Title: Molecular Targets of Cannabidiol warn against its consumption during pregnancy

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Abstract: People use cannabidiol (CBD), the primary non-psychoactive cannabinoid of cannabis, as a treatment for symptoms that are commonly associated with pregnancy including nausea, pain, and anxiety. Many people believe CBD is safe to take during pregnancy. However, CBD crosses the placenta and affects the activity of protein targets that are expressed in the fetal brain. Cannabidiol alters the activity of ion channels including voltage-gated sodium, potassium, and calcium channels that control the electrical activity of neurons. Abnormal electrical activity could disrupt brain function via changes in axon growth and synapse structure and function. Furthermore, CBD alters the activity of G-protein coupled receptors that are expressed in the fetal brain and are important for axon growth and guidance suggesting that fetal exposure could prevent axons from reaching their correct targets. Indeed, cannabidiol exposure reduces axon growth in vitro and in vivo. This raises the possibility that CBD consumption during pregnancy could disrupt fetal brain development. Recent studies show that oral cannabidiol consumption during pregnancy alters the excitability of the pyramidal neurons of the prefrontal cortex and affects postnatal cognitive function in mouse offspring. Furthermore, fetal CBD exposure increases thermal pain sensitivity in offspring. Gestational cannabidiol exposure affects compulsivity and memory in a different rodent model. Here, we discuss how CBD affects various ion channels and G-protein coupled receptors, the roles of these proteins in neurodevelopment, and evidence that CBD affects neurodevelopment.

Significance Statement:
Cannabidiol (CBD) is taken to help with nausea and other symptoms that are common in pregnancy. Cannabidiol may be an alluring remedy for pregnancy symptoms. However, CBD readily crosses the placenta and reaches molecular targets important for fetal brain development. Animal studies suggest that gestational CBD exposure may affect offspring brain development and function.

Introduction:

CBD is the primary non-psychoactive cannabinoid of cannabis that is federally legal and is sold commercially across the United States, and in many other countries. Whole cannabis and its psychoactive component, tetrahydrocannabinol (THC), are legal to sell and consume in fewer countries. Whole cannabis and its component parts (THC and CBD) are used to treat nausea, anxiety, and pain, symptoms that are common to pregnancy pain (1-6). Among pregnant women, cannabis can be detected in 19-22% of umbilical cord tissue samples in Colorado and California (1, 2), where cannabis is legal. Self-reported and tissue assessments do not include consumption of CBD alone (without THC), suggesting that the total proportion of pregnancies exposed to CBD in some form is likely much higher. Given its touted therapeutic effects and unregulated market, a segment of the population including pregnant women will readily consume the federally legal CBD, even if they would be unwilling to consume whole marijuana or THC. In fact, in addition to the number of people who consume CBD as a component of whole cannabis (1, 2), survey data show that an additional 19% of pregnant people in the United States and Canada consume CBD alone, placing the percentage of pregnancies exposed to

CBD in some form at nearly 40% (6). In contrast to THC, CBD is primarily consumed orally or topically (6).

Cannabidiol crosses the placenta and accumulates in fetal brain tissue (7) suggesting that maternally consumed CBD can directly interact with receptors that are expressed in the fetal developing brain. CBD acts upon several ion channels and G-protein-coupled receptors (GPCRs) that are expressed in the developing brain (8-17). Human CBD consumption results in plasma concentrations from the nanomolar to 3 micromolar range depending upon the route of administration suggesting interactions that require higher CBD concentrations are likely not relevant to effects on humans (18-20). However, note that CBD accumulates in maternal plasma during pregnancy and the fetal brain, and thus may affect brain development at lower doses in humans (7, 21). This review compiles animal research about how CBD affects protein targets that are expressed in the central and peripheral nervous system, how CBD targets are important for fetal brain development, and what we know about how gestational CBD exposure affects offspring brain development and postnatal behavior.

Fetal CBD exposure affects postnatal behaviors

Gestational oral CBD consumption in two independent dosing paradigms alters postnatal mouse behavior. CBD and its metabolites are detectable in plasma of E18.5 pups and dams two hours after an oral 50 mg/kg CBD dose and are still detectable at P0, but are negligible at P4 and undetectable at P8 suggesting that any differences in offspring postnatal behaviors are due to differences in embryonic brain development rather than the effects of acute CBD exposure (22). Oral administration of 50 mg/kg CBD in sunflower seed oil or vehicle from embryonic day (E)5 until birth impairs problem-solving behavior in female, but not male, offspring (22). While gestational exposure to whole cannabis is associated with increased incidence in anxiety in humans, E5-birth fetal CBD exposure does not significantly alter anxiety behaviors in both female and male mice as measured by the elevated zero maze, the open field test, and the light-dark box (22).

Administration of 20 mg/kg CBD in honey daily starting two weeks before copulation and continuing throughout pregnancy and lactation *improves* spatial memory measured by the Y maze in female offspring (23). Oral consumption of 20 mg/kg CBD increased compulsivity as measured by marble burying in female, but not male offspring (23). Fetal CBD exposure resulted in large scale reduction in DNA methylation in the cortex and hippocampus of the exposed dam and her exposed offspring (23). In contrast, 50 mg/kg CBD oral CBD daily from E5-birth did not result in a difference in spatial memory as measured by the Y-maze and did not increase compulsivity (22). Of note, in these studies, fetal CBD exposure affects behaviors that are mediated by the prefrontal cortex (PFC) solely in the female offspring (22, 23). The differences between results in spatial memory and marble burying tests between the two studies may be due to differences in duration of exposure or the CBD dose administered to the dam. CBD could induce differences in postnatal behavior through its effects on ion channel function or G-protein coupled receptors that are expressed during embryonic and fetal development (Tables 1 and 2, Figure 1).

Fetal Cannabidiol exposure increases offspring thermal pain sensitivity

Oral consumption of 50 mg/kg CBD during pregnancy increases sensitivity to thermal pain in male, but not female offspring in mice (22). Several thermal sensing calcium channels such as Transient Receptor Potential Villanoid (TRPV) 1-4 are activated by CBD (9, 10, 24) (Table 1). Canabidiol-induced activation of these channels is followed by a refractory desensitization of the channels (8, 25). In contrast, CBD *antagonizes* a cold-sensing calcium channel called TRPM8 (25, 26). Many of these channels are expressed in the dorsal root ganglion and other neurons in the central and peripheral nervous system during fetal development (27-31), suggesting that their aberrant regulation following early CBD exposure could contribute to fetal CBD-induced thermal pain sensitivity in adult. Along with these results, fetal CBD exposure does not significantly affect thermal sensitivity in *TRPV1*$^{ko/ko}$ male mice like it does in wild type mice, demonstrating the excessive activation of TRPV1 by CBD is, at least in part, responsible for CBD-induced thermal pain sensitivity in male offspring (22).

Cannabidiol alters function of ion channels expressed in the developing central nervous system (Table 1)

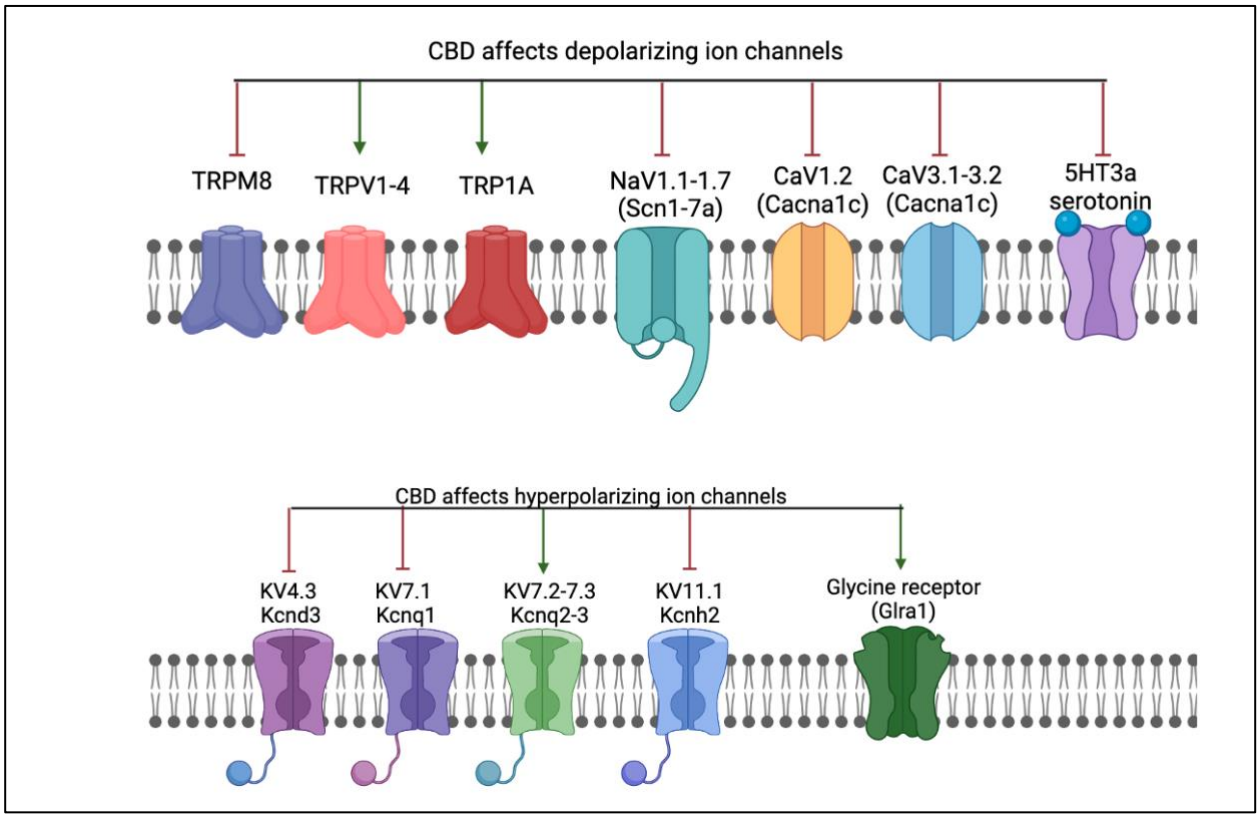
Ion Channel	Channel Function	Effect of CBD on channel	Embryonic/Fetal Expression
NaV1.1 (Scn1a)	Sodium influx (depolarizing) Loss of function mutations associated with epilepsy, Dravet syndrome (32) (33, 34) Important for neurite outgrowth (35, 36)	Inhibit-stabilizes closed state and prevents channel opening (37-41)	Human and mouse cortex (42) Human fetal astrocytes, P7 mouse neurons (28, 31)
NaV1.2 (Scn2a)	Sodium influx (depolarizing) Loss of function mutations cause epilepsy (34, 43) (44)	Inhibit-stabilizes closed state (38, 45)	Human and mouse cortex (42)
NaV1.3 (Scn3a)	Sodium influx (depolarizing)	Inhibit-stabilizes closed state (38)	E18 rat brain (46) Human fetal astrocytes (28, 47) P7 mouse neurons, OPCs, oligodendrocytes (31)

NaV1.4 (Scn4a)	Sodium influx (depolarizing) (48)	Inhibit-stabilizes closed state (37-39)	Human fetal astrocytes (28) (31)
NaV1.5 (Scn5a)	Sodium influx (depolarizing) Regulates cardiac muscle contraction (48)	Inhibit-stabilizes closed state (38, 41)	Human fetal astrocytes (28) (31, 49) Cardiac muscle (50, 51)
NaV1.6 (Scn8a)	Sodium influx (depolarizing) Loss of function mutations lead to epilepsy (34)	Inhibit-stabilizes closed state (38, 51)	P7 mouse astrocytes, neurons, OPCs, oligodendrocytes (31)
NaV1.7 (Scn9a)	Sodium influx (depolarizing) Loss of function mutations cause epilepsy (44)	Inhibit-stabilizes closed state (38, 40)	Dorsal Root Ganglion Neurons (Rat) (52)
Ca_V1.2 (Cacna1c) L-type calcium	Calcium influx (depolarizing) (53)	Inhibit (41)	P7 mouse neurons, OPCs (31)
Ca_V3.1 (Cacna1g) T-type calcium	Calcium influx (depolarizing) Cardiac pacemaker activity, neuronal excitability	Inhibit (54, 55)	P7 mouse neurons, OPC (31)
CaV3.2 (Cacna1h) T-type calcium	Calcium influx (depolarizing)	Inhibit (54-56)	P7 mouse neurons, astrocytes, OPCs (31)
KV4.3 (Kcnd3)	Potassium efflux (hyperpolarizing effect) in cardiac muscle (41, 57)	Inhibit (41)	P7 mouse OPC, neurons, Astrocytes (31)
KV7.1 (Kcnq1) mink Potassium voltage-gated channel subfamily KQT member 1 (58)	Potassium efflux (hyperpolarizing effect) (58)	Inhibit (IC50 2.7uM) (41)	P7 mouse endothelial cells (31)
KV7.2 (Kcnq2)	Potassium efflux (hyperpolarizing effect)	Agonize (59, 60)	P7 mouse neurons and OPCs (31), Human fetal astrocytes (28)
KV7.3 (Kcnq3)	Potassium efflux (hyperpolarizing effect)	Agonize (59)	Human fetal astrocytes (28)

			P7 mouse neurons oligodendrocytes (31)
KV11.1 (Kcnh2 or hERG- human ether a go go)	Potassium efflux (hyperpolarizing effect) (61)	Inhibit (41)	P7 mouse neurons and OPCs (31)
Alpha-1/Alpha1-Beta Glycine receptor (Glra1)	Chloride influx (62-71) (hyperpolarizing effect) Important for motor coordination, respiration, muscle tone, pain processing	Activate (100 umol/l (EC50 132.4+/- 12 umol/l and 144 +/- 22 umol/l) (62, 65, 72)	E11-18 rat spinal cord (73)
5-HT_{3A} (HTR3A)	Serotonin gated ion channel-transient membrane depolarizing(74)	Allosteric inhibitor (IC50 0.6uM) (EC50 1.2 and 1.4uM in absence and presence of CBD)(75, 76)	GABAergic (77) Neocortical interneurons (78) P7 neurons (31)
TRPV1 (79, 80)	Heat activated Sodium/Calcium influx (depolarizing): Neural crest (30)- excessive activation causes craniofacial and heart abnormalities	Activate and then desensitize (8-10, 24)	Human fetal astrocytes (28): Dorsal root ganglion (DRG) sensory neurons. Peripheral organs, skin, urinary tract, rectum, respiratory organs, stomach, colon, skeletal muscles (27) E10 Lens of the eye (29) Neural crest cells (30) Spinal cord neurons and Dorsal Root Ganglion from E13.5 mouse through adulthood (81)
TRPV2 (79, 80)	Heat activated Sodium/Calcium influx(depolarizing)	Activate followed by desensitization (10, 24, 82-85)	Spinal cord neurons and Dorsal Root Ganglion from E 10.5 mice (81)

TRPV3 (79, 80) (86)	Heat activated Sodium/Calcium influx (depolarizing)	Agonist followed by desensitization (87, 88)	Expressed in Keratinocytes(86) dorsal root ganglion, tongue, trigeminal ganglion, spinal cord, and brain (89)
TRPV4 (79, 80)	Heat activated Sodium/Calcium influx (depolarizing) (30) excessive activation causes craniofacial and heart abnormalities	Agonist followed by desensitization (87)	E10 mouse Lens of the eye (29) neural crest cells (30)
TRPM8 (79, 80) (90)	Cold activated Sodium/Calcium influx (depolarizing)	Antagonist (25, 26)	E13.5-P0 mouse DRG and spinal cord(81). Human fetal astrocytes (28) P7 mouse astrocytes, neurons, OPC, oligodendrocytes, endothelial cells, microglia (31)
TRPA1 (79, 80)	Heat activated Sodium/Calcium influx (depolarizing) in pain sensory neurons (91)	Agonist (26, 92)	Human fetal astrocytes (28)

Figure 1. Cannabidiol targets ion channels expressed in the central nervous system



Gestational Cannabidiol affects postnatal neuronal excitability and synapse function in the PFC

Consistent with female-specific altered problem-solving behaviors that are known to be mediated by the PFC, fetal CBD exposure decreases the excitability and synaptic strength of layer 2/3 pyramidal neurons of the female PFC at postnatal days (P)14-21 (22). Specifically, fetal CBD exposure increased minimum currents required to trigger action potentials. In addition, the amplitude of excitatory postsynaptic currents induced by uncaged glutamate was decreased only in female mice (22). These results suggest that gestational exposure to CBD disrupts prefrontal neuronal and synaptic function. One potential mechanism by which CBD could affect intrinsic excitability and synapse development is through its effect on multiple ion channels (Figure 1). For example, CBD inhibits several voltage-gated sodium channels that are expressed in the fetal central nervous system in humans and rodents (28, 31, 38, 42, 46, 93). Loss of function mutations in these voltage-gated sodium channels cause severe epilepsy which is associated with cognitive impairment (33, 34, 42, 44, 94). Perhaps CBD-induced inhibition of voltage-gated channels that are expressed in the cortex could alter neuronal activity and further affect activity-dependent cortical synapse development long term. Cannabidiol inhibits three voltage-gated calcium channels that are expressed in neurons and astrocytes in the

human and rodent fetal central nervous system (31, 54). CBD also alters voltage-gated potassium channels. Opening of potassium channels returns a depolarized neuron to resting membrane potential. CBD shifts the voltage at which voltage-gated potassium channels KV7.2/3 open so that they will bring neurons back to resting membrane potential faster (59). However, CBD inhibits KV4.3 and KV11.1(41), which may increase the duration of action potentials in cells that express these channels. In addition to the direct regulation of voltage-gated channels, CBD inhibits 5Ht3a receptor, a serotonin-gated calcium channel that is expressed in the fetal GABAergic interneurons, which regulate cortical excitability and synaptic plasticity in the rodent cerebral cortex (78, REF). Cannabidiol acts as an agonist at 5HT1a receptors in humans and rodents, which can hyperpolarize pyramidal neurons via Gαi coupled inhibitory mechanisms (95-97). Thus, CBD directly affects multiple ion channels and GPCRs that are expressed in the developing cortex, which may explain how gestational exposure to CBD could disrupt synapse development and alter neuronal excitability of regions of the brain that express these protein targets.

Cannabidiol interacts with G-protein coupled receptors (Table 2)

G-protein Receptor	**Protein Function**	**Effect of CBD on GPR**	**Expression**
GPR 3 G-protein coupled receptor 3 (98, 99)	Stimulates cyclic AMP accumulation Promotes neurite outgrowth (100, 101)	Inverse agonism (102, 103)	Retinal Ganglion Cells (104), Cerebellar granular neurons (101, 104) Cortex, pituitary, thalamus, hypothalamus, amygdala, hippocampus, cerebellum, eye, lung, kidney, liver, testes, ovary (13, 99, 105-107)
GPR 6 G-protein coupled receptor 6 (108)	Stimulates cyclic AMP accumulation (increases levels) Promotes neurite outgrowth (100)	Inverse agonism (102, 103)	Higher expression in rodent cerebellar granular neurons (100)
GPR 12 G-protein coupled receptor 12 (109, 110)	Stimulates cyclic AMP accumulation Promotes neurite outgrowth (100)	Inverse agonist (103, 111)	Frontal cortex, Cerebral cortex, hippocampus, striatum, hypothalamus, thalamus, piriform cortex, olfactory

			bulb, pituitary, lateral septal nuclei (112, 113) starting at E14.5 in mouse (114)
GPR 55 G-protein coupled receptor 55 (115)	Release of calcium from ER stores, Activates the ERK1/2 and RhoA pathways, Activates transcription factors (116-118)	Antagonism (118)	E14-P0 Embryonic mouse retina neurons (119) Embryonic zebrafish central nervous system and sensory neurons (120)
$5HT_{1A}R$ 5-hydroxytryptamine receptor 1A	Inhibition of adenylyl cyclases (via Gai/o) and regulation of potassium and calcium ion channels to inhibit neuronal activity and reduce intra cellular calcium concentration (121) (122)	Agonism (14, 97, 123)	Rat brain starting at E12 (124) Hippocampus (125) Prefrontal cortex, (126-129)
CB1 Cannabinoid Receptor 1 (130, 131)	Gi/o inhibition of adenylate cyclase and arrestin recruitment (132, 133) (134) Activation of extracellular signal-regulated kinase (ERK) signaling (135)	Increases availability of endogenous ligand, but can have negative allosteric effects (136)	Highly expressed in the central nervous system of mouse, rat, and human (137, 138)
CB2 Cannabinoid Receptor 2 (139)	Signals through G-alpha-S to induce IL6 and IL10 (140) Signals through Gi/o to inhibit adenylate cyclase (141)	Increases availability of endogenous ligand, but can have negative allosteric effects (136)	Immune system (138), Lower expression in cortex, striatum, hippocampus, amygdala, brainstem, cerebellum (142-147)

Cannabidiol disrupts axon growth and guidance.

Cannabidiol reduces axon growth rate and disrupts axon guidance through its effect on G-protein-coupled receptors (119). CBD inhibits GPR55 to cause growth cone collapse and reduce axon growth rate overall in cultured neurons (118, 119). Furthermore, CBD exposure disrupts retinal projection axon growth and guidance in mice and hamsters (118, 119). In addition, CBD also disrupts function of GPR3 (102), a G-protein coupled receptor that induces neurite outgrowth in multiple neuronal cell types (101, 104). While CBD does not directly bind CB1, it can increase the availability of an endogenous ligand, endocannabinoid, that activates CB receptors (148). Both CB1 and CB2 are important for axon guidance (149, 150). The activation of CB1 causes the collapse of growth cones (151-153). Regulation of CB1 is important for axon growth, guidance, and fasciculation (154, 155), suggesting that aberrant activation of CB1 could disrupt correct axon guidance. At very high concentrations, CBD is a partial agonist for D2 dopamine receptors which are expressed in the developing cerebral and cerebellar cortex in rodents, but this interaction is likely not physiologically relevant because the CBD concentrations reached in humans are not sufficient for the interaction (156, 157). CBD activates TRPV2, a channel that is expressed embryonically and stimulates axon growth (81), suggesting that the effect of CBD on axon growth likely depends on cell types and the population of receptors it expresses. In other cellular contexts, CBD interferes with sonic hedgehog (Shh) signaling, which is required for axons crossing from one hemisphere of the brain to the other (158, 159). In addition to disrupting multiple molecular signaling cascades that are important for axon growth and guidance, CBD affects ion channel function (Table 1, Figure 1) and neuronal activity that modulates axon growth (160). Thus, there are many mechanisms by which CBD may disrupt axon growth and guidance during brain development.

Cannabidiol may alter the number of neurons and astrocytes in the developing brain

Cannabidiol decreases viability of several cell types in the developing brain. CBD concentrations as low as 0.1 μM induce apoptosis of perinatal rat cortical neurons (161). Similar CBD concentrations reduce viability of oligodendrocytes (162). A slightly higher CBD concentration (0.5 to 5 μM) causes apoptosis of rat perinatal cortical astrocytes (161). The neurotoxic effects of CBD are not observed in all neuronal types. For example, lower concentrations of CBD have a protective effect on mouse hippocampal neurons (163). In fact, while whole cannabis or THC exposure is associated with reduced hippocampal volume in adult humans, CBD exposure diminishes this effect through increasing neurogenesis in the hippocampus (164). These results may help explain how 20 mg/kg CBD during gestation improves female offspring performance in spatial memory tasks that depend upon hippocampal function (23). However, fetal exposure to higher concentrations of CBD does not improve or reduce spatial memory in offspring (22). CBD may have varying effects on cells depending upon the protein targets they express at the time of exposure.

Conclusion

Whole cannabis and its psychoactive component, THC, have been extensively studied for adverse effects on fetal development (21, 164-171). However, studies on CBD usage in pregnant women remain scarce likely because it is not psychoactive and has been widely legalized. This is concerning because CBD helps with pregnancy symptoms (172, 173) many believe CBD is without risk (174). In this review, we presented a summary of the available data on the molecular CBD targets that are expressed in the fetal and perinatal brain and peripheral neurons. Specifically, we identify many ion channels and receptors expressed in the developing central and peripheral nervous system that could mediate the effects of CBD during prenatal exposure. While the prevalence of CBD use is on the rise (172), the mechanistic links between early CBD exposure and its potential impact upon neurodevelopmental pathology remain elusive. Importantly, experimental evidence shows that CBD consumption during pregnancy causes poor cognition and thermal pain sensitivity in offspring in mice (22), and thus could have detrimental effects on offspring if exposed during pregnancy. More studies are needed to better understand the biological mechanisms behind CBD-mediated effects on brain development during this critical time. Larger studies are thus needed to assess the public health impact of CBD treatment and to elucidate the safety of CBD during pregnancy use.

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