# APELIN-13 AND EPILEPSY

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## ABSTRACT

Apelin, a neuropeptide, is a typical endogenous ligand of G protein-coupled apelin receptor, APJ. Apelin mRNAs, proteins and APJ are commonly found in peripheral tissues and the central nervous system (CNS). Thus apelin-APJ system may be related to many physiological and pathological processes such as epilepsy. Epilepsy is severe chronic neurological disease and affects millions of people worldwide. Disruption of the balance between excitation and inhibition can cause epilepsy. There are few studies about apelin and epilepsy interactions. Apelin-13 decreased the incidence of PTZ-induced seizure in rats and appeared preservative effects and decreased markers of cell injury and death in primary cortical glia-neuron co-culture of rat against PTZ-induced toxicity through its calcium blocking, antioxidant, anti-apoptotic and anti-inflammatory properties. Other study demonstrated protective effects of apelin against neuronal death in epilepsy both *in vitro* and *in vivo* . Conversely, apelin-13 increased the spike frequency of penicillin-induced epileptiform activity in rat. In another study investigating the relationship between cannabinoid CB1 receptors and apelin, it was also shown that apelin-13 has a proconvulsant effect in penicillin model epilepsy. Clarifying the effect of apelin on epilepsy will be important for the development of treatment.

***Keywords:***

*Apelin-13, APJ, Neuroprotection, Epilepsy*

## INTRODUCTION

In 1993, O'Dowd et al. discovered a gene with a similar sequence to the angiotensin-II type I receptor gene. This gene, named APJ, was referred to as the orphan receptor till its endogenous ligand was explored by Tatemato et al. in 1998 (Tatemato et al., 1998). Since APJ can not bind to angiotensin II and there was no endogenous ligand which interacts it, APJ considered as orphan receptor (Ivanov et al., 2022). In humans, mRNA of APJ has been found in many peripheral and central tissues, such as stomach, liver, pancreas, vascular endothelial and smooth muscle cells, adipose tissue, placenta, lungs, heart, thymus, prostate, testis, ovary, spleen, intestines and brain (Devic et al., 1999; Lee et al., 2000; O'Carroll et al., 2000; Medhurst et al., 2003).

Apelin was first described in 1998 by Tatemato et al. (1998) from bovine gastric juice. In humans, the apelin gene is located on chromosome Xq 25–26, 1 (Lee et al., 2000) and originates from 77 amino acids (Kawamata et al., 2001). Preproapelin is then broken down into fragments with different numbers of amino acids such as 12, 13, 17, 36 (Figure 1). It is suggested that apelin-13 is eight times more effective than apelin-17 and sixty times more effective than apelin-36 (Tatemoto et al., 1998). Dissimilar apelin isoforms have distribution, expression and binding capacity, so its

effect can be different, apelin-13 has the most powerful bioactivity and receptor binding capacity, also has a lot of biological functions (Zhang et al., 2023). The apelin-APJ system is mostly found in the central nervous system (CNS) (Zhang et al., 2023) for example hippocampus, cerebellum, striatum, and hypothalamus in addition to peripheral tissues (Hosoya et al., 2000; Reaux et al., 2001). All of these findings show that apelin may participate important processes in the CNS and periphery.

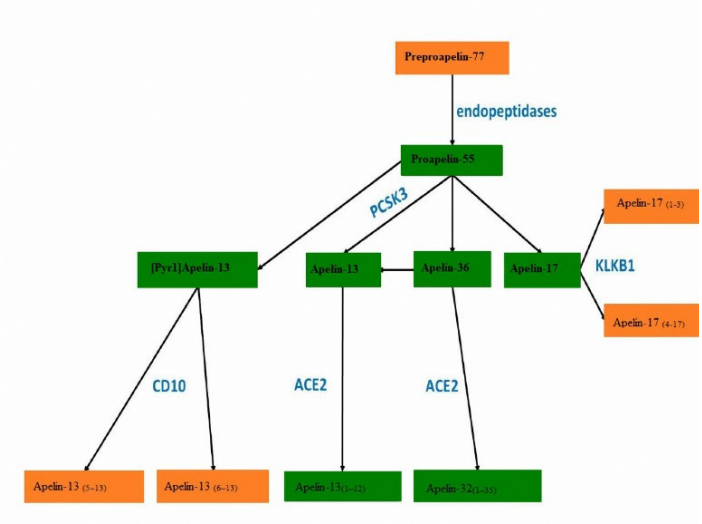


**Fig 1.** The inactive 77-amino acid preproapelin is converted to Apelin-55, which can bind to the apelin receptor via endogenous nucleases. Apelin-55 can form 4 isoforms; Apelin-13, Apelin-17, Apelin-36 and [Pyr1] Apelin-13. CD10 (Neprilysin) inactivates Apelin-13 and thus can create two inactive isoforms of Apelin-13 (5–13aa and 6–13aa). Additionally, angiotensin-converting enzyme (ACE2) converts Apelin-13 and Apelin-36 into their active forms, Apelin-13(1–12) and Apelin-32(1–35). (Green color indicates functional fragments, red color indicates non-functional fragments, blue color indicates cleavage enzymes.) (Ivanov et al., 2022).

A recent literature study has been conducted to reveal the role of apelin in epilepsy. And these scans were carried out by combinations of the keywords Apelin, Apelin-13, APJ, Neuroprotection, Epilepsy (scanned in Pubmed, Google Academic and Web of Science databases). Epilepsy is a neurological disease which is repetitive, stereotyped, and transient, induced by abnormal discharge of brain neurons (Zhang et al., 2023). Previous studies have generally focused on the neuroprotective effects of the apelin-APJ system in epilepsy (Kalantaripour et al., 2017; Dong et al., 2020; Zhou et al., 2021). Increased exogenous apelin-13 blocked upregulation of APJ receptor, it reduced seizure threshold and cortical neuronal inflammatory damage (Kalantaripour et al., 2016). The reason of APJ expression's increase may be related to the protective mechanisms for prevent in PTZ toxicity (Kalantaripour et al., 2016). Also, APJ activation decreased epileptic activity in kainic acide-induced status epilepticus (SE) and according to patch-clamp recordings the apelin-APJ system regulated postsynaptic currents mediated by NMDA receptor (Zhang et al., 2023). Apelin induces cellular prosurvival signaling in neurons, it protects neurons from excitotoxicity which is induced by NMDA receptor (Zeng et al., 2009; 2010). Down regulation of GluN2B expression can be possible mechanism which is facilitated inflammatory pain by apelin-13 (intrathecally) (Lv et al., 2020). Thus, treatments that regulate the activities of the apelin-APJ system may protect against diseases that involve excitotoxicity (mediated by NMDA receptor), including stroke, epilepsy, neurodegenerative disease (Zhang et al., 2023).

Naloxone or apelin antagonist F13A did partial inhibition of seizure, APJ and opioid receptors have a role in apelin-13's antiepileptic effects but the different mechanism may be involved (Xu et al., 2009; Lv et al., 2012). Apelin's and its receptor's mRNA and protein are located in amygdala, hippocampus and cerebral cortex (Hosoya et al., 2000; Lee et al., 2000; Medhurst et al., 2003). These regions are releated to learning and memory. Epilepsy is often associated with cognitive dysfunction, including poor memory (Yu et al., 2024). Intracerebroventricular injection of apelin-13 (2 µg/rat/d) enhanced memory impairment in rats, mediated by the PI3K and ERK1/2 pathways (Li et al., 2016). On the other hand there are some studies shown opposite result of these. Apelin-13 (1 nmol/mouse, i.c.v.) afflicted the formation of short-term memory, and inhibited

consolidation (Han et al., 2014). Although apelin (i.c.v.) inhibited fear acquisition, did not block fear consolidation or expression in fear memory of rats (Han et al., 2014). Apelin-13 (1, 2 and 3 µg/rat) applicated into the substantia nigra decreased both the increase inescape latency and distance traveled in the Morris water maze test in the rat parkinson model (Haghparast et al., 2018). The treatment methods, doses, animal species, and memory models may be cause of the contradictory effects of apelin on learning and memory (Lv et al., 2020). To understand apelin-APJ system on memory, more studies are needed.

Neuro inflammatory is a major element in seizure's pathophysiology (Vezzani et al., 2008). Seizure raised inflammatory mediators in brain which involved in production and promotion of epileptic activities in experimental studies (Simoni et al., 2000; Gorter et al., 2006). For example, interleukin-1 beta (IL-1b), TNF-α (Turrin and Rivest, 2004) and interleukin-1 beta receptor type I (Ravizza and Vezzani, 2006) expression increased during seizure. Astrocytes are the most abundant glia cell type in the CNS and have important roles in the pathology of neurological disorders. These cells have talent to release inflammatory cytokines which support neuro-inflammation (Simoni et al., 2000). Apelin-13 inactivated astrocytes in the brain cortex of rat while PTZ activates astrocytes. Supression of astrocyte activation and following neuro inflammation can be another mechanism for apelin's antiepileptic and protective effects. (Kalantaripour et al., 2016).

The neuroprotective effect of apelin against NMDAR-mediated excitotoxic damage and its effect in raising the activation of kinases that ensure cell survival investigated in primary rodent hippocampal cultures and human NT2.N neurons (O'Donnell et al, 2007). Apelin induces neuronal activation of Raf/ERK-1/2 and AKT, which is protective against neuronal excitotoxicity caused by quinolinic acid (QUIN) exposure, as well as in HIV-infected human macrophages (O'Donnell et al., 2007). Apoptosis and necrosis events cause mitochondrial depolarization and increase in reactive O2 species (ROS). ROS and oxidative stress have role in the pathogenesis of epilepsy (Taiwo et al., 2023). Apelin-13 inhibited oxidative stress via regulating the activities of ROS, malondialdehyde and superoxide dismutase. These results shown that apelin-13 have a neuroprotective effect (Chen et al., 2022) (Figure 2). The role of apelin-13 (1-5 nM) on apoptosis in mouse primary cortical neuron culture was investigated and it was shown that it significantly reduced serum deprivation-induced ROS production, mitochondria depolarization, caspase-3 activation and cytochrome c release in neurons (Zeng et al., 2010). Apelin-36 inhibits NMDA-mediated $Ca^{2+}$ accumulation in cerebrocortical neurons but does not affect the $Ca^{2+}$ accumulation induced by $K^{+}$ depolarization (Cook et al., 2011). G protein-coupled receptor ligands can induce neuronal $Ca^{2+}$ transmission (Deiva et al., 2004). Similarly, apelin induces $Ca^{+2}$ transition in cerebrocortical neurons in a dose-dependent manner (Cook et al., 2011). Considering the intense expression of the apelin receptor by human NT2.N neurons, apelin-36, apelin-17, and apelin-13 have been shown to increase intracellular $Ca^{2+}$ levels (Choe et al., 2000). The decrease in response, especially after repeated exposures, is the first evidence of the desensitization process that regulates apelin signaling (Masri et al., 2004).

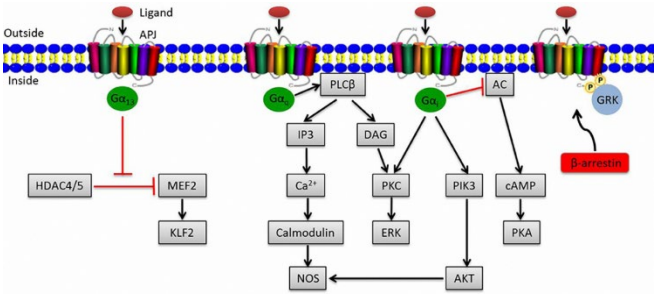


**Fig 2.** Signaling pathways of the apelin/APJ system. Gi and Gq-mediated APJ signaling causes activation of protein kinase C (PKC), phosphatidylinositide 3-kinase (PI3K), and nitrous oxide synthase (NOS) pathways, while inhibiting adenylate cyclase (AC). In endothelial cells, binding of the ligand activates the G13-dependent pathway, allowing transcription of myocyte enhancer factor-2 (MEF2). G protein-coupled receptor kinase (GRK) and β-arrestin are

involved in the G protein-independent pathway of the apelin/APJ system (Tian et al., 2020).

In patients with temporal lobe epilepsy, apelin's expression level increases in comparison to healthy controls, and raises gradually after seizures (Dingledine et al., 2014). Disruption of apelin-APJ signaling aggravates PTZ-induced seizures, and apelin-13 suppresses astrocyte activation and subsequent neuroinflammation (Zhang, 2011). By means of the ability of apelin decrease intracellular $Ca^{2+}$, inhibit ROS generation and COX2 (Cyclooxygenase2), has neuroprotection in the PTZ model of epilepsy (Kalantaripour et al., 2017). Although apelin expression is upregulated in epileptic models, neurological death is still continue (Lv et al., 2020). Endogen apelin isn't enough to keep nerve survival, so more experiments should be done about exogenous apelin (Li et al., 2022). The reason of apelin expression increased in lithium–pilocarpine-induced epilepsy in rats and in patients with drug-resistant temporal lobe epilepsy, it can be related to compensatory mechanism (Zhang et al., 2011). Apelin-13 blocked seizure induction and neuronal loss in an experimental rat epilepsy (Kalantaripour et al., 2016). Apelin expression was significantly higher according to normal control in the hippocampus and adjacent cortex (Zhang et al., 2011). Apelin regulates apoptosis-associated protein expression, inhibits mGluR1 pathway, and increases p-AKT level in neurons, thus providing protection against neuronal damage (Dong et al., 2020).

In patients with temporal lobe epilepsy and in a pilocarpine-induced rat experimental epilepsy model, apelin expression increased in hippocampus and cortex structures (Zhang et al., 2011). The plasma apelin level in children with idiopathic generalized epilepsy treated with valproic acid was higher according to the control group (Meral et al., 2011). However, the reason for the increase in both the expression and plasma levels of apelin is unknown. The antinociceptive effect of apelin-13 (0.3, 0.5, 0.8 and 3 µg, i.c.v.) on opioid receptors, they also obtained a bell-shaped dose response curve (Xu et al., 2009). They determined that the most effective dose was 0.8 µg apelin-13 (i.c.v.) (Xu et al., 2009). A possible mechanism may be that apelin acts as an agonist at low concentrations and as a partial agonist at high concentrations (Xu et al., 2009). Apelin may act as a partial calcium agonist in $Ca^{2+}$ influx into the cell (Zeng et al., 2010). Uçar (2015) examined the effect of apelin-13 on epileptiform activity in penicillin model epilepsy, 15 µg apelin-13 (the most effective dose) increased the epileptic activity and a bell-shaped dose-response curve was obtained. Effective doses of apelin may have acted as a calcium agonist (Uçar, 2015). In different studies showing the chemotaxic effect of apelin-13 and its effect on gastrointestinal transit, a bell-shaped dose-response curve was obtained (Hosoya et al., 2000; Lv et al., 2011). In our previous study, we shown that the proconvulsant effect of apelin-13 on penicillin-induced epilepsy (Şen, 2016). This effect of apelin-13 may be since it induces neuronal $Ca^{2+}$ transfer. Because apelin dose-dependently induces $Ca^{2+}$ permeation in cerebrocortical neurons, it is also compatible with studies conducted on human NT2.N neurons (Choe et al., 2000). Activating neuronal $Ca^{2+}$ transients, blocking NMDA receptor-mediated $Ca^{2+}$ influx to defend against excitotoxicity, can stimulated by some GPCR ligands (Meucci et al. 2000, Deiva et al. 2004, Limatola et al. 2005, Yao et al. 2009). Likewise, apelin triggered dose-dependent and oscillatory $Ca^{2+}$ transients in cerebrocortical neurons (Cook et al., 2011). Neuroprotective chemokine GPCR ligands which trigger IP3 signaling can stimulate transient receptor potential canonical channels, a superfamily of $Ca^{2+}$ permeable channels. These channels blocked intracellular $Ca^{2+}$ during NMDAR activation (Yao et al. 2009). The modulation of apelin on channels can be a possibility for further investigation (Cook et al., 2011).

Apelin-36 activation of conventional (α, βI-βII, γ) or novel (δ, ε, η, θ) PKC isoforms. PKC activation necessitates $Ca^{2+}$ and/or lipid second messengers, i.e. DAG (Cook et al., 2011). PKC phosphorylation by apelin is inhibited via inhibitors of conventional and novel PKC isoforms, GF109203X and chelerythrine chloride. On the other hand 2-APB (inhibitor of $Ca^{2+}$ release from IP3 receptors) did not inhibit PKC phosphorylation because PKC phosphorylation happens

before its activation by $Ca^{2+}$. On the contrary, 2-APB inhibited ERK1/2 phosphorylation mediated by apelin, thus $Ca^{2+}$ -dependent conventional PKC isoforms may underlying mechanism apelin activation of ERK1/2 (Cook et al., 2011). Apelin activates $Ca^{2+}$ transients and reduces excitotoxic NMDA-R and calpain activity. And also, they correlate to raised $Ca^{2+}$ response to apelin with decreased response to NMDA, directly linking apelin-induced $Ca^{2+}$ transients to NMDA receptor attenuation (Cook et al., 2011). Some dissimilarity of apelin's effect suggest a different mechanism of low-dose apelin neuroprotection, including no apelin-induced $Ca^{2+}$ transients, widely delayed of NMDA-mediated $Ca^{2+}$ accumulation, decreased severity of the excitotoxic insult, and diminished rescue with apelin (Zeng et al. 2010). Difference in dose-dependent apelin signaling can give new perspective about apelinergic treatment.

## CONCLUSION

Apelin is widely expressed in some parts of the brain, such as the hypothalamus and hippocampus, and apelin levels change depending on pathological changes. Many studies on apelin have emphasized its neuroprotective properties. This review concentrates on the effect of apelin-13 on epilepsy. The role of apelin in epilepsy is contradictory. Because in different studies, it has been found that apelin has both anticonvulsant and proconvulsant effects in epilepsy. It is obvious that the role of apelin in epilepsy is unclear. While studies have shown that apelin has neuroprotective properties against NMDA-mediated excitotoxicity and prevents NMDA-mediated $Ca^{2+}$ accumulation, it has been reported that it does not affect $K^{+}$-dependent $Ca^{2+}$ accumulation. Based on this, apelin may have a proconvulsant effect on epilepsy by increasing intracellular calcium in different ways. Multiple mechanisms may mediate these effects of apelin including ROS, apoptosis. Advanced molecular and genetic studies are needed to clarify the confusion in epilepsy.

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