profile of VPA tablets. Enteric coatings comprising HPMC and other polymers can protect VPA from degradation in the stomach's acidic environment and delay drug release until the tablet reaches the small intestine [45]. This can particularly benefit patients with sensitive stomachs or those requiring extended-release formulations. The mechanism of action of enteric coatings involves forming a protective barrier around the tablet, which prevents drug release in the stomach. Once the tablet reaches the small intestine, where the pH is higher, the enteric coating dissolves, allowing for drug release and absorption [46]. In the context of VPA therapy, enteric coatings help in minimizing gastrointestinal side effects and ensuring optimal drug absorption. By delaying drug release until the tablet reaches the small intestine, enteric coatings optimize the bioavailability of VPA, leading to sustained plasma concentrations and prolonged therapeutic effects [47].

3.7 Plasticizer (if needed, e.g., Polyethylene glycol)

Plasticizers are used in coatings to improve their flexibility and elasticity. Polyethylene glycol (PEG), a commonly used plasticizer, can be added to coating formulations to enhance their properties [48]. PEG's mechanism of action involves reducing the brittleness of the coating material and improving its flexibility. This ensures that the coating remains intact during tablet handling and ingestion, thereby maintaining its protective function until the drug is released in the desired location. In the context of VPA therapy, plasticizers like PEG contribute to the stability and integrity of enteric coatings, ensuring that they remain intact until the tablet reaches the small intestine [49]. This helps in optimizing the release profile of VPA, leading to sustained plasma concentrations and prolonged therapeutic effects. In conclusion, excipients play a crucial role in modifying the mechanism of action of VPA in neurological disorders by ensuring consistent tablet quality, dissolution, and absorption [50]. By optimizing these factors, excipients contribute to the therapeutic effectiveness of VPA in various neurological disorders, including epilepsy, bipolar disorder, and migraine.

4. Conclusion

In conclusion, the multifaceted mechanisms of action of valproic acid (VPA) contribute to its efficacy in treating various neurological disorders. By modulating neurotransmitter systems such as GABA, glutamate, and dopamine, VPA influences synaptic transmission and neuronal excitability, providing antiepileptic and mood-stabilizing effects. Its ability to modulate voltage-gated ion channels further reduces neuronal hyperactivity, particularly beneficial in epilepsy management. Moreover, VPA's histone deacetylase inhibition enhances gene transcription, promoting neuroprotection, synaptic plasticity, and neurotransmission. Its neuroprotective properties against excitotoxicity, oxidative stress, and apoptosis further safeguard against neuronal damage. The role of excipients in VPA tablet formulations cannot be overstated. Sustained-

release formulations ensure stable plasma concentrations, while enteric coatings protect against gastric degradation, enhancing bioavailability. Excipients also influence solubility and drug delivery, with surfactants and solubilizers enhancing dissolution and disintegrants promoting rapid release, crucial for acute conditions like seizures. Understanding how different excipients modify VPA's mechanisms of action provides valuable insights into optimizing therapy and developing novel treatments for neurological disorders. Future research focusing on refining excipient formulations could lead to improved VPA therapies, offering better outcomes and enhanced patient care in the management of epilepsy, bipolar disorder, migraine, and other neurological conditions.

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