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TOPICAL REVIEW

Cannabinoid exposure during pregnancy: Cardiorespiratory effects and offspring outcomes

Luis Gustavo A. Patrone[1] and Luciane H. Gargaglioni[2]

[1]*Department of Physiology and Biophysics, Institute of Biological Science, Federal University of Minas Gerais – UFMG, Belo Horizonte, MG, Brazil*
[2]*Department of Animal Morphology and Physiology, São Paulo State University – UNESP/FCAV, Jaboticabal, SP, Brazil*

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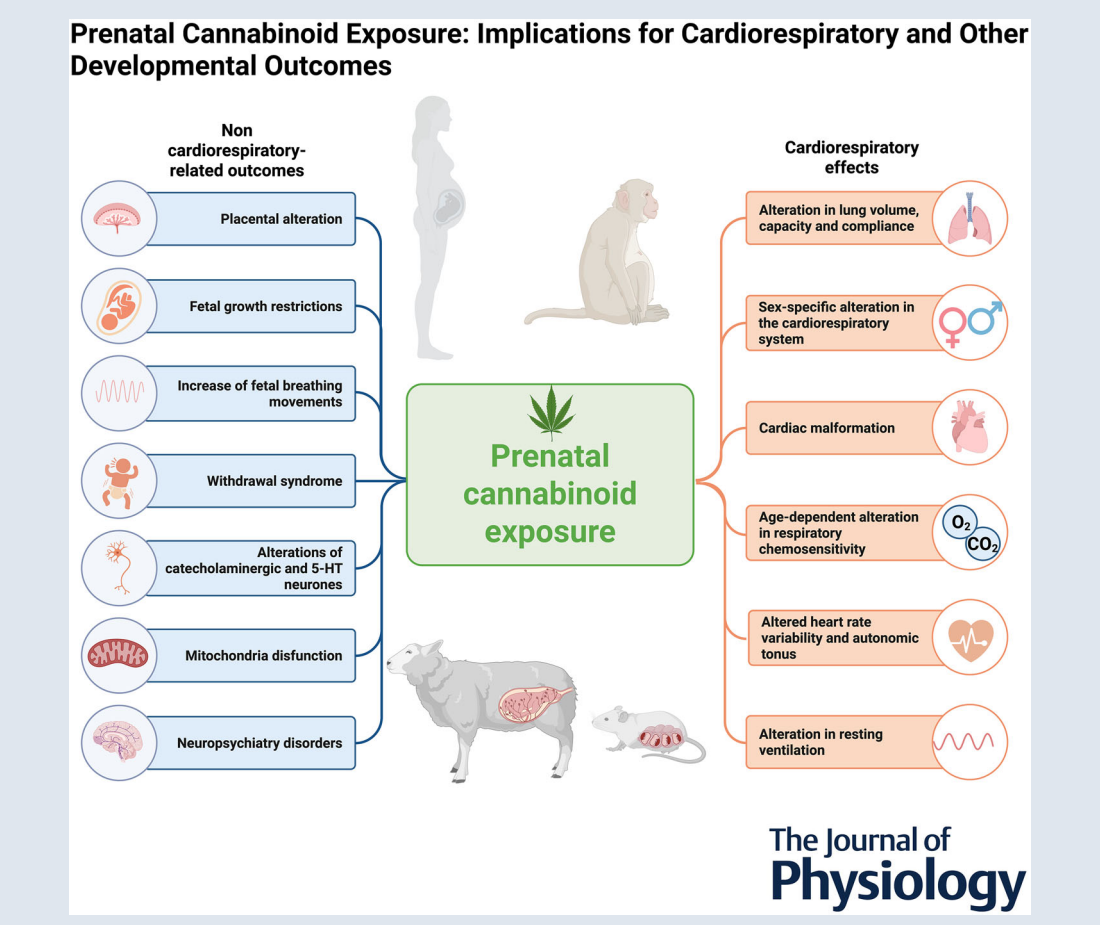

Abstract figure legend Prenatal exposure to cannabinoids has been investigated across human and animal studies to understand its impact on physiological development. Evidence suggests that early-life cannabinoid exposure influence multiple developmental processes, extending beyond neurodevelopmental outcomes to potentially affect placental function, metabolic and cellular pathways, and the maturation of cardiorespiratory control systems. These observations raise important questions about how prenatal environmental exposures shape integrated physiological regulation and long-term health trajectories. This review synthesises current evidence from human and experimental models, highlighting developmental pathways relevant to cardiorespiratory regulation, potential sex-dependent effects, and important gaps in our understanding of these processes.

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Abstract Cannabinoid use during pregnancy has risen worldwide in recent years, driven by both recreational use and perceived therapeutic benefits. While most existing research has concentrated on neuropsychiatric outcomes and structural or functional changes in the offspring's forebrain regions, comparatively little attention has been given to the potential effects on cardiorespiratory control. This gap is important, as prenatal exposure to cannabinoids may disrupt the development of neural circuits responsible for autonomic and respiratory functions, including brainstem networks, potentially resulting in long-lasting changes in ventilatory responses, cardiovascular regulation and homeostatic reflexes. Understanding these effects is especially vital due to the role of the endocannabinoid system in modulating neuronal excitability, neurotransmission and developmental processes. This review synthesises current evidence from both clinical and experimental studies, emphasising the mechanisms by which prenatal cannabinoid exposure could influence cardiorespiratory physiology in a sex-dependent manner, identifying key methodological limitations in the field and gaps in the literature, and proposing future research directions to fill this knowledge gap.

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Corresponding authors: L. G. A. Patrone: Departamento de Fisiologia e Biofísica, ICB/UFMG, Avenida Presidente Antônio Carlos, 6627; Campus UFMG, 31270-901, Belo Horizonte, MG, Brasil. luisgustavo.patrone@gmail.com
L. H. Gargaglioni: Via de acesso Paulo Donato Castellane s/n, 14870-000, Departamento de Morfologia e Fisiologia Animal, Faculdade de Ciências Agrárias e Veterinárias, Universidade Estadual Paulista Júlio de Mesquita Filho, Jaboticabal, SP, Brasil. Email: luciane.gargaglioni@unesp.br

Introduction

Cannabis is now one of the most widely used drugs globally, after alcohol and tobacco, and is the most consumed psychoactive substance under international control. According to the World Drug Report 2024 published by the United Nations Office on Drugs and Crime (UNODC), an estimated 228 million individuals (5.6% of the world's population aged 15–64 years) used cannabis at least once in 2022, marking a 20% increase in the number of users over the past decade (UNODC, 2024) (Fig. 1*A*). Between 2003 and 2020, the prevalence of cannabis use among women grew significantly worldwide by 136%, compared to a 64% rise among men, leading to a narrowing of the sex gap in cannabis consumption (UNODC, 2022) (Fig. 1*B*). Estimates indicate that these numbers continue to grow, reflecting changing social attitudes, trends towards legalisation, and increasing availability across various regions of the globe (Doggett et al., 2025; Wang et al., 2024).

The legalisation and regulation of cannabis worldwide vary considerably at both national and sub-national levels (Room, 2004). This includes differences in legal status (illegal, decriminalised, or legal for medical or recreational use), regulation systems (e.g. licensing, production controls, taxation), and the priorities and scope of law enforcement efforts, leading to diverse experiences and outcomes globally. Epidemiological studies demonstrate that cannabis is the most widely used psychoactive substance among pregnant women worldwide, with a pre-


Luis Gustavo A. Patrone holds a PhD in Physiological Sciences from the Federal University of São Carlos (UFSCar) within an interinstitutional programme with São Paulo State University (UNESP), and is a newly appointed faculty member at the Federal University of Minas Gerais (UFMG), Brazil, where he investigates developmental physiology, respiratory control, and the effects of prenatal exposure to pharmacological agents on neural and cardiorespiratory function. His work combines in vivo and in vitro approaches, integrating developmental biology, pharmacology, and neurophysiology to advance understanding of how early-life environments shape physiological systems and influence susceptibility to behavioural and respiratory disturbances later in life. **Luciane Gargaglioni** holds a degree in Biological Sciences from the University of São Paulo (1994) and MSc and PhD degrees in Physiology from the School of Medicine at the University of São Paulo (1998, 2002). During her doctoral training, she was a visiting researcher at the University of British Columbia (Canada). She completed postdoctoral training at the University of Calgary (Canada) and at the Centre national de la recherche scientifique (CNRS), France. She is currently an Associate Professor at São Paulo State University (UNESP). Her research focuses on respiratory and comparative physiology, with expertise in hypoxia, hypercapnia, sexual dimorphism, prenatal stress, ventilation, thermoregulation, locus coeruleus and serotonin, and she has 125 publications focusing on breathing control.

valence ranging from 3% to 16%, and even higher within specific demographic subgroups (NIDA, 2025; Singh et al., 2020; Volkow et al., 2019). Moreover, cannabis use during pregnancy is expected to continue rising, particularly where recreational marijuana has been legalised. Evidence indicates a link between legalisation and increased marijuana consumption during pregnancy and postpartum, likely due to reduced perceived risk and easier access (Brown et al., 2017; Skelton et al., 2020). Interestingly, between 34% and 60% of women who used marijuana before pregnancy continue to do so afterwards (Young-Wolff et al., 2019). Self-report studies over the past decade reveal a notable rise in cannabis use during the first trimester of pregnancy, with significant increases also observed in later stages (Hayes et al., 2023; Young-Wolff et al., 2018) (Fig. 1*C*). One of the most common reasons cited by pregnant women for ongoing use is the belief that cannabis is relatively harmless to maternal and fetal health, despite growing evidence of its potential adverse effects on neurodevelopment. Additionally, its use for alleviating symptoms such as nausea, anxiety and sleep disturbances, which may encourage continued use throughout pregnancy (Brown & Graves, 2013; Jarlenski et al., 2017), acts as a motivator.

Due to their lipophilic nature, cannabis products readily cross the placenta and can reach high fetal concentrations with repeated exposures (Richardson et al., 2016). Exposure to exogenous cannabinoids *in utero* may interfere with fetal endocannabinoid signalling pathways during neurodevelopment, causing long-lasting effects (Bara et al., 2018). Many components present in *Cannabis sativa* influence neural and physiological functions, including motor, cognitive, nociceptive, thermoregulatory and cardiorespiratory processes, through the interaction with cannabinoid receptors (Devane et al., 1988; Onaivi et al., 2002; Patrone et al., 2023, 2024, 2025). Furthermore, during fetal life, endocannabinoids are vital for brain development, regulating the differentiation of neural progenitor cells, the formation of synaptic junctions (synaptogenesis), the chemoattraction and repulsion guiding axonal migration, and the activity-dependent refinement and stabilisation of synaptic transmission (Bernard et al., 2005; Fernández-Ruiz et al., 2000; Fride et al., 2009; Maccarrone et al., 2014). Therefore,

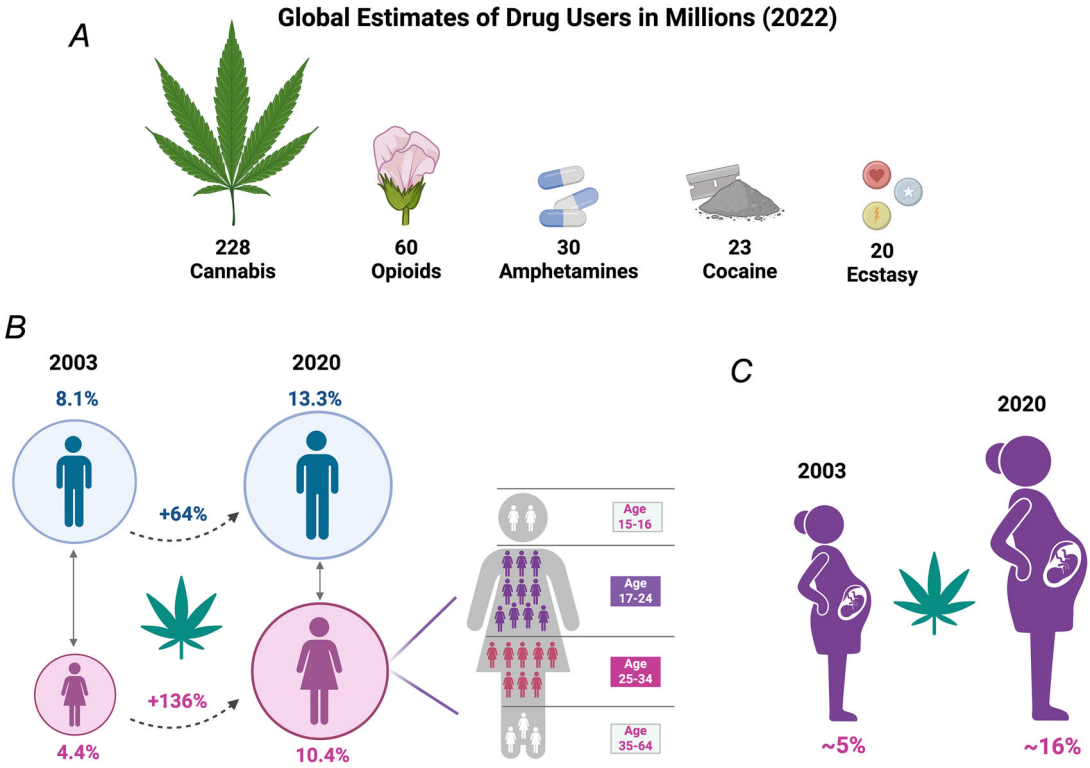

Figure 1. Schematic overview of global drug use estimates and trends, with an emphasis on cannabis use during pregnancy
A, estimated number of users (millions) in 2022 for the most widely used drugs worldwide. *B*, increases in the prevalence of cannabis use among men and women between 2003 and 2020, with a notable rise in women; most female users are aged 17–34 years. *C*, increases in the prevalence of cannabis use among pregnant women from 2003 to 2020. Data adapted from UNODC (2022, 2024) and Hayes et al. (2023). Created with BioRender – licensed to L.H.G.

disruption of endocannabinoid signalling during critical developmental windows can have enduring neurodevelopmental consequences, and understanding prenatal cannabis exposure is essential due to its potential to induce fetal programming effects – long-lasting alterations in the structure, physiology and metabolism of the developing fetus that can persist into postnatal life and elevate the risk of various health issues later on.

In this review, we explore the implications of chronic stimulation of the endocannabinoid system (ECS) during gestation, focusing on its effects on the cardiorespiratory system in both humans and pre-clinical models. We explore how prenatal exposure to cannabinoids, whether endogenous, plant-derived (such as Δ^9-tetrahydrocannabinol, Δ^9-THC), or synthetic, may influence the cardiorespiratory system across short-, medium- and long-term periods. Additionally, we assess current evidence to determine whether the effects of prenatal exposure to synthetic cannabinoids show sex-dependent differences. Finally, we highlight critical gaps in the existing literature, particularly regarding dose–response relationships, sex-specific outcomes, and long-term effects. These gaps present challenges to establishing causality but also offer valuable opportunities for intervention, especially amid increasing cannabis use during pregnancy and the rise of high-potency synthetic cannabinoids.

Cannabinoids and their modes of action

Endocannabinoid system and its role in development. The ECS comprises G-protein-coupled cannabinoid receptors type 1 and 2 (CB_1 and CB_2), endogenous ligands (endocannabinoids), and proteins involved in the synthesis and inactivation of endocannabinoids (Di Marzo et al., 2005; Di Marzo & Petrocellis, 2006; Piomelli, 2003). CB_1 and CB_2 receptors have been identified in the preimplantation mouse embryo (Yang et al., 1996). Research has shown that the CB_1 receptor is the most prevalent G-protein-coupled receptor in the central nervous system (CNS), including in regions involved in cardiorespiratory control and the sleep–wake cycle (Calik & Carley, 2017; Herkenham et al., 1991; Méndez-Díaz et al., 2021; Pilowsky & Goodchild, 2002; Tsou et al., 1998) (Fig. 2). For a thorough overview of both cannabinoid receptors, their ligands and the mechanism of action, see the report by the International Union of Pharmacology (Howlett et al., 2002).

In 2018, Dr Vincenzo Di Marzo and his research group introduced the concept of the 'endocannabinoidome' to describe a signalling network significantly broader and more complex than the classical ECS. This expanded system includes not only the well-characterised endocannabinoids but also a diverse array of related lipid mediators, their receptors and metabolic enzymes, thereby surpassing the traditional boundaries of the ECS (Di Marzo, 2018). The endocannabinoidome incorporates various non-endocannabinoid long-chain fatty acid amides and esters, including: (i) congeners of anandamide (AEA), such as *N*-acylethanolamines (NAEs), and congeners of 2-arachidonoylglycerol (2-AG), known as 2-acyl-glycerols (2-AcGs); (ii) *N*-acyl amino acids; (iii) acylated neurotransmitters, including *N*-acyl-dopamines and *N*-acyl-serotonins; and (iv) primary fatty acid amides. Many of these lipid mediators share biosynthetic and degradative enzymes with AEA and 2-AG, particularly for their respective congeners, but do not necessarily target the classical cannabinoid receptors (CB_1 and CB_2). Instead, the broader network of receptors engaged includes orphan G protein-coupled receptors (GPCRs), ligand-gated ion channels, and peroxisome proliferator-activated nuclear receptors (PPARs). Due to this diversity, these small molecules are more accurately described as endocannabinoid-like (eCB-like) mediators rather than strict ECS components (Cristino et al., 2020; Iannotti & Di Marzo, 2025; Di Marzo, 2018). The entire endocannabinoidome comprises over 100 lipid mediators, approximately 20 metabolic enzymes and around 20 receptors, forming a highly intricate and pleiotropic signalling system with broad physiological and pharmacological roles (Iannotti & Di Marzo, 2025).

Aside from the endocannabinoidome, the 'paracannabinoidome' includes additional signalling molecules and pathways that may interact with or run parallel to cannabinoid signalling but are not strictly part of the endocannabinoidome (Passani et al., 2023). The paracannabinoidome comprises lipid mediators, including *N*-acylethanolamines (NAEs), such as oleoylethanolamide (OEA) and palmitoylethanolamide (PEA), as well as fatty acyl esters, such as 2-oleoyl-*sn*-glycerol. Unlike endocannabinoids, paracannabinoids do not primarily act through the CB_1 and CB_2 receptors. Instead, they target other molecules, such as nuclear receptors including peroxisome proliferator-activated receptor-α (PPAR-α), transient receptor potential vanilloid-1 (TRPV1) channels, and G-protein-coupled receptor 119 (GPR119) (Friuli et al., 2025; Passani et al., 2023). Emerging research highlights their role in a broad range of pathological conditions, including chronic pain, metabolic disorders and neurodegeneration, emphasising their potential as versatile modulators of both physiological functions and disease processes (Friuli et al., 2025).

Endocannabinoid signalling plays a vital role throughout early pregnancy, affecting preimplantation embryo development, oviductal transport and uterine implantation (Sun & Dey, 2009). Both CB_1 and CB_2 receptors are present in preimplantation embryos, with

CB_1 being uniquely localised in the oviduct and uterus (Paria et al., 1995). CB_1 and CB_2 receptor mRNAs show temporally distinct expression patterns, with CB_2 mRNA appearing to be maternally derived, as it is present in the mouse preimplantation embryo from the one-cell stage onward and persists through the blastocyst stage. In contrast, CB_1 mRNA accumulation coincides with embryonic genome activation. Therefore, the overlapping expression of both receptors during this period suggests that the embryo may be responsive to cannabinoid agonists at all preimplantation stages. AEA and its metabolic enzymes exhibit carefully regulated spatial and temporal gradients that control embryo movement through the oviduct and the timing of implantation (Wang, Guo et al., 2004).

The ECS was also found to exist in the CNS during mid-gestation (Harkany et al., 2007; Herkenham et al., 1991; Rodriguez de Fonseca et al., 1993), as CB_1 receptors and their ligands, along with mRNA levels, were identified between the 11th and 14th day of gestation in rats. This period coincides with the phenotypic expression of most neurotransmitters (Morozov et al., 2009; Mulder

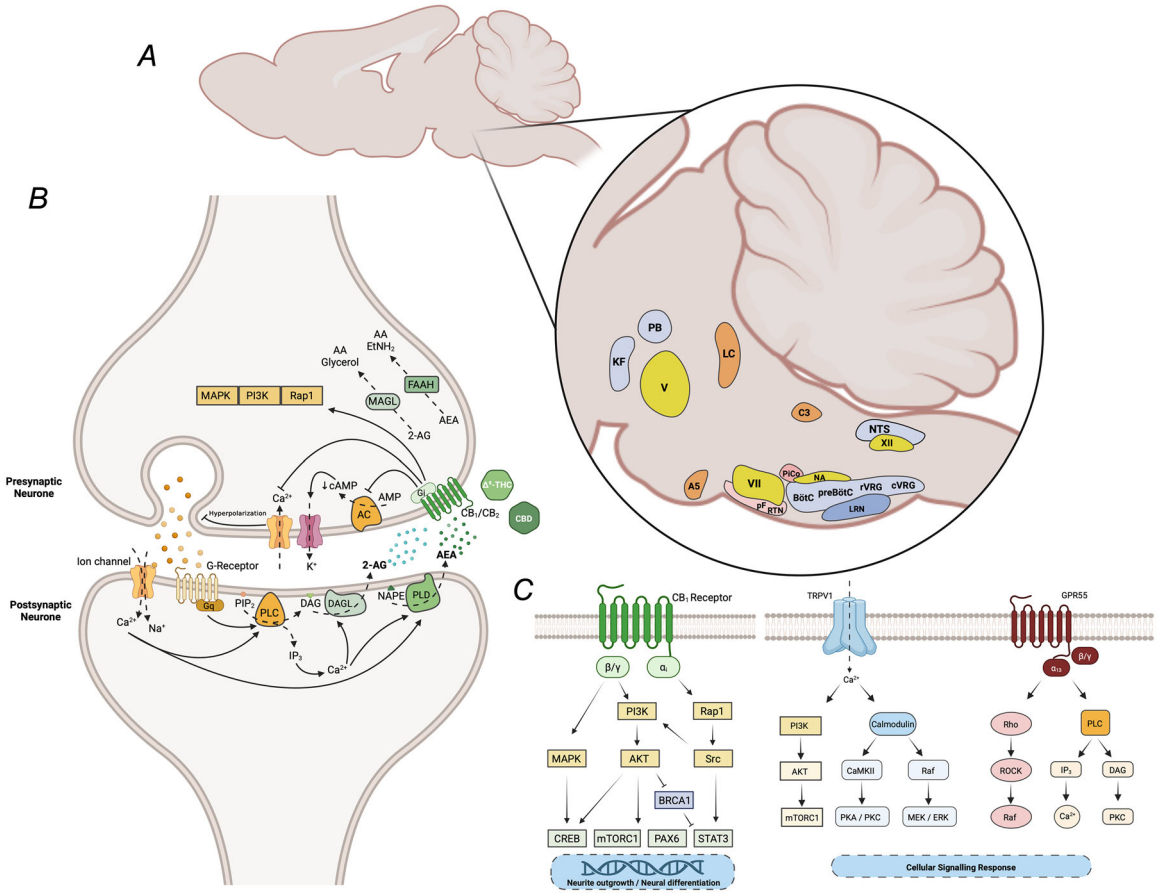

Figure 2. Schematic illustration of the brainstem cardiorespiratory network and endocannabinoid signalling via CB_1, TRPV1 and GPR55
A, sagittal section of a rodent brain showing key brainstem nuclei involved in cardiorespiratory control, including the A5 region (A5), Bötzinger complex (BötC), C3 region (C3), caudal ventral respiratory group (cVRG), facial motor nucleus (VII), hypoglossal nerve (XII), Kölliker–Fuse (KF), lateral reticular nucleus (LRN), locus coeruleus (LC), nucleus ambiguus (NA), nucleus of the solitary tract (NTS), parabrachial nucleus (PB), parafacial region (pF), post-inspiratory complex (PiCo), preBötzinger complex (preBötC), rostral ventral respiratory group (rVRG) and trigeminal motor nucleus (V). *B*, endocannabinoid signalling through pre- and postsynaptic neurones. Neurotransmitters are released from presynaptic terminals and activate ionotropic and/or metabotropic receptors, causing postsynaptic depolarisation via Ca^{2+} influx and G_q-protein signalling. Elevated Ca^{2+} levels promote endocannabinoid synthesis through PLC and PLD, with 2-AG production also facilitated by G_q-protein activation. Endocannabinoids then diffuse into the synaptic cleft and engage presynaptic CB_1 and CB_2 receptors. Key downstream effects of CB receptor activation and G_i-protein signalling include inhibition of AC activity, membrane hyperpolarisation via modulation of K^+ and Ca^{2+} channels resulting in reduced neurotransmitter release, and activation of protein kinase cascades such as the MAPK, PI3K and Rap1 pathways. *C*, signal transduction mechanisms via activation of CB_1, TRPV1 and GPR55 receptors; arrows indicate stimulation, whereas barred arrows indicate inhibition. Created with BioRender – licensed to L.H.G.

et al., 2008). CB_1 receptors are expressed early in neural progenitors and on growing axons, particularly in white-matter neuronal fibres during embryonic stages, where they regulate growth cone dynamics, which are crucial for accurate axonal pathfinding and target selection (Berghuis et al., 2007). This mechanism was reported by Berghuis et al. (2007), who showed that endocannabinoid activation causes growth cone collapse or repulsion, thereby guiding interneuron axons appropriately. Beyond direct axon guidance, the ECS does not act in isolation but interacts hierarchically with classical developmental signalling pathways (Berghuis et al., 2005, 2007). For example, brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) converge with CB_1 signalling through extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase (PI3K) kinase cascades (Fig. 2). Fibroblast growth factor receptor (FGF) activation can enhance local 2-AG synthesis via diacylglycerol lipase, and eCB modulation of growth-cone responsiveness integrates with Slit/Robo and other guidance cues (Alpár et al., 2014). In fact, the absence of CB_1 receptor-mediated Robo1 accumulation in growth cones likely disrupts the intracellular signalling required for appropriate responsiveness to Slit cues, thereby impairing axonal navigation (Alpár et al., 2014). Such deficits may underlie, at least in part, the abnormal topography of corticofugal axons reported in CB_1 receptor knockout mice. These interactions enable the ECS to modulate excitatory and inhibitory neurotransmission, which is essential for circuit-level homeostasis and refinement during development and adolescence.

CB_1 receptors are already present in the cortical plate of 9-week-old human embryos (Zurolo et al., 2010). During mid-gestation (18–22 weeks of human embryonic development), CB_1 mRNA expression was most prominent in the hippocampal formation, particularly in the CA2 and CA3 subfields; this distribution persisted into adulthood (Wang et al., 2003). At this developmental stage, the amygdaloid complex was the only other structure to exhibit expression levels comparable to those of the hippocampus. In contrast, neocortical, thalamic, and other subcortical regions displayed markedly lower transcript abundance. The overall CB_1 mRNA expression pattern in the human brain was similar to that of the rat for most brain structures studied in both adult and fetal brains (Wang et al., 2003).

A strong signal of CB_1 receptor mRNA is expressed across numerous brainstem and midbrain regions in rats at various stages of fetal development (Berrendero et al., 1998). In contrast, faint expression is observed in these regions in the adult brain (Mailleux & Vanderhaeghen, 1992). Additionally, intermediate CB_1 receptor binding densities are observed in these structures on gestational days (GD)16 and 18, consistent with earlier findings at GD21 (Romero et al., 1997). Conversely, maximal stimulation of $[^{35}S]GTP\gamma S$ binding by the CB_1 agonist WIN55,212-2 is detected in the brainstem and midbrain but not in the typical CB_1-rich areas such as the hippocampus, cerebellum and caudate-putamen. These findings suggest that CB_1 receptor signalling plays a unique and previously unrecognised role in the brainstem and midbrain during fetal development.

Indeed, during fetal life, endocannabinoids play a crucial role in brain development, regulating the interneuron migration and differentiation (Berghuis et al., 2005), synaptogenesis (Keimpema et al., 2010), guiding axonal migration (Berghuis et al., 2007), and consolidating synaptic communication (Bernard et al., 2005; Fernández-Ruiz et al., 2000; Fride et al., 2009; Maccarrone et al., 2014). CB_1 receptor expression exhibits a region-specific, developmentally regulated profile in the rat brain. Early studies demonstrated that CB_1 receptor density (Rodríguez de Fonseca et al., 1993) and mRNA levels (McLaughlin & Abood, 1993) steadily increase in the cerebellum and brainstem during the first postnatal weeks, reaching a plateau between postnatal days (P) 18 and 21. In contrast, CB_1 receptor expression in forebrain regions remains relatively stable during this same period (McLaughlin & Abood, 1993). As development progresses, CB_1 receptor levels in cortical and subcortical areas rise progressively throughout the juvenile period, peaking between P30 and P40, which corresponds to the peripubertal stage, before declining to reach stable levels in adulthood (Berrendero et al., 1999; Rodríguez de Fonseca et al., 1993). This temporal pattern suggests that the ECS undergoes a dynamic maturation, with particularly high receptor availability during critical windows of synaptic pruning and network reorganisation. Such transient overexpression of CB_1 receptors in specific brain regions may modulate neuroplasticity, neuronal connectivity and behavioural programming during postnatal development.

As to the expression of CB_1 receptors in areas involved in cardiorespiratory control during development, CB_1 mRNA is differentially expressed in peripheral arterial chemoreceptors, with the highest abundance in the nodose–petrosal–jugular complex, moderate levels in the superior cervical ganglion and minimal expression in the carotid body, and this expression increases progressively throughout postnatal development for P5–P14 (McLemore et al., 2004). Immunohistochemical analyses reveal a unique subcellular localisation of CB_1 receptors predominantly within the nuclei of ganglion cells in sensory and autonomic ganglia, in contrast to its cytoplasmic distribution in cortical and hippocampal neurons, suggesting distinct functional roles across central and peripheral sites. Furthermore, a subset of petrosal ganglion neurons coexpresses tyrosine hydroxylase (TH) and CB_1 receptors, indicating potential involvement in

catecholaminergic (CA) sensory pathways that modulate cardiorespiratory reflexes during early life (McLemore et al., 2004).

Regarding CB_2 receptors, the expression of mRNA for this receptor has been detected in the embryonic rat brain around GD11 (Buckley et al., 1998). Although their presence has been reported in the CNS, for example, in the cerebellum, hippocampus and restricted areas of the brainstem (Chen et al., 2017; Onaivi et al., 2006; Van Sickle et al., 2005), these are mainly expressed in cells of the immune system (Munro et al., 1993). However, it is now well established that both receptors are expressed in the periphery and the CNS, including peripheral chemoreceptors and the neuronal circuitry responsible for cardiorespiratory control (McLemore et al., 2004; Padley et al., 2003).

Among cannabinoid receptor ligands, AEA (Devane et al., 1992) and 2-AG (Mechoulam et al., 1995) were the first compounds identified and isolated, and they are the most extensively studied among the endocannabinoids. These compounds are also present from early development and play critical roles in the formation and maturation of the nervous system. During the fetal period, AEA is present at significantly lower concentrations than 2-AG (Fernández-Ruiz et al., 2000), and the developmental trajectories of these two endocannabinoids differ markedly. AEA levels gradually increase throughout ontogeny, reaching adult concentrations only after birth (Berrendero et al., 1999). In contrast, 2-AG is already present at relatively high levels during fetal development, with concentrations comparable to those seen in juvenile and adult brains. Interestingly, 2-AG levels peak on the first postnatal day in rats, suggesting a specific role in the perinatal transition (Berrendero et al., 1999).

Additionally, various enzymes such as diacylglycerol lipase (DAGL), monoacylglycerol lipase (MAGL), *N*-acyl phosphatidylethanolamine-specific phospholipase D (NAPE-PLD), and fatty acid amide hydrolase (FAAH) also play vital roles in the development of brain circuitry (Maccarrone et al., 2014; Punt et al., 2022). The expression of key endocannabinoid enzymes, including DAGLα, MAGL, NAPE-PLD and FAAH, follows distinct temporal patterns aligned with their functional roles during brain development (Maccarrone et al., 2014). DAGLα, primarily responsible for synthesising 2-AG, is present early in embryogenesis in axonal tracts, where it facilitates retrograde signalling; supports axonal growth and projection through 2-AG synthesis; and its expression remains strong throughout embryogenesis and into adulthood, shifting to a postsynaptic localisation (Bisogno et al., 2003). This enzyme shows higher levels in excitatory neurons within hippocampal and cortical circuits, supporting its role in synaptic modulation (Punt et al., 2022). MAGL, the primary enzyme responsible for degrading 2-AG, exhibits high activity during the postnatal period, thereby maintaining regulation of 2-AG levels, which are crucial for synaptic pruning and maturation (Maccarrone et al., 2014). It is highly expressed in presynaptic terminals of GABAergic interneurons within basal ganglia circuits, thereby controlling inhibitory tone (Punt et al., 2022). NAPE-PLD, which synthesises *N*-acylethanolamines, including AEA, works alongside DAGLα to promote neural progenitor proliferation and differentiation (Punt et al., 2022). Its expression increases with age, rising from early postnatal stages through adolescence (Psychoyos et al., 2012). FAAH, which breaks down AEA, is observed in neural progenitors and radial glia during late gestation and the postnatal period, participating in astroglial differentiation and neural progenitor maturation (Aguado et al., 2006). FAAH is particularly abundant in neurons of the limbic system, influencing AEA signalling in circuits related to emotion and stress (Punt et al., 2022). Collectively, these enzymes coordinate the dynamic endocannabinoid signalling essential for neurodevelopmental processes such as neurogenesis, synaptogenesis and circuit plasticity.

Due to their lipophilic nature, endocannabinoids are not stored in synaptic vesicles but are synthesised by neurones on demand via hydrolysis of cell membrane precursor lipids following membrane depolarisation and increased intracellular Ca^{2+} levels (Freund et al., 2003; Piomelli, 2003). More recently, Straub et al. (2025) proposed that endocannabinoids are released in a stimulus-dependent manner ('on-demand release model') via extracellular enriched 2-AG vesicles. This process, regulated by protein kinase C (PKC), DAGL and ADP-ribosylation factor 6 (Arf6), enables each microvesicle, which carries ∼2000 2-AG molecules, to mediate efficient intercellular signalling. Once released, newly synthesised endocannabinoids move retrogradely towards the synaptic cleft, binding to cannabinoid receptors located in presynaptic cell terminals (Freund et al., 2003) (Fig. 2*B*). Activation or inhibition of ion channels is a key consequence of cannabinoid receptor activation (Szabo & Schlicker, 2005), which can stimulate or inhibit neurotransmitter release from axon terminals, thus playing an essential role in various forms of short- and long-term synaptic plasticity (Chevaleyre et al., 2006; Mackie, 2006; Viganò et al., 2005). Furthermore, cannabinoid receptor activation can modulate intracellular signalling pathways, such as the mitogen-activated protein kinase (MAPK) cascade (ERK, p38, JNK), influencing gene expression and cellular processes, including survival, proliferation and differentiation (Walsh & Anderson, 2020) (Fig. 2*C*). This unique aspect of the production and action mechanisms of endocannabinoids suggests that these compounds primarily function as parts of a complex neuromodulatory system rather than as classical neurotransmitters.

Exogenous cannabinoids. *Cannabis sativa* is chemically complex, containing mono- and sesquiterpenes, sugars, hydrocarbons, steroids, flavonoids, nitrogenous compounds and amino acids, reflecting the plant's rich secondary metabolism (ElSohly & Slade, 2005; Keimpema et al., 2021). It comprises over 566 different chemical compounds, with the most well-known being: Δ^9-tetrahydrocannabinol (Δ^9-THC), the most recognised and psychoactive constituent, first isolated and structurally identified by Mechoulam and Gaoni in 1967; cannabidiol (CBD), a non-psychoactive compound with various therapeutic properties (Mechoulam, 1970); and cannabigerol (CBG), cannabinol (CBN), cannabichromene (CBC), tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA) (Al Ubeed et al., 2022; Fordjour et al., 2023; Pellati et al., 2018). Δ^9-THC and CBD are the most extensively studied and prevalent phytocannabinoids in cannabis, mainly due to their potent pharmacological effects and the fact that some high-potency cannabis strains can contain over 20% of either compound by dry weight (Keimpema et al., 2021). These compounds interact with the ECS mainly via CB_1 and CB_2 receptors in the CNS and peripheral tissues. While CB_1 activation accounts for the characteristic psychoactive effects of cannabis, CB_2 is primarily found in various immune cells, and its activation does not produce psychoactivity, being generally linked to protective and immunomodulatory actions (Pertwee, 2015). In addition to direct receptor binding, cannabinoids may influence other signalling pathways, including transient receptor potential (TRP) channels and peroxisome proliferator-activated receptors (PPARs), contributing to their diverse physiological effects (Lu & Mackie, 2016; Pertwee, 2008). In fact, many cannabinoids directly influence mitochondrial function independently of traditional cannabinoid receptors, affecting processes such as bioenergetics, calcium balance and apoptosis through receptor-independent pathways (Puighermanal et al., 2024).

Δ^9-THC is a terpene-resorcinol derivative that acts as a partial agonist at both CB_1 and CB_2 cannabinoid receptors, displaying several therapeutically significant properties, including anti-inflammatory, immunosuppressive and analgesic effects (for review, see Maccarrone et al., 2023). However, despite its partial agonism, Δ^9-THC can functionally behave as an antagonist in the developing brain by competing with high-affinity endogenous cannabinoids at their receptors (Tortoriello et al., 2024). This competitive displacement explains why prenatal Δ^9-THC exposure has been shown to mimic aspects of a CB_1 knockout-like phenotype during neurodevelopment (Tortoriello et al., 2024). When such interference occurs during critical developmental periods, it may lead to long-lasting neurobiological changes. It was the first cannabinoid approved by the US Food and Drug Administration (FDA) as a medication under the generic name dronabinol (Marinol). However, Δ^9-THC use is restricted by CNS-mediated psychotropic side effects (Maccarrone et al., 2023). Beyond CB_1 and CB_2, Δ^9-THC interacts with numerous other molecular targets such as G protein-coupled receptors (GPR18 and GPR55), ion channels including TRPA1, TRPV2 and glycine receptors, as well as nuclear receptors like PPARγ (De Petrocellis et al., 2011; McHugh et al., 2012; Mechoulam et al., 2014). According to these authors, Δ^9-THC acts as a partial agonist (GPR18), an agonist (GPR55, TRPA1, TRPV2, PPARγ) and a positive allosteric modulator (glycine receptors), depending on the target receptor or channel. Δ^9-THC also affects serotonergic, noradrenergic and dopaminergic neurotransmission by modulating the uptake of serotonin, noradrenaline and dopamine (Pertwee, 2008, 2010, 2015). Furthermore, Δ^9-THC can inhibit 5-HT_3 and TRPM8 channels and influence enzymes such as phospholipase C and A2. These diverse interactions contribute to its intricate pharmacological profile (Pertwee, 2008).

Regarding CBD, this compound shares the same molecular formula ($C_{21}H_{30}O_2$) as Δ^9-THC; however, they differ in chemical structure: Δ^9-THC contains a cyclic ring, whereas CBD has a hydroxyl group (Manzoni et al., 2025). This seemingly minor structural difference results in notable variations in their pharmacological profiles (Manzoni et al., 2025). Unlike Δ^9-THC, CBD is non-psychoactive, likely because of its low affinity for CB_1 and CB_2 receptors (Rock et al., 2021). Instead, CBD produces a wide range of therapeutic effects, particularly in neuropsychiatric disorders, through various molecular targets (Crippa et al., 2018). It acts as a non-competitive antagonist and negative allosteric modulator at CB_1 receptors, and as an inverse agonist at CB_2 (Thomas et al., 2007). CBD also antagonises GPR55 and TRPM8 channels (Pertwee, 2008), while acting as an agonist at TRPV1, TRPV2 and the nuclear receptor PPARγ (Bisogno et al., 2001; Iannotti et al., 2014). Furthermore, it enhances endocannabinoid signalling by inhibiting the breakdown of AEA (Bisogno et al., 2001). Notably, CBD interacts with the 5-HT_{1A} receptor as a positive allosteric modulator, contributing to its anti-nausea and anxiolytic effects (De Gregorio et al., 2019; Rock et al., 2012; Russo et al., 2005).

High-potency cannabis preparations, now increasingly accessible worldwide, are linked with a range of adverse health outcomes when used indiscriminately. These include a higher incidence of cannabis use disorder, increased emergency room visits related to cannabis use, a heightened risk of developing psychosis, and a greater likelihood of relapse in individuals with a history of psychotic disorders (Schoeler et al., 2016). Also, sinsemilla, commonly known as 'skunk', is increasingly

displacing traditional cannabis preparations across many countries, including the UK. Sinsemilla has progressively taken over the market, rising from 51% of police seizures in 2005 to 94% in 2016. This shift has been accompanied by consistently high Δ^9-THC concentrations averaging around 14% between 2005 and 2016 (Di Forti et al., 2009). However, it is important to recognise that cannabinoid-derived compounds also possess potential therapeutic benefits. Compounds such as CBD have shown promise in treating epilepsy, anxiety, chronic pain, spasticity in multiple sclerosis, and inflammation, highlighting the complex and dual nature of cannabis pharmacology (Keimpema et al., 2021; Schlag, 2020; Whiting et al., 2015). Additionally, CBD enhances antioxidant cellular defences by scavenging hydroxyl radicals and can reduce Δ^9-THC's intracellular action through CB_1 receptors located in mitochondrial membranes (Jimenez-Blasco et al., 2020).

Alongside Δ^9-THC and CBD, the synthetic cannabinoid receptor agonist WIN55,212-2 is widely used in preclinical research due to its ability to produce the full range of *in vivo* effects typically associated with Δ^9-THC and other cannabimimetic substances (Compton et al., 1992). However, some pharmacodynamic and pharmacokinetic differences occur between WIN55,212-2 and naturally occurring cannabinoids, such as its lack of action at GPR55 receptors (Johns et al., 2007) and its full agonism at both CB_1 and CB_2 receptors, displaying higher intrinsic efficacy than Δ^9-THC, which behaves as a partial agonist and produces lower maximal receptor activation (An et al., 2021; Childers, 2006), as well as compared with CBD, which shows relatively low affinity for the CB_1 orthosteric site and acts as a negative allosteric modulator, reducing both the potency and the efficacy of Δ^9-THC and endogenous ligands in CB_1-mediated signalling assays (e.g., via PLCβ3, ERK1/2, β-arrestin2 recruitment, and receptor internalization) (Chung et al., 2019; Laprairie et al., 2015). Moreover, WIN55,212-2 can differentially modulate downstream effectors, activating GIRK responses at low concentrations but interfering with GIRK1/2 currents at higher concentrations – a complexity not observed for Δ^9-THC or CBD (An et al., 2021). Together, these pharmacological distinctions in agonist efficacy, allosteric modulation, downstream signalling, regional receptor adaptation, and differential interactions with non-CB receptors suggest that results obtained with WIN55,212-2 may not always fully generalise to phytocannabinoids such as Δ^9-THC or modulatory cannabinoids like CBD. However, in rodent models, WIN55,212-2 consistently reproduces the characteristic pharmacological and behavioural effects of Δ^9-THC and mimics many of the physiological, emotional, and cognitive responses triggered by phytocannabinoid exposure (Bara et al., 2018; Viveros et al., 2005).

Pregnancy cannabinoid exposure

Routes and pharmacokinetics. The prevalence of prenatal cannabis use has more than doubled over the past two decades (Volkow et al., 2019), with 7–10% of women reporting cannabis use during pregnancy (Ko et al., 2015; Merritt, 2016; Young-Wolff et al., 2017), often citing nausea management as the primary reason (First et al., 2022; Porath et al., 2018). Both Δ^9-THC and CBD easily cross the placental barrier, reaching the fetal circulation and directly affecting the developing fetus (Grotenhermen, 2003; Kim et al., 2018). The transfer of cannabinoid components through the placenta is particularly high for Δ^9-THC, allowing significant fetal exposure following maternal use (Little & VanBeveren, 1996). Due to its high lipophilicity, Δ^9-THC quickly diffuses across the placental barrier and accumulates in fetal tissues, including the brain, where it can interact with fetal cannabinoid receptors during critical neurodevelopmental periods (Bailey et al., 1987; Grotenhermen, 2003; Hurd et al., 2005). Studies employing *ex vivo* human placental perfusion models have demonstrated notable transfer rates of Δ^9-THC, with fetal-to-maternal concentration ratios approaching 0.3–0.5 within a short timeframe, highlighting the efficiency of transplacental transfer (Little & VanBeveren, 1996). Although CBD transfer has been less thoroughly researched, CBD's similar physicochemical properties suggest it may also cross the placenta with relative ease, potentially impacting fetal physiology and signalling pathways (Grant et al., 2018). A further concern is the fetus's limited capacity to metabolise these substances, as the hepatic cytochrome P450 system remains immature (Alcorn & McNamara, 2003; Bailey et al., 1987). Placental cells not only express the classical cannabinoid receptors CB_1 and CB_2 but also a variety of non-canonical targets that bind or respond to cannabinoids, including the G-protein-coupled receptors GPR18 and GPR55; the transient receptor potential vanilloid channels TRPV1, TRPV2, TRPV4, TRPV5 and TRPV6; and the nuclear receptor PPARγ (for a detailed review, see Rokeby et al., 2023). The distinct receptor affinities, signalling efficacies and modulatory profiles of different cannabinoids across this receptor network provide a mechanistic basis for the variability in physiological and behavioural outcomes. This complexity also helps to explain the often-striking differences in both therapeutic potential and adverse effects reported for various cannabinoid preparations and exposure conditions. Notably, in the context of prenatal exposure, such receptor–ligand diversity may significantly influence the developmental trajectories of the lung, heart and central circuits controlling cardiorespiratory function, thereby shaping long-term health outcomes. During human gestation, analysis of cannabinoid receptor transcript levels in the placenta between gestational weeks

7 and 12 showed that CB_1 receptor expression peaks at approximately week 10, followed by a significant decline of about 91% by week 12. In contrast, CB_2 receptor expression stays relatively stable throughout this developmental period (Habayeb et al., 2008).

The route of cannabis consumption, whether oral ingestion, inhalation or various methods of smoking, can significantly influence the degree of fetal exposure and overall toxicity. Different administration routes affect the absorption, metabolism and bioavailability of cannabinoids, thereby modulating their pharmacokinetics and potentially altering their impact on fetal development (Grotenhermen, 2003; Huestis, 2007; Ryan et al., 2018).

To investigate how exogenous cannabinoids may interfere with developmental processes, various preclinical models of cannabinoid exposure during pregnancy have been developed in rodents. These models use different routes of exogenous administration (summarised in Table 1), each with distinct pharmacokinetic profiles, levels of maternal–fetal transfer, and relevance to human consumption patterns. Injection-based methods are the most employed, offering precise dose control and rapid systemic distribution. These include intravenous (I.V.) injection, which enables immediate cannabinoid bioavailability and mimics acute high-dose exposure (Ellis et al., 2022; Silva et al., 2012; Spano et al., 2007), and intraperitoneal (I.P.) injection, frequently used for its ease and reproducibility, though it may involve variable absorption and potential peritoneal irritation (Black et al., 2023; de Salas-Quiroga et al., 2015; Gillies et al., 2020; Natale et al., 2020; Vargish et al., 2017). Subcutaneous (S.C.) administration permits slower, sustained release, which may better simulate chronic low-dose exposure patterns (Bara et al., 2018; Brancato et al., 2020; Frau et al., 2019; Mereu et al., 2003; Newsom & Kelly, 2008; Sagheddu et al., 2021; Tree et al., 2014).

More recently, osmotic pumps implanted subcutaneously in pregnant female rats have been utilised and have effectively delivered the synthetic cannabinoid WIN55,212-2 biologically during pregnancy (Patrone et al., 2023, 2024, 2025), maintaining steady plasma drug levels and providing prolonged therapeutic effects, although not reproducing the characteristic peaking and waning of cannabinoid intake observed in real-life human use (e.g., smoking, vaping, edibles). These systems reduce dosing frequency, thereby improving compliance, and release drugs at a controlled rate, unaffected by physiological factors such as gastrointestinal motility, food intake, pH and fluid dynamics (Patel et al., 2021). Still, it also raises concerns regarding the need for surgical implantation and requires further benchmarking against established extraction techniques to confirm reproducibility and quantitative accuracy, especially when considering the use of phytocannabinoids. In Patrone et al.'s study, WIN55,212-2 was administered continuously at 2.5 µl/h using subcutaneous osmotic pumps, with average plasma levels of 5.1 ± 0.9 ng/ml at GD10 and 4.7 ± 1.3 ng/ml at GD20, demonstrating the selectivity and effectiveness of this delivery system for maintaining consistent exposure during pregnancy (Patrone et al., 2023). Notably, these levels are within the range reported in humans after marijuana smoking, where Δ^9-THC peaks at 10–14 ng/ml shortly after onset and declines to 1–5 ng/ml within 3 h, remaining detectable for up to ∼10 days due to its long half-life for frequent users (Mosaed et al., 2022; Sharma et al., 2012; Wurz & DeGregorio, 2022), and are comparable to the 7.2 ng/ml (∼15 nM) plasma concentration observed in pregnant women (Kumar et al., 2025; Monfort et al., 2022).

According to Black et al. (2023, 2025), the route of cannabinoid administration considerably affects maternal plasma levels in pregnant rats. Specifically, injecting phytocannabinoids intraperitoneally led to higher peak levels of Δ^9-THC and CBD compared to smoke exposure, measured 30 min after treatment. In the lungs, Δ^9-THC is highly lipophilic and quickly diffuses across the blood–air barrier (Huestis, 2007; Leuschner et al., 1986). Once absorbed, it accumulates in adipose tissue, where it has a prolonged half-life of roughly 7–10 days, leading to a total elimination period of up to 30 days after a single exposure (Bergamaschi et al., 2013; Huestis, 2007; Nahas & Latour, 1992). These pharmacokinetic traits are especially concerning during pregnancy, as maternal fat stores serve as reservoirs for Δ^9-THC, while fetal metabolism and excretion remain limited (Bailey et al., 1987; Metz & Borgelt, 2018). Consequently, fetal exposure may continue long after maternal use has stopped, with Δ^9-THC detectable in tissues for weeks following a single marijuana cigarette (Hatch & Bracken, 1986; Volkow et al., 2017).

Oral administration of Δ^9-THC, although less frequently used, is especially relevant for modelling edibles and tinctures in humans. This route causes a slower onset, lower peak plasma levels, and significant first-pass hepatic metabolism, resulting in the formation of active metabolites such as (±)-11-hydroxy Δ^9-THC (11-OH-THC), which can have different or even more potent effects than the parent compound (Campolongo et al., 2007; Di Bartolomeo et al., 2021; Drazanova et al., 2019; Trezza et al., 2008). These models facilitate the study of prolonged, low-level cannabinoid exposure during gestation.

Effects on fetal development. Cannabis use before and during early pregnancy (the first trimester) may disturb ECS balance, potentially leading to infertility and adverse pregnancy outcomes such as restricted embryonic development and spontaneous abortion (Correa et al.,

Table 1. Summary of exogenous cannabinoid administration routes in rodent models of prenatal exposure

Route	Cannabinoids used	Pharmacokinetics	Key developmental findings in offspring	Representative studies
Intraperitoneal	Δ^9-THC, WIN55,212-2, CBD	Moderate to rapid absorption; avoids first-pass metabolism; short duration	Disrupt the neurodevelopmental role of CB_1 signalling; synaptic plasticity disruption, sex-specific effects in cognitive deficits and glucose homeostasis; altered HPA axis regulation; transient changes in endocannabinoid signalling	Singh et al. (2006); Vargish et al. (2017); Gillies et al. (2020); Natale et al. (2020); de Salas-Quiroga et al. (2015, 2020); Sarikahya et al. (2022, 2023); Black et al. (2023)
Subcutaneous	Δ^9-THC, WIN55,212-2	Slower absorption; prolonged exposure; bypasses first-pass metabolism	Sex-specific alterations of behavioural, locomotor activity and synaptic functions; altered emotional reactivity, impaired of memory formation and dopaminergic function	Newsom and Kelly (2008); Baglot et al. (2022); Bara et al. (2018); Brancato et al. (2020); Frau et al. (2019); Sagheddu et al. (2021); Traccis et al. (2021); Manduca et al. (2020)
Intravenous	Δ^9-THC, WIN55,212-2	Immediate onset; 100% bioavailability	Long-term perturbations in natural reward-related motivation and anhedonia; learning impaiment; transient changes in endocannabinoid signalling	Spano et al. (2007); Silva et al. (2012); Ellis et al. (2022)
Oral (gavage or in food)	Δ^9-THC, CBD	Slow onset; low and variable bioavailability; high first-pass metabolism	Long-term neurofunctional and neurodevelopmental deficits; behavioural alterations, cognitive impairment, long-term alteration in dopaminergic signalling	Campolongo et al. (2007, 2009); Trezza et al. (2008); Drazanova et al. (2019); Di Bartolomeo et al. (2021)
Inhalation (vapour/smoke)	Δ^9-THC, CBD	Rapid onset; high bioavailability; mimics real-world use	Transient changes in endocannabinoid signalling and locomotor activity; changes in brain volume and brain structures; decreased cytokine and chemokine levels in the placenta and fetal brain; long-term alterations in anxiety-like behaviors; disrupted social behaviour	Baglot et al. (2022); Benevenuto et al. (2022); Breit et al. (2020, 2022); Weimar et al. (2020); Black et al. (2023); Sandini et al. (2023); Black et al. (2025)
Osmotic minipump	WIN55,212-2	Continuous, low-dose delivery; bypasses fluctuations	Sex- and age-specific respiratory alterations; sex-dependent disruption of offspring's central cardiorespiratory control and behaviour alterations	Patrone et al. (2023, 2024, 2025)

HPA, hypothalamic–pituitary–adrenal.

2016; Hutchings et al., 1989; Little & VanBeveren, 1996; Mulligan & Hamre, 2023 Vardaris et al., 1976). Despite some inconsistencies in the literature, human studies indicate that cannabis consumption during pregnancy can impair fetal development, resulting in intrauterine growth restriction, low birth weight, congenital anomalies and even neonatal death (Bailey et al., 2025; El Marroun et al., 2009; Grzeskowiak et al., 2020; Gunn et al., 2016; Hurd et al., 2005; Zuckerman et al., 1989). Consistent with these findings, rodent models show that both cannabis smoke inhalation (Benevenuto et al., 2017) and intraperitoneal administration of Δ^9-THC (Natale et al., 2020) during gestation reduce fetal weight and increase stillbirth rates following prenatal exposure to synthetic cannabinoids (Patrone et al., 2023), without evidence of malformations. Interestingly, Benevenuto et al. (2017) observed a sex-dependent effect, with only male offspring exhibiting decreased fetal weight. Male fetuses tend to exhibit greater vulnerability to prenatal marijuana exposure, showing more significant neurodevelopmental alterations compared to females (Wang, Dow-Edwards et al., 2004). Natale et al. (2020) reported placental morphological changes, including compromised fetal blood spaces and vascular abnormalities in the labyrinth zone of fetuses exposed to Δ^9-THC. Placental transcriptome analyses revealed altered gene expression profiles associated with maternal cannabis use, including downregulation of the CB_1 receptor gene (Rompala et al., 2021). Therefore, placental modifications caused by cannabinoid exposure can lead to reduced nutrient and oxygen transfer to the fetus, detrimentally affecting its development (Allen et al., 2024; Chang et al., 2017; Kenchegowda et al., 2017; Maia et al., 2020; Roberts et al., 2022). Notably, differences in fetal developmental outcomes reported across studies may stem from variations in experimental protocols, including the route, timing, and dosage of prenatal cannabinoid exposure, as well as the specific compounds tested (Mulligan & Hamre, 2023; Nashed et al., 2021).

Elevated AEA levels or excessive cannabinoid exposure hinder embryo development, decrease the number of trophectoderm cells, and prevent zona hatching. In contrast, lower AEA and CB_1 receptor levels in the uterus enhance uterine receptivity and successful blastocyst implantation (Schmid et al., 1997). Therefore, exact regulation of endocannabinoid tone via CB_1 signalling in both embryo and maternal tissues is crucial for normal reproductive success, and disruption can result in implantation failure or pregnancy loss.

Effects on fetal neurodevelopment. During the second and third trimesters, the ECS plays a critical role in fetal brain development, especially in neurite outgrowth. CB_1 receptor activation leads to a cascade of signalling events, including the GTPases Rap1, Ral and Rac, as well as the kinases Src and JNK, ultimately resulting in phosphorylation of the transcription factor Stat3 (Fig. 2*C*). In Neuro2A cell cultures and rat hippocampal slice studies, CB_1 agonism induced degradation of the GTPase-activating protein Rap1GAPII, which triggers Rap1 activation (Jordan et al., 2005), followed by Src and JNK activation and Stat3 phosphorylation, promoting neurite outgrowth (He et al., 2005). In parallel with Rap1 activation, CB_1 stimulation also activates the lipid kinase PI3K, which in turn activates the kinase Akt, promoting activation of the transcription factor PAX6 and initiating neurite outgrowth processes. Adjacent to this pathway, Akt appears to modulate the activity of the regulatory protein BRCA1, which exerts an inhibitory role on transcription factors, including Stat3 phosphorylation (Bromberg et al., 2008). Additionally, CB_1-induced cell growth can be regulated independently by the Ras–MAPK pathway, which coexists with the Src–Stat3 pathway (Fig. 2*C*). For further details on intracellular signalling processes driving ECS-induced cellular growth and differentiation, see Galve-Roperh et al. (2013).

The binding of Δ^9-THC to CB_1 and CB_2 receptors is known to disrupt key neurodevelopmental processes, leading to issues with neuronal differentiation, migration, and synaptic connectivity during brain maturation (Alpár et al., 2016; Friedrich et al., 2016; Maccarrone et al., 2014). Preclinical studies have shown that pharmacological modulation of CB_1 activity during gestation or early postnatal periods causes impaired axonal pathfinding, changes in progenitor cell proliferation, reduced neurogenesis, and abnormalities in the development and maturation of both neuronal and glial lineages (Diaz-Alonso et al., 2012; Mulder et al., 2008; Vargish et al., 2017). A molecular study showed that prenatal exposure to Δ^9-THC leads to activation of the CB_1 receptor in the mouse fetal cerebral cortex, which triggers JNK-mediated phosphorylation of the microtubule-binding protein SCG10/stathmin-2 in axons of cortical projection neurons, promoting its rapid degradation (Tortoriello et al., 2024). This degradation disrupts microtubule dynamics, leading to impaired axonal growth and miswiring of the cortical network. Notably, decreased SCG10 mRNA and protein levels were observed in the hippocampus of mid-gestational human fetuses exposed *in utero* to cannabis, providing translational evidence that the mechanism may hold in humans.

In this context, prenatal cannabis exposure in mice has been found to hinder brain development, evidenced by decreased brain volume at embryonic day (E)18, especially in males (Benevenuto et al., 2017). Previous studies suggest that fetal exposure to cannabinoids or CB_1 receptor agonists can alter brain volume and structure, with most research focusing on forebrain regions and the cerebellum (de Salas-Quiroga et al., 2015; Peng et al., 2023; Pinky et al., 2021; Ryan et al., 2024), while brainstem areas remain largely unexplored, highlighting a

notable gap in current knowledge. Several studies report that prenatal exposure to external cannabinoids can influence the development of multiple neurotransmitter systems. Findings demonstrate that cannabinoids impact the maturation of the catecholaminergic (CA) system (Fernández-Ruiz et al., 1999, 2004; Portillo et al., 2025). Tree et al. (2010) found that CB_1 receptors are densely distributed around the soma of medullary CA neurones, indicating that endocannabinoids may influence CA neurotransmission. The effects of cannabinoids on the development of CA pathways become more apparent during the differentiation and maturation of these neurones' projections to their target regions. Near the end of gestation, cannabinoids may modify the expression of key genes involved in CA transmission, such as the tyrosine hydroxylase (TH) enzyme (Bonnin et al., 1996). Cultured rat neurones from fetuses exposed daily from GD5 to Δ^9-THC showed higher TH activity compared to controls (Hernández et al., 2000). These findings suggest that external cannabinoids may interfere with the expression of the TH gene during embryonic development, possibly contributing to abnormal maturation of CA neurones and their target nuclei both before and after birth. In fact, previous research indicates that changes in the CA system during the neonatal period could be responsible for the development of clinical respiratory disorders (Viemari et al., 2005).

Similarly, Molina-Holgado and colleagues (1996, 1997) highlighted the ontogenic effects of prenatal cannabinoid exposure on the development of the serotonergic neurotransmission system. A reduction in serotonin content at birth was observed in diencephalic regions of rats prenatally exposed to Δ^9-THC (Molina-Holgado et al., 1996). Later in life, these animals showed decreased serotonin levels and increased concentrations of 5-hydroxyindoleacetic acid in limbic-related regions and the midbrain raphe nuclei (Molina-Holgado et al., 1997). Manipulation of the fetal ECS appears to alter monoamine oxidase (MAO) enzymatic activity, as evidenced by a significant reduction in MAO levels in the cerebellum of rats prenatally exposed to WIN55,212-2, which may impair the metabolism of monoaminergic neurotransmitters (Pinky et al., 2021). Overall, this body of evidence suggests that prenatal cannabinoid exposure can disrupt serotonergic neurotransmission, potentially impairing neurodevelopmental plasticity (Harkany et al., 2007; Portillo et al., 2025). Impaired serotonergic function has been linked to various pathophysiological conditions, including respiratory disturbances (Hilaire et al., 2010), such as increased respiratory variability and impaired autoresuscitation in neonates (Lee et al., 2018), a higher incidence of sudden infant death syndrome (SIDS) (Richerson, 2004), and increased vulnerability to panic disorder (Annerbrink et al., 2003), considering its role in the chemoreflex (Ray et al., 2011). *In utero* exposure to cannabinoids also disrupts the development of other neurotransmitter systems, such as GABAergic and glutamatergic pathways, leading to notable alterations in neurodevelopment and postnatal behaviour (see Ferraro et al., 2009; Pinky et al., 2019; Song et al., 2021).

Effects on fetal cardiorespiratory system. Regarding the respiratory system, Szeto et al. (1992) investigated the effects of a single or repeated maternal marijuana smoke exposure on fetal breathing movements (FBMs) of lambs during the third trimester. Maternal inhalation of marijuana smoke containing 1.84% Δ^9-THC led to an increase in FBMs and promoted a more stable breathing pattern in the fetus (Fig. 3). These respiratory effects were attributed to a direct action of cannabinoids rather than to non-specific factors such as the stress of smoke inhalation or elevated carboxyhaemoglobin levels, as placebo smoke exposure did not produce similar changes. Interestingly, the fetal response to this respiratory stimulation was rapidly attenuated with repeated exposures, such that no significant increase in breathing parameters was observed after the second exposure. These findings contrast with maternal responses, which typically include sedation and respiratory depression, highlighting differential maternal and fetal effects of cannabinoids (Alon & Saint-Fleur, 2017; Herbst & Musgrave, 2020; Jinwala & Gupta, 2012; Manini et al., 2022; Szeto et al., 1991). This contrast is likely due to markedly lower Δ^9-THC concentrations in the fetus, approximately threefold lower, as shown in pharmacokinetic studies.

A study in pregnant rhesus macaques examined the effects of daily prenatal Δ^9-THC exposure (2.5 mg/7 kg/day), a dose comparable to heavy medical cannabis use in humans (Ohlsson et al., 1980), on lung development (Shorey-Kendrick et al., 2025). Lung blood-oxygen level dependent (BOLD) magnetic resonance imaging (MRI) was performed in male and female fetuses between GD100 and 150, and at 6 months of age (P180), infants underwent pulmonary function testing prior to necropsy. Interestingly, by GD110, approximately equivalent to the late second trimester in humans, Δ^9-THC-exposed fetuses showed significant reductions in key lung growth and neurotrophic factors (Fig. 3), including brain-derived neurotrophic factor (BDNF), basic fibroblast growth factor (FGF-b), vascular endothelial growth factor (VEGF), and the pleiotropic cytokine interleukin-15 (IL-15). Prenatal Δ^9-THC was also associated with decreased oxygenation and lung volume by BOLD-MRI in Δ^9-THC-exposed fetuses at approximately gestational day 150 (late-third trimester). These changes suggest that prenatal Δ^9-THC may disrupt critical pathways involved in pulmonary development. The authors did not mention sex differences.

At 6 months of age, offspring exposed to Δ^9-THC *in utero* exhibited persistent deficits in lung structure

and function, including reduced lung volume, impaired perfusion and decreased gas exchange capacity. These functional impairments were associated with lower levels of VEGF, BDNF and FGF-b in bronchoalveolar lavage fluid, suggesting that early suppression of these factors may lead to long-term alterations in lung physiology. Spatial transcriptomic profiling revealed cell-type-specific alterations relevant to lung development and function, including changes in extracellular matrix organisation, response to hyperoxia, and wound healing in ciliated cells, as well as growth factor binding and regulation of tube size in airway smooth muscle cells. Significantly, several genes involved in extracellular matrix remodelling, such as members of the collagen, lysyl oxidase (LOXL), matrix metalloproteinase (MMP), and ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) families, were downregulated in lungs from Δ^9-THC-exposed infants. Overall, these findings indicate a possible mechanism by which prenatal cannabis exposure might cause pulmonary dysfunction, raising significant concerns regarding the long-term respiratory health of exposed offspring.

Maternal exposure to Δ^9-THC in mice, administered orally at doses of 5 or 10 mg/kg/day starting at E3.5, has been linked to various cardiac abnormalities in the developing fetus with no sex specified (Robinson et al., 2024). By E17.5, the incidence of cardiac defects was 44% in the 5 mg/kg group and 55% in the 10 mg/kg group (Fig. 3). The malformations observed included ventricular septal defects, increased semilunar valve volume-to-orifice ratios, and elevated myocardial wall thickness. Notably, increased cell proliferation was detected within the ventricular myocardium, alongside downregulation of several key cardiac transcription factors in Δ^9-THC-exposed fetuses at E12.5. These findings indicate that early gestational Δ^9-THC exposure interferes with normal cardiogenesis through both structural and molecular pathways (Robinson et al., 2024).

A study using a model of edible Δ^9-THC consumption assessed the effects of *in utero* exposure to Δ^9-THC on cardiac extracellular matrix expression and vascular transcriptome in rhesus macaques (Le et al., 2024). Δ^9-THC exposure was associated with a significant reduction in the fetal heart weight-to-body weight ratio, which

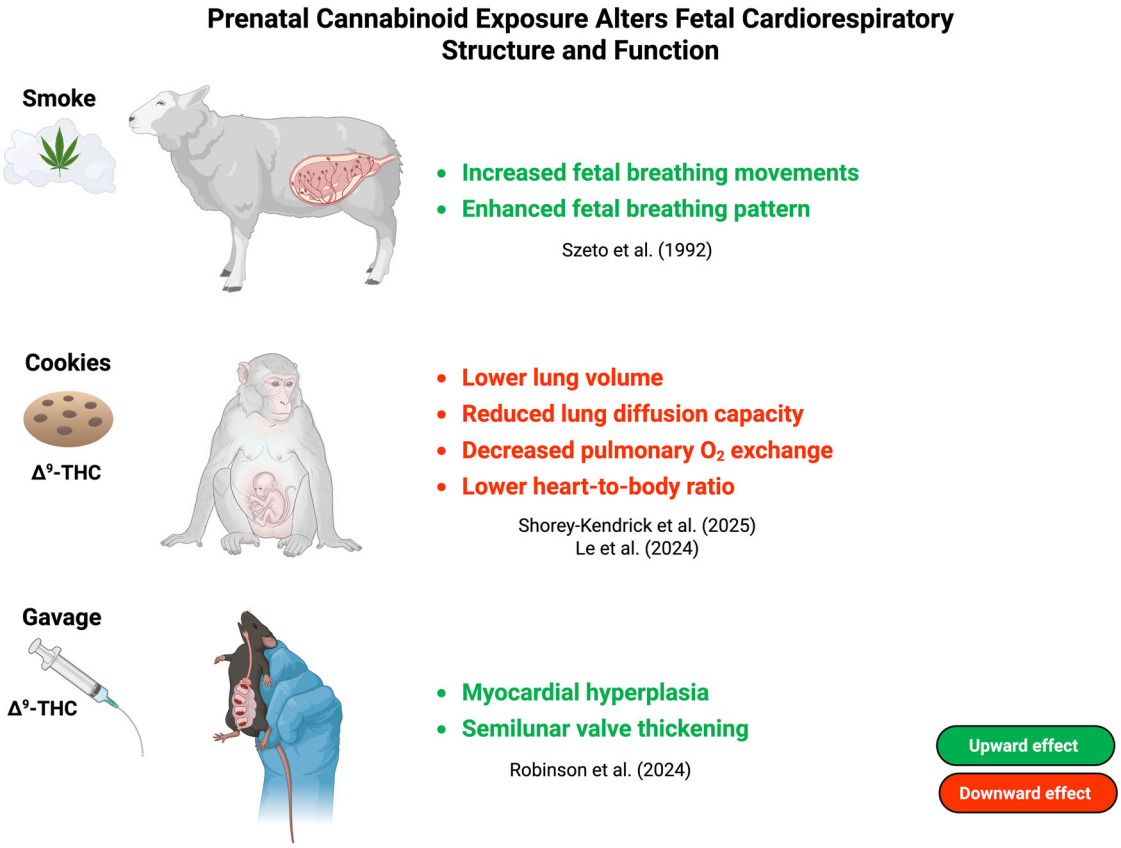

Figure 3. Changes in fetal cardiorespiratory structure and function caused by prenatal cannabinoid exposure
Results from prenatal exposure to cannabis smoke in lambs, Δ^9-THC-containing edible cookies in rhesus macaques, and oral Δ^9-THC administration in mice. Created with BioRender – licensed to L.H.G.

was not observed in other fetal organs. Additionally, transcriptional changes in an endothelial-enriched cell population vital for vascular development were observed following *in utero* Δ^9-THC exposure. Although sex differences were not statistically evaluated, there was a trend for lower CB_1 expression in Δ^9-THC males compared with Δ^9-THC females in the umbilical vein, umbilical artery and fetal aorta.

Regarding humans, a cohort study showed that prenatal cannabis exposure increases infant mortality risk within the first year, hinting at detrimental effects on heart development (Shi et al., 2021). The available preclinical studies provide valuable mechanistic insights and raise concerns for potential developmental impacts, but translation to humans is limited. Human studies in this field are particularly challenging due to confounding variables, such as concurrent exposure to nicotine, alcohol or other substances, as highlighted by Crosland et al. (2024).

Postnatal cardiorespiratory outcomes

Respiratory dysfunction in the early life stage. The ECS has consistently been shown to exert a broad regulatory influence on respiratory control, acting through both central and peripheral pathways (for review, see Wiese et al., 2023). Therefore, maternal cannabis consumption during pregnancy has become a significant concern due to its potential to negatively affect the postnatal developmental trajectory and function of the offspring's respiratory system. Evidence links prenatal cannabis exposure to impaired lung development and increased respiratory problems, potentially caused by respiratory control dysfunction after birth (Cáceres et al., 2023; Scragg et al., 2001; Shorey-Kendrick et al., 2025).

Beyond the respiratory field, clinical and preclinical studies have documented morphological and functional changes in the CNS throughout the offspring's postnatal life following prenatal exposure to exogenous cannabinoids. However, most of the literature has concentrated on cortical and forebrain regions, examining structural volume, specific dopaminergic and glutamatergic neuronal populations, excitability, synaptic plasticity, and transcriptomic profiles in relation to cognitive and affective functions (Peterson et al., 2020; for review: Jenkins et al., 2025). At least in these regions, prenatal cannabinoid exposure has been shown to induce postnatal alterations in ECS signalling, including changes in CB_1 receptor expression (de Salas-Quiroga et al., 2020; Di Bartolomeo et al., 2021), disrupted CB_1 receptor activity (Navarro et al., 2024) and modified AEA levels alongside activity of endocannabinoid-metabolising enzymes (Castelli et al., 2007), with responses varying according to the brain region and the specific cannabinoid to which the organism was exposed.

While these studies highlight the potential detrimental effects of exogenous cannabinoids on the development of higher brain regions, there remains a substantial gap regarding their impact on brainstem circuits critical for respiratory control, which are largely unexplored. Notwithstanding this scarcity, recent findings indicate that prenatal WIN55,212-2 (0.5 mg/kg/day) exposure transiently increases CB_1 receptor expression in the brainstem of male rat offspring during early postnatal development, with no comparable effect observed in females (Patrone et al., 2023) (Table 2). This transient upregulation could underpin early neurochemical and functional changes, supporting the idea that fetal cannabinoid exposure enhances CB_1 signalling in the developing brain. In parallel, WIN55,212-2 exposure was associated with sex- and age-dependent alterations in monoaminergic neuronal populations within key brainstem regions involved in respiratory control (Table 2), including increased CA neurone numbers in males and reduced serotonergic (5-HT) neurones within the nucleus raphe magnus (RMg) in females during early postnatal development (Patrone et al., 2023). Collectively, these transient, sex-specific changes may reflect early adaptations of the neurotransmission systems in the brainstem to prenatal cannabinoid exposure, potentially influencing short-term modulation of respiratory and autonomic functions, given the critical role of these nuclei in respiratory control (da Silva et al., 2011; Hodges et al., 2009; Patrone et al., 2018; Sun & Ray, 2017; Tree et al., 2010).

Indeed, Tree et al. (2014) observed functional alterations in respiratory control following *in utero* exposure to WIN55,212-2 (0.5 mg/kg/day), with increased resting ventilation in mixed-sex neonatal mice at P0–2 and P10–12 *in vivo* experiments. Similarly, male rats prenatally exposed to comparable doses of WIN55,212-2 exhibited increased baseline ventilation at birth and during the juvenile stage (Patrone et al., 2023) (Fig. 4). Importantly, in male offspring at birth, this ventilatory phenotype was accompanied by increased metabolic demand and behavioural signs – namely head shaking and motor hyperactivity – previously reported in both rats (Mereu et al., 2003) and humans (Fried et al., 1987) following prenatal cannabinoid exposure and consistent with cannabinoid withdrawal, suggesting that these behavioural and physiological responses at early-life may underlie the observed increase in resting ventilation; notably, these effects were not observed in female offspring (Patrone et al., 2023).

In parallel, potential synergistic effects of exogenous cannabinoids on the maturation of the respiratory central network may also be occurring, as significant alterations in baseline respiratory variability were documented throughout early postnatal life in both male and female rats prenatally exposed to WIN55,212-2

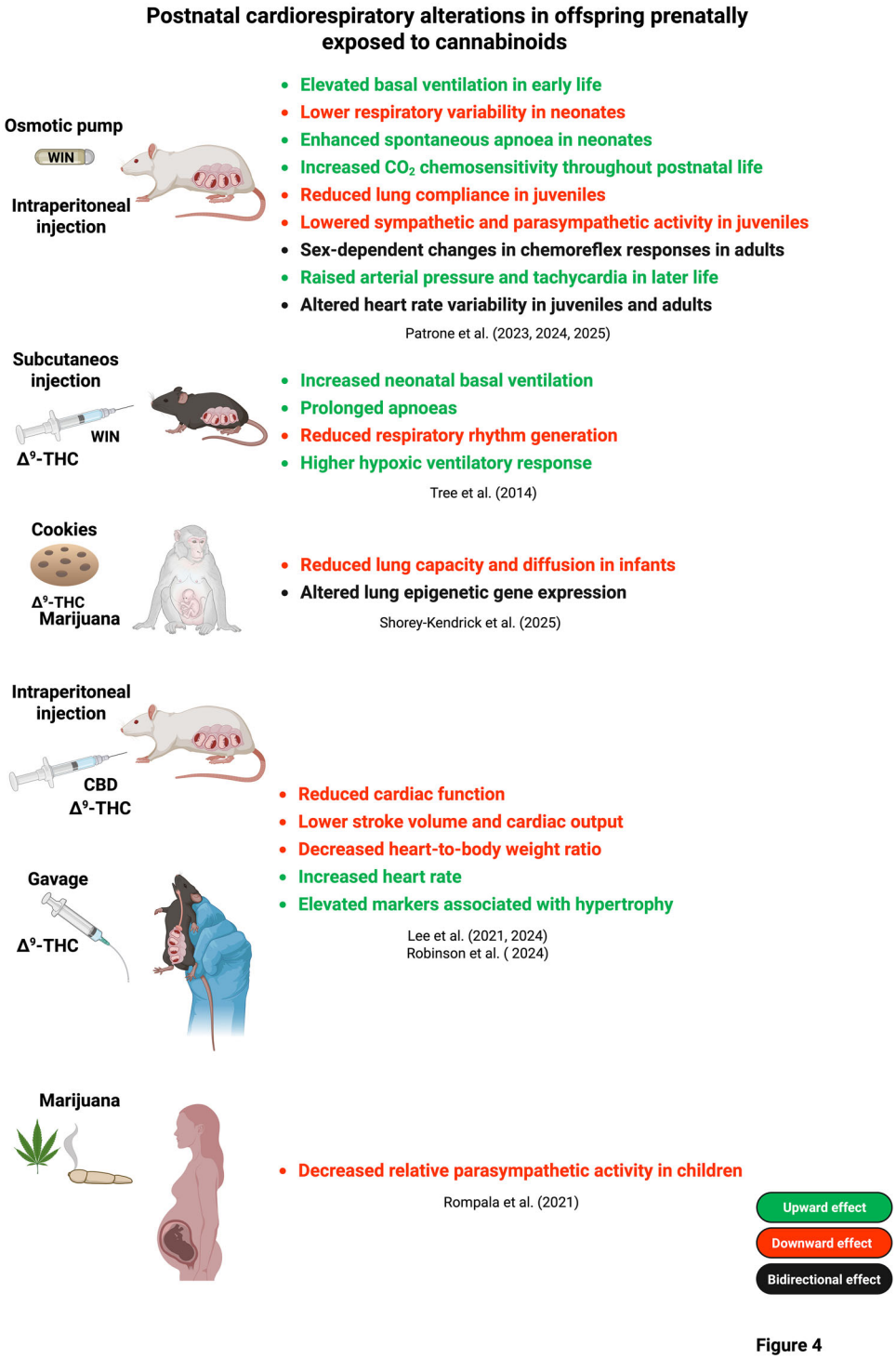

Figure 4. Overview of postnatal cardiorespiratory changes caused by prenatal cannabinoid exposure across various animal models and routes of administration
Findings from prenatal exposure to the synthetic cannabinoid agonist WIN55,212-2 via osmotic pump implantation in rats, subcutaneous WIN55,212-2 injections in mice, Δ^9-THC-containing edible cookies in rhesus macaques, intraperitoneal injections of cannabidiol (CBD) or Δ^9-THC in rats, oral Δ^9-THC administration in mice, and marijuana cigarette smoking in women. Created with BioRender – licensed to L.H.G.

Table 2. Summary of major effects of prenatal WIN55,212-2 exposure via osmotic pump on cardiorespiratory and neurophysiological variables in neonatal (P0, P6–7, P12–13), juvenile (P27–28), and adult (P80–81) male and female rats (Patrone et al., 2023, 2024, 2025).

Variable analysed	Male	Female
Tremour	↑P0	—
Head movements	↑P0	↑P0
Basal $\dot{V}_E$	↑P0; ↑P27–28	—
Basal $\dot{V}_{O_2}$	↑P0	—
Basal $\dot{V}_E$ variability	↓P6–7; ↓P12–13; ↑P27–28	↑P12–13; ↑P27–28
Spontaneous apnoeas	—	↑P0
HCVR	↑P0; ↓P6–7; ↑P12–13; ↑P27–28; ↑P80–81	↑P27–28; ↓P80–81
HVR	↑P0; ↓P6–7; ↑P80–81	↓P80–81
Pulmonary compliance	↓P27–28	—
Sleep quality	↓P80–81	↓P80–81
Basal MAP	—	↑P80–81
Hypoxic MAP	↑P80–81	↑P80–81
Hypercapnic HR	—	↓P80–81
Hypoxic HR	—	↑P80–81
CB_1 expression	↑P0; ↑P6–7; ↑P12–13	—
CA neurone counting	↑P0; ↑P6–7	—
5-HT neurone counting	—	↓P0
Mitochondrial efficiency	↓P0; ↓P12–13	—
Panic-related behaviour	—	↓P80–81
Tonic cVN activity	—	↓P27–28
Chemoreflex cVN activity	—	↓P27–28
Chemoreflex AbN activity	↓P27–28	↓P27–28
Chemoreflex tSN activity	↓P27–28	—

A dash indicates that no changes were observed. 5-HT, serotoninergic; AbN, abdominal nerve; CA, catecholaminergic; CB_1, cannabinoid receptor type 1; cVN, central vagal nerve; HCVR, hypercapnic ventilatory response; HR, heart rate; HVR, hypoxic ventilatory response; MAP, mean arterial pressure; tSN, thoracic sympathetic nerve; $\dot{V}_E$, ventilation; $\dot{V}_{O_2}$, oxygen consumption. Increases are indicated in green and decreases in red.

(Patrone et al., 2023) (Table 2). These changes may reflect a cannabinoid-induced disruption in the balance of excitatory and inhibitory inputs that govern respiratory network excitability (Gao et al., 2011; Wong-Riley et al., 2019). Additionally, WIN55,212-2 exposure induces an increase in spontaneous apnoeas at birth in female rats (Patrone et al., 2023) and mixed-sex mice (Tree et al., 2014) (Fig. 4), which may be linked to the observed reduction of 5-HT neurones in the RMg of P0-treated females, potentially compromising respiratory stability in early life through impaired modulation of hypoglossal motoneurones and upper airway tone (Barker et al., 2009; Li et al., 1993). Supporting this, mice lacking central 5-HT neurones exhibit frequent apnoeas early in life, likely due to impaired raphe-driven modulation of respiratory outputs (Hodges et al., 2009; Richter et al., 1997).

Moreover, the persistent increase in resting ventilation in juvenile male rats reinforces the concept of prenatal exposure-induced plasticity, which may occur across multiple levels of the respiratory system, like central and peripheral pathways, in a sex-specific manner (Patrone et al., 2023). Notably, because larger tidal volumes primarily drove this enhanced ventilation, it aligns with the reduced lung compliance identified in these juvenile males – a pattern also reported in primates prenatally exposed to Δ^9-THC (Shorey-Kendrick et al., 2025) (Fig. 4). Such a compensatory increase in tidal volume, rather than respiratory frequency, reflects a more energy-efficient strategy in response to a stiffer respiratory system (Vitalis & Milsom, 1986), thereby offsetting the compliance deficit induced by WIN55,212-2 exposure. Supporting a peripheral contribution, CB_1 receptors are present in lung tissue (Kicman et al., 2021), and CB_1 activation has been shown to inhibit cholinergic-mediated airway contraction (Wang et al., 2016) and to improve static lung compliance while reducing collagen fibre content (Vuolo et al., 2019).

As fetal ECS manipulation disrupts steady-state breathing control during postnatal life, such dysfunction may render the newborn more vulnerable to respiratory challenges. In this regard, male rats prenatally exposed to WIN55,212-2 show an augmented hypercapnic ventilatory response (HCVR) from birth through the juvenile stage (Patrone et al., 2023) (Table 2 and Fig. 5). This persistent hyperventilatory state points to altered CO_2 chemosensitivity, likely reflecting enduring plasticity

within central CO_2/pH-sensitive circuits. Interestingly, a reduced HCVR was observed in P6–7 males following prenatal exposure to WIN55,212-2. This transient blunting coincides with a developmental window during which CO_2 responsiveness typically reaches a physiological nadir (Stunden et al., 2001; Wickström et al., 2002) and the respiratory system is particularly vulnerable (Greer, 2012; Putnam et al., 2005). Thus, the hypoventilation observed at this age may reflect a temporary disruption of central chemosensory maturation, with prenatal cannabinoid exposure likely enhancing this developmental fragility. Moreover, given that CB_1 mRNA expression peaks between P5 and P7 (McLemore et al., 2004), a contributory peripheral component – potentially involving altered carotid-body sensitivity – cannot be excluded. In contrast, female rats showed an increased CO_2 chemoreflex only at the juvenile stage, reinforcing a sex-dependent difference in cannabinoid sensitivity (Patrone et al., 2023). These findings suggest a heightened vulnerability of the male respiratory network to prenatal cannabinoid exposure, potentially compromising early-life ventilatory control mechanisms.

Parallel alterations emerge when considering hypoxic responsiveness, indicating that the impact of prenatal exposure on breathing control is not restricted to CO_2 drive. In neonatal (P0–2) mouse medullary preparations, prenatal WIN55,212-2 exposure intensified the hypoxic suppression of C4 nerve root activity, suggesting altered function of the central respiratory rhythm generator (Tree et al., 2014). Consistently, *in vivo* experiments by the same authors showed an augmented hypoxic ventilatory response (HVR) and prolonged apnoeas in P0–2 and P10–12 newborns. Somewhat similarly, P0 WIN55,212-2-treated male rats exhibited an enhanced HVR, whereas P6–7 animals showed reduced hypoxic chemosensitivity, with no effects observed in females (Patrone et al., 2023) (Table 2). Hence, the heightened hypoxic sensitivity at P0 may reflect peripheral actions

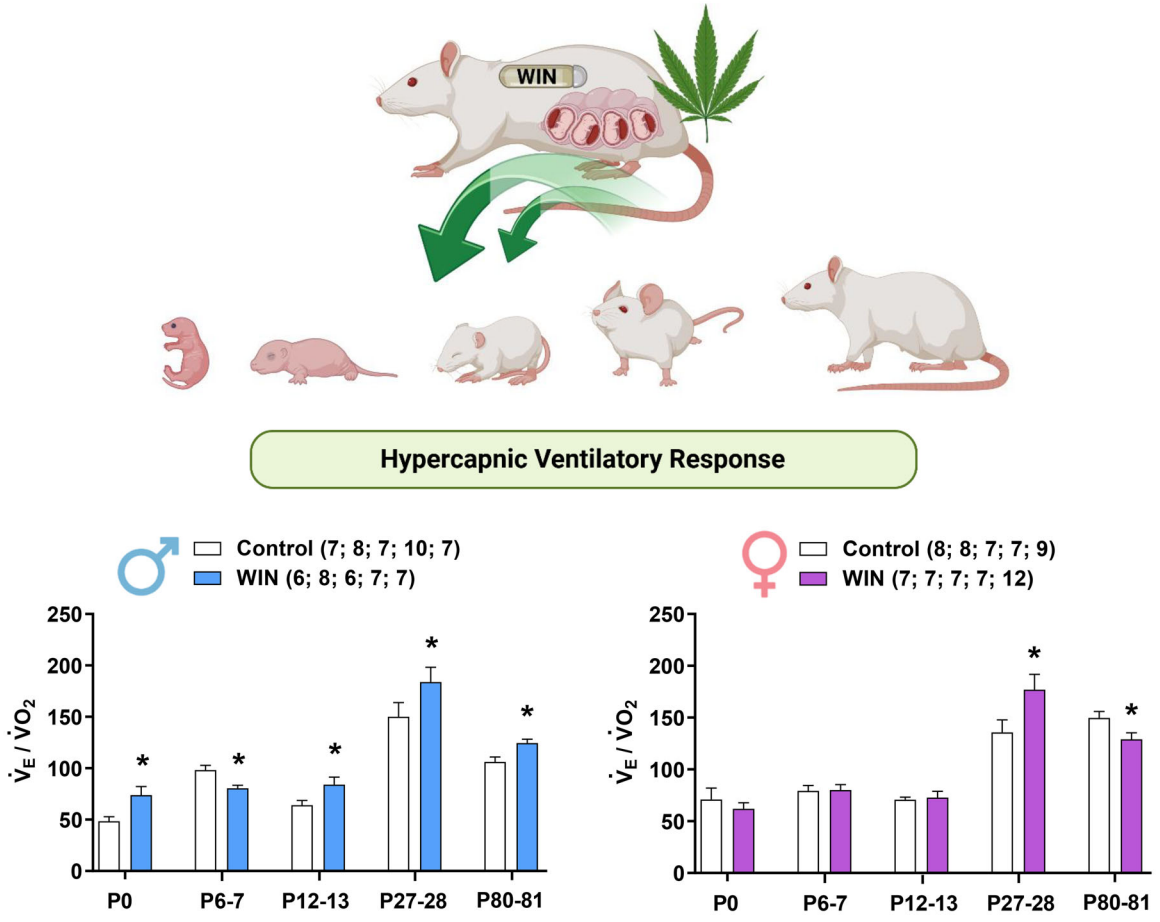

Figure 5. Intrauterine exposure to WIN55,212-2 alters the hypercapnic ventilatory response in rat offspring throughout postnatal life in a sex- and age-dependent manner
Air convection requirement ($\dot{V}_E/\dot{V}_{O_2}$) in neonate (P0, P6–7, P12–13), juvenile (P27–28), and adult (P80–81) male and female rats prenatally exposed to vehicle (control) or the synthetic cannabinoid agonist WIN55,212-2 (0.5 mg/kg/day). An asterisk indicates significant differences between treatments within the same sex. Created with BioRender – licensed to L.H.G.

of circulating cannabinoids, as compounds like AEA can excite the carotid body and improve its responsiveness to hypoxia (Kobayashi & Yamamoto, 2010). The contrasting responses at P0 and P6–7 probably arise from the developmental changes in CB_1 receptor expression and chemoreceptor sensitivity, further highlighting a sex-specific vulnerability in males to prenatal cannabinoid exposure.

It is highly relevant to note that alterations in respiratory control, whether of central or peripheral origin, may result not only from cannabinoid-induced changes in neural activity patterns, excitability and connectivity within the network, but also from potential impacts on neural bioenergetics. The identification of functional CB_1 receptors on the mitochondrial membranes of hippocampal neurones (Bénard et al., 2012; Hebert-Chatelain et al., 2016) and cortical astroglial cells (Jimenez-Blasco et al., 2020), where they regulate bioenergetic processes essential for neural function, suggests that these receptors could be susceptible to alterations induced by cannabinoid exposure during pregnancy, leading to cellular metabolic impairment. In this regard, findings on mitochondrial respiration in homogenized whole brainstem tissue of P0 and P12–13 neonatal rats exposed to WIN55,212-2 *in utero* (Patrone et al., 2023) point to the contribution of this mechanism, with P0 males showing increased mitochondrial uncoupling and reduced ATP production efficiency, and P12–13 males exhibiting impaired respiratory capacity and decreased bioenergetic reserve (Table 2). Indeed, phytocannabinoids have been shown to markedly reduce oxygen consumption in brain homogenates, under both *in vitro* and *in vivo* conditions (Bose et al., 1963; Dembert & Harclerode, 1974). They also suppress cellular respiration by interfering with mitochondrial electron transport (Bartova & Birmingham, 1976) and promote mitochondrial swelling (Mahoney & Harris, 1972). Therefore, exogenous cannabinoids may exert a direct and detrimental influence on neuronal structure and bioenergetics (Beiersdorf et al., 2020), potentially through the activation of mitochondrial CB_1 receptors, which can alter energy metabolism, suppress respiration and modify endocannabinoid-mediated physiological responses (Alger & Tang, 2012; Lipina et al., 2014).

Although still limited, these data to date indicate that *in utero* manipulation of endocannabinoid signalling causes short- and mid-term changes in the CNS, especially in brainstem regions critical for respiratory control. These changes lead to basal respiratory dysfunction and altered chemosensitivity during environmental challenges in a sex-specific way, potentially predisposing offspring to long-lasting impairments and greater vulnerability to respiratory and/or breathing-related psychiatric disorders later in life.

Respiratory control dysfunction in adulthood. Research studies addressing long-term effects of maternal cannabinoid use during gestation on respiratory control in the offspring are even scarcer. Consequently, the potential long-lasting adverse impacts on respiratory ontogeny, in both central and peripheral pathways, and the possible links between the dysfunction in this system with pathological conditions later in life, remain largely unclear. To date, the few studies conducted shows that neuroanatomical changes in the brainstem across postnatal development – such as increased CB_1 receptor expression and changes in CA and 5-HT neuronal populations observed early in life following prenatal WIN55,212-2 exposure – are no longer present in adult rats (P80) (Patrone et al., 2024). Moreover, the chronic prenatal WIN55,212-2 exposure-induced changes in basal ventilatory parameters and lung compliance were absent in adulthood in both sexes. Although these early-life alterations did not persist, indicating no enduring structural deficits, functional modifications in respiratory chemosensitivity remained. Specifically, adult male rats prenatally exposed to WIN55,212-2 exhibited an enhanced respiratory response to CO_2 and O_2, whereas females showed a contrasting pattern, characterised by reduced HCVR and HVR (Patrone et al., 2024). These findings underscore the lasting impact of prenatal cannabinoid exposure on respiratory control, especially on chemoreflex pathways (Fig. 5), despite apparent structural recovery during postnatal development. This raises the possibility that alterations, particularly at molecular, synaptic, or circuit-level domains not assessed yet, may persist and contribute to the functional deficits. Thus, it is plausible that fetal ECS manipulation could induce long-lasting functional changes in structures involved in chemoreflex integration, potentially mediated by epigenetic modifications established *in utero*, as overstimulation of ECS signalling during critical periods of CNS development can alter gene expression and interfere with the maturation of key neurotransmitter systems (Bara et al., 2021; Ellis et al., 2022; Smith et al., 2020).

In the absence of brainstem-specific data, a mechanism consistent with this interpretation emerges from studies showing that prenatal Δ^9-THC exposure alters neuronal excitability and synaptic plasticity, including NMDA-dependent long-term potentiation and depression, as well as endocannabinoid-mediated long-term depression, in the prefrontal cortex of adult male rats, but not females (Bara et al., 2018). Studies have consistently demonstrated long-lasting effects of *in utero* cannabinoid exposure on offspring brain function across molecular, epigenetic, electrophysiological and behavioral domains, with findings showing sex-dependent patterns (for details: Bara et al., 2021; Hurd et al., 2019). Indeed, sex differences in CB_1 receptor affinity have been observed in particular brain regions, with males showing greater

binding affinity in the limbic forebrain and midbrain (Rodríguez de Fonseca et al., 1994). Because CB_1 receptors are widely expressed during early brain development, such sex-specific differences are likely to influence multiple neural networks. Thus, such differences in CB_1 receptor affinity might also involve the respiratory control network, implying that fetal cannabinoid exposure could enhance sex-specific effects on CB_1 receptor function that persist into adulthood. Beyond CB_1 receptor-mediated differences, other sex-dependent mechanisms may also shape ventilatory control throughout life. For exemple, sex hormones modulate ventilatory responses to hypercapnia and hypoxia in adult animals (Gargaglioni et al., 2019). In particular, β-progesterone receptors seem to modulate the hypercapnic response differently in males and females (Boukari et al., 2016), and their activity within key respiratory nuclei may be impacted by prenatal cannabinoid exposure. Equally important is the fact that essential nuclei involved in respiratory pattern regulation and central chemosensitivity, such as the retrotrapezoid nucleus (Niblock et al., 2010, 2012), locus coeruleus (Bangasser et al., 2016; Gargaglioni et al., 2019), and medullary raphe (Cordero et al., 1999), are sexually dimorphic and undergo vital development during the fetal period. Therefore, chronic stimulation of the ECS during fetal life could have sex-specific effects on the maturation of central respiratory control circuits. Moreover, the long-term effects of prenatal cannabinoid exposure on the development of peripheral chemoreceptors cannot be ruled out, since fetal cannabinoid exposure may hinder the development and function of peripheral chemoreceptors, since postganglionic neurones expressing CB_1 receptors innervate the carotid body and its vasculature (McLemore et al., 2004; Zapata, 1997), and local blood flow changes could further contribute to the chemoreflex deficits.

Consistent with these potential central and peripheral alterations, functional changes in respiratory nerve activity have been observed in animals prenatally exposed to WIN55,212-2, as assessed using the *in situ* working heart–brainstem preparation (WHBP) (Patrone et al., 2025) (Table 2). In early-adult male rats, prenatal exposure to WIN55,212-2 resulted in a slight increase in baseline phrenic burst amplitude, indicating enhanced diaphragmatic motor drive. Given the absence of peripheral inputs affecting inspiratory motor activity, such as lung vagal afferents, it is plausible that this increased phrenic output arises from persistent changes in premotor and motoneuron activity within the brainstem or spinal cord. Supporting this notion, CB_1 receptors have been identified in the ventral medulla (Padley et al., 2003), a key region for respiratory rhythm and pattern generation (Flor et al., 2020; Molkov et al., 2011). Additionally, systemic administration of AEA reduces resting phrenic activity in neonatal *en bloc* preparations (Tree et al., 2010), and acute Δ^9-THC application *in vitro* decreases phrenic nerve-evoked diaphragm responses in rats (Hoekman et al., 1976). Together, these findings reinforce the potential role of the ECS in modulating phrenic nerve activity. In contrast, WIN55,212-2-treated female preparations exhibited a significant reduction in basal vagal efferent activity (Patrone et al., 2025). Since the vagus nerve transports motor fibres that innervate the laryngeal muscles, key regulators of upper airway resistance, expiratory flow and lung emptying (Paton & Dutschmann, 2002), the decreased postinspiratory vagal drive suggests impaired laryngeal motor output, which may destabilise upper airway patency and potentially contribute to breathing irregularities or obstructive events. Indeed, AEA was found to induce bronchospasm when the constricting influence of the vagus nerve was eliminated (Calignano et al., 2000).

Regarding chemoreflex response, fetal ECS signalling disruption also induced sex-specific alterations in respiratory motor nerve activity, with males exhibiting reduced expiratory motor drive to CO_2, while females showed reduced inspiratory shortening with depressed vagal excitation. Consistent with this, carotid body activation with KCN elicited a blunted increase in respiratory frequency and attenuated abdominal expiratory activity in both sexes, indicating compromised motor drive for active expiration (Patrone et al., 2025). Together, these findings suggest that prenatal cannabinoid exposure disrupts the neural mechanisms controlling inspiratory–expiratory phase transitions and expiratory flow regulation, with potential implications for chemoreflex function.

Thus, future studies should explore how prenatal cannabinoid exposure affects the development of both central and peripheral modulatory mechanisms underlying respiratory control. Understanding these processes is essential, as the present findings indicate persistent, sex-specific alterations in inspiratory and expiratory motor output, phrenic and vagal nerve activity, and chemoreflex responses. Such insights could clarify the mechanisms by which *in utero* ECS disruption leads to long-lasting changes in respiratory regulation and may help identify potential targets for intervention in individuals prenatally exposed to cannabinoids.

Cardiovascular dysfunction. Similarly to the respiratory network, the central nuclei that coordinate cardiovascular control, mainly located within the brainstem, are known to express CB_1 receptors (Padley et al., 2003; Schaich et al., 2015). Accumulating evidence indicates that the ECS is closely related to cardiovascular physiology, modulating angiogenic process, blood pressure, cardiac contractility and heart rate (HR) (Ibrahim & Abdel-Rahman, 2014; Maia et al., 2023; Pfitzer et al., 2004;

Sierra et al., 2018). These effects are mediated through the regulation of neurotransmitter release within the CNS and sympathetic/parasympathetic terminals, as well as by local β-adrenergic modulation of vascular smooth muscle (Beaconsfield et al., 1972; Hillard, 2000; Niederhoffer & Szabo, 2000). Consequently, intrauterine exposure to exogenous cannabinoids may disrupt the development and maturation of central autonomic circuits, peripheral sensors such as baroreceptors, as well as cardiac and vascular structures, ultimately leading to cardiovascular dysautonomia in postnatal life. Despite its great importance for individual health and physiological integrity, only a few studies have investigated whether cannabinoid exposure during pregnancy is associated with postnatal cardiovascular dysfunction in the offspring (Fig. 4).

In line with this emerging evidence, Lee et al. (2024) reported, via echocardiographic analysis, that *in utero* CBD exposure (30 mg/kg) caused a 30% reduction in stroke volume and cardiac output, along with a 10% decrease in ejection fraction in P21 male rats, indicating lower contractile function, with no effects seen in females. Also, there was a notable reduction in CB_2 receptor expression in the heart, along with decrease in DAGL enzyme levels. Interestingly, CB_2 has been recognized for its protective effects in cardiovascular pathophysiology. Rodent models deficient in CB_2 exhibit maladaptive cardiac responses and diminished left ventricular function when subjected to challenges like repeated ischaemia–reperfusion or increased pressure load (Duerr et al., 2019). In addition to the functional alterations, Lee et al. (2024) reported significant changes in the cardiac transcriptome of P21 male offspring prenatally exposed to CBD. Several genes exhibited differential expression, with upregulated pathways related to mitochondrial function and metabolic processes, suggesting an impact on cardiac bioenergetics. Conversely, downregulated pathways encompassed multiple developmental processes, including cell and tissue morphogenesis, indicating that prenatal CBD exposure may interfere with the maturation and structural development of the heart in male offspring.

Similar impairments in cardiac function also occur following prenatal Δ^9-THC exposure in rats (Lee et al., 2021), although sex-specific effects were not assessed in that study. At birth, exposed male offspring exhibited lower heart weights and reduced stroke volume, likely leading to a compensatory increase in HR (Lee et al., 2021). The study also found that postnatal catch-up growth was accompanied by persistent alterations, including increased left ventricular wall thickness and reduced stroke volume and cardiac output at age P21. Changes in cardiac cellular composition were also observed, as evidenced by an increase in cardiac collagen content, which is associated with fibrosis and cardiac hypertrophy. This effect may be linked to a concomitant reduction in protein levels of MMP-2, an enzyme responsible for collagen breakdown, suggesting impaired extracellular matrix remodeling in the heart (Lee et al., 2021). A potential mechanism contributing to these structural changes is the activation of GPR55 by Δ^9-THC, which can stimulate the RhoA/ROCK pathway (Sharir & Abood, 2010). Enhanced Rho-kinase activity is known to promote pathological cardiac remodelling, including increased fibrosis and hypertrophic responses (Zhao & Rivkees, 2003), which aligns with the collagen accumulation and impaired extracellular matrix turnover observed in treated offspring.

Exposure to the synthetic cannabinoid WIN55,212-2 during fetal life also resulted in marked postnatal disturbances in cardiovascular regulation, with several responses displaying a sex-dependent pattern. The effects were modest during the juvenile stage (P27–28), with exposed males showing a slight increase in resting systolic arterial pressure and bradycardia during hypercapnic challenge. In adulthood, however, sex-specific alterations became more evident, with males exhibiting elevated mean arterial pressure (MAP) and HR under hypoxia, whereas females presented higher resting MAP, marked CO_2-induced bradycardia, and an exaggerated tachycardic response to hypoxia accompanied by a sustained pressor response (Patrone et al., 2023, 2024) (Table 2). In line with these findings, *in situ* experiments revealed sex-dependent autonomic alterations following prenatal WIN55,212-2 exposure, characterised by reduced sympathetic responses to carotid body stimulation in males, suggesting impaired blood flow redistribution during hypoxic conditions and compromised support to energy-demanding organs, and by reduced tonic vagal activity in exposed females, which may contribute to the hypertensive phenotype observed *in vivo*, given that parasympathetic fibres of the vagus nerve innervate the heart and contribute to cardiovascular regulation (Fazan et al., 2005; Janssen & Smits, 2002). Moreover, the pronounced bradycardic response to hypercapnia in adult females may partly reflect altered thermoregulatory influences on cardiac control, given the role of the ECS in thermogenesis (Krott et al., 2016) and the well-established impact of temperature on heart rate (Davies & Maconochie, 2009). These findings suggest that prenatal cannabinoid exposure may disrupt the maturation of central CB_1 receptor-mediated autonomic pathways involved in cardiovascular adjustments, although a contribution of altered peripheral pressure-sensing mechanisms cannot be excluded.

Consistent with these findings, new analyses of heart rate variability (HRV) in juvenile and adult rats prenatally exposed to WIN55,212-2 further highlight the detrimental impact of fetal ECS manipulation on sex-dependent cardiovascular control. In juvenile

males, the SD1 index increased in response to CO_2 challenge. In contrast, females exhibited the opposite response (Fig. 6), reflecting the *in situ* observations of lower sympathetic activity in males and reduced parasympathetic modulation in females during CO_2 stimulation (Patrone et al., 2025). In adulthood, males displayed elevated SD1 and SD2 values during hypoxic exposure. In contrast, females showed higher HRV both at baseline and under hypercapnia (Fig. 7), suggesting a sex-specific shift in autonomic balance potentially driven

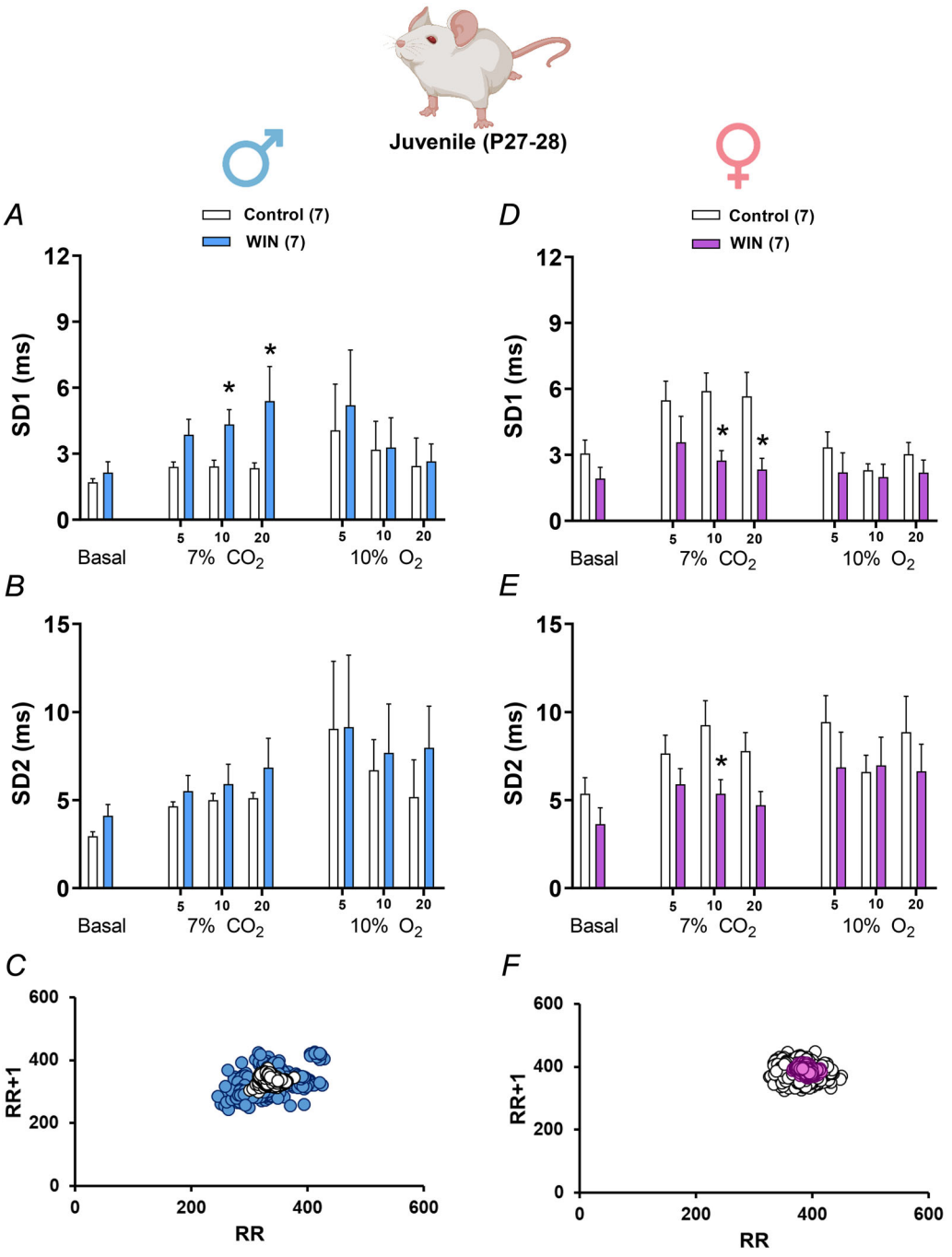

Figure 6. *In utero* exposure to WIN55,212-2 significantly affects heart rate variability in juvenile rats in opposite directions under environmental challenge
A, *B*, *D* and *E*, heart rate variability (HRV; mean ± SEM) during resting conditions (basal) and at 5, 10 and 20 min of exposure to hypercapnia (7% CO_2) and hypoxia (10% O_2) in juvenile (P27–28) control and WIN-treated male (*A*, *B*) and female (*D*, *E*) rats. SD1, short-term HRV; SD2, long-term HRV. *C* and *F*, representative Poincaré plots show heart period (RR) versus the duration of the subsequent beat (RR+1) for juvenile males (*C*) and females (*F*).

by ECS disruption. Notably, Rompala et al. (2021) also reported a significant main effect of maternal cannabis use on HRV in early childhood (Fig. 4).

Overall, *in utero* exposure to cannabinoids seems to disrupt normal cardiac developmental trajectories, increasing susceptibility to maladaptive responses and cardiometabolic dysfunction (Moore, 2024). These effects are driven by impaired cardiomyocyte growth, altered autonomic regulation and changes in atrioventricular contractility, potentially mediated by dysregulation of CB_1 and CB_2 signalling in the developing heart and its neural control pathways. Altered sympathetic and vagal responses to physiological challenges indicate modifications in brainstem chemoreflex circuits, with

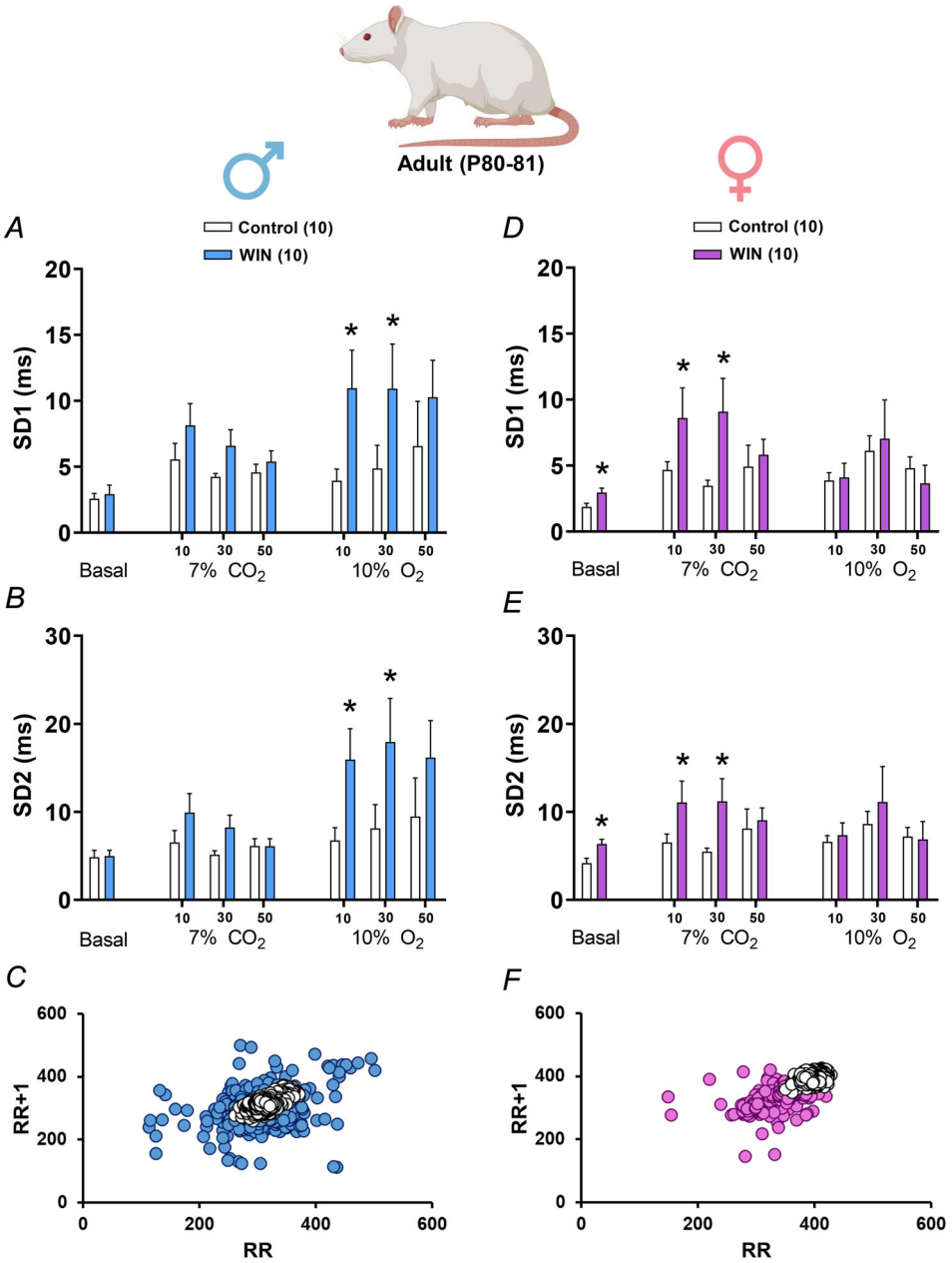

Figure 7. Prenatal WIN55,212-2 exposure alters heart rate variability in adult rats during respiratory challenge
A, *B*, *D* and *E*, heart rate variability (HRV; mean ± SEM) is shown during resting conditions (basal) and at 10, 30, and 50 min of exposure to hypercapnia (7% CO_2) and hypoxia (10% O_2) in adult (P80-81) control and WIN-treated male (*A*, *B*) and female (*D*, *E*) rats. SD1, short-term HRV; SD2, long-term HRV. *C* and *F*, representative Poincaré plots display heart period (RR) versus the duration of the subsequent beat (RR+1) for adult males (*C*) and females (*F*). Derived from analysis of unpublished data.

possible contributions from peripheral sensors such as the carotid sinus baroreflex. Notably, some of these outcomes are sex-dependent, highlighting the potential influence of hormonal factors and reinforcing the need for sex-based analyses. The definitive impact of cannabinoids on the developing cardiovascular system remains incompletely understood and warrants further investigation.

Clinical and translational implications

Disorders caused by drug of abuse during pregnancy remain a significant public health issue, posing risks to child development and imposing socioeconomic burdens due to increased demand for healthcare and social support services (NIDA, 2025). As discussed in this review, pregnancy comprises critical windows of neurodevelopmental plasticity and increased vulnerability, during which disruption of the ECS by exogenous compounds may result in lasting adverse effects linked to physiological dysfunctions, behavioural disturbances and even psychiatric disorders (Adriani & Laviola, 2004; Bara et al., 2018; Black et al., 2025; Manduca et al., 2020). These insults interfere with CNS ontogenetic development and lead to maladaptive changes in neuronal circuits, including respiratory and autonomic networks. In accordance with the Developmental Origins of Health and Disease (DOHaD) concept, such early-life disruptions may cause epigenetic modifications that contribute to long-lasting functional changes, potentially persisting throughout life (Bara et al., 2021; Gluckman et al., 2016; Lo et al., 2023; Silveira et al., 2007). Similarly, Shorey-Kendrick et al. (2023) demonstrated that prenatal Δ^9-THC exposure alters DNA methylation in rhesus macaques, affecting genes associated with autism (Corsi et al., 2020).

In this context, prenatal cannabis exposure has also been associated with increased rates of respiratory complications, hypotonia, growth restriction and neonatal withdrawal, and is considered a potential risk factor for SIDS (Crosland et al., 2024; Scragg et al., 2001). Clinical evidence suggests that prenatal cannabis exposure may raise the risk of respiratory issues in newborns (Lacroix et al., 2007). While endogenous cannabinoids at birth appear to modulate breathing and offer protection against apnoea, prenatal exogenous exposure could interfere with the development of respiratory networks, as well as lung surfactant synthesis and secretion (Cherlet & Scott, 2002), potentially increasing neonatal susceptibility to environmental stressors such as hypoxia (González et al., 2005; Desai et al., 2013). Additionally, childhood lung dysfunction may serve as a predictor for adult chronic obstructive pulmonary disease and asthma (Bui et al., 2017).

Epidemiological data suggest a link between prenatal exposure to cannabis and increased vulnerability to neuropsychiatric conditions, including panic disorder, later in life (Higuera-Matas et al., 2015; Jutras-Aswad et al., 2009; Leech et al., 2006). Clinical and experimental studies consistently show a strong connection between anxiety, panic disorder and heightened sensitivity of the ventilatory CO_2 chemoreflex (Coryell et al., 2001; Dominiquini-Moraes et al., 2025; Okuro et al., 2020; Ripamonte et al., 2024; Spiacci et al., 2018), implying that prenatal cannabinoid exposure may predispose individuals to panic-like responses by increasing CO_2 sensitivity, thereby raising their risk of experiencing the 'false suffocation alarm' that can trigger panic attacks. *In vivo* studies have also found a greater CO_2 ventilatory response in neonatal, juvenile and adult males exposed prenatally to a synthetic cannabinoid, with adult males more prone to exhibit panicogenic behaviour than females (Patrone et al., 2023, 2024).

Moreover, children with prenatal cannabis exposure have been shown to report increased anxiety symptoms (Goldschmidt et al., 2004; Grey et al., 2005; Nashed et al., 2021). In fact, P12 rat pups prenatally exposed to Δ^9-THC exhibited increased ultrasonic vocalisations when separated from the nest, a behaviour that may be analogous to infant crying and indicative of early-life neurobehavioural changes (Trezza et al., 2008). In adolescence and adulthood, these animals demonstrated reduced play and social interaction, along with heightened anxiety-like behaviour in the elevated plus-maze. Cohort studies have found an association between maternal self-reported cannabis use and children exhibiting symptoms related to various sleep disturbances, including problems with sleep onset and maintenance, arousal-related disorders, disruptions in the sleep–wake cycle, excessive daytime sleepiness and mixed sleep disorders (Winiger & Hewitt, 2020). Interestingly, prenatal WIN55,212-2 exposure predominantly affected adult male rat sleep, leading to shorter sleep episodes under room air and more fragmented sleep during normocapnia and CO_2 exposure. In contrast, females were less impacted but exhibited more frequent wake–sleep transitions in room air and prolonged wake episodes under hypercapnia (Patrone et al., 2024). Indeed, CB_1 receptors are implicated in sleep regulation, as they are distributed across brain areas crucial for regulating the sleep–wake cycle (Bowles et al., 2017).

Regarding cardiovascular function, current evidence suggests that ECS is involved in the response to threatening pathophysiological circumstances (Chandy et al., 2025; Hiley, 2009). Endocannabinoid signalling dysfunctions have been associated with conditions such as hypertension, heart disease and atherosclerosis (Alfulaij et al., 2018; Duerr et al., 2015; Hiley & Ford, 2003; Randall & Kendall, 1997). Cardiovascular health

impairments, such as myocardial valve thickening and ventricular septal defect, are linked to prenatal exposure to Δ^9-THC (Moore, 2024). Epidemiological studies have highlighted associations between maternal cannabis use and congenital heart anomalies in offspring, a condition affecting approximately 1 in 100 newborns and representing one of the leading causes of infant mortality due to birth defects (Bolin et al., 2022). Cannabis use during gestation has also been associated with an increased risk of Ebstein's anomaly, characterised by displacement of the tricuspid valve leaflet, which disrupts normal cardiac blood flow and may lead to heart enlargement or failure (Lurie & Ferencz, 1997). Evidence from preclinical studies suggests that CB_2 receptor activation mitigates ischaemia–reperfusion injury by downregulating chemokine receptors and tumour necrosis factor-α-driven endothelial activation (Joyeux et al., 2002; Montecucco et al., 2008, 2009). Consequently, chronic maternal cannabis use during pregnancy may increase the risk of cardiac complications in both the prenatal and postnatal periods (Richardson et al., 2016). Moreover, altered HRV is associated with multiple anxiety-related disorders in both young children and adults and is considered a risk factor for cardiovascular disease (Chalmers et al., 2014).

Conclusion and future directions

The increasing use of cannabis among pregnant women, whether for recreational or medicinal purposes, reflects a global trend supported by the mistaken belief that its natural origin guarantees safety. This idea is further reinforced by evolving government policies that support its legalisation and increased accessibility. Adding to this issue, the concentration of Δ^9-THC has risen from about 4% to 15% between 1995 and 2020, substantially increasing the potential for developmental harm (Chandra et al., 2019; Freeman et al., 2021). At the same time, cannabinoid-based medications are being prescribed more frequently during pregnancy to manage gestational symptoms (e.g., nausea and sleep disturbances) and pre-existing maternal conditions (e.g., anxiety, depression and chronic pain) (Vanstone et al., 2022; Young-Wolff et al., 2022). This growing exposure during a critical developmental phase highlights the urgent need to better understand the risks posed to the developing fetus.

Current evidence indicates that male offspring are more susceptible to prenatal cannabinoid exposure, characterised by significant alterations in placental structure, gene expression profiles, neuroanatomy, and enduring impairments in cardiorespiratory and behavioural regulation. However, the biological mechanisms underlying these outcomes remain unclear, including the relative roles of direct fetal exposure *versus* maternal-mediated pathways. Moreover, the field still lacks a clear understanding of how sex-specific placental function, hormonal environments and metabolic differences influence vulnerability trajectories throughout development. Notably, male and female embryos differ not only in sex chromosome composition but also in metabolic profiles shaped by sex-linked and autosomal gene expression, which may contribute to their differential vulnerability (Donjacour et al., 2014; Gardner et al., 2010; Kobayashi et al., 2006).

Moving forward, research needs to delineate not only the consequences of prenatal exposure but also how disrupted circuits might be rescued or compensated for. Promising avenues include interventions that restore endocannabinoid signalling during critical windows, strategies that modulate maladaptive synaptic plasticity in brainstem networks, and approaches to improve placental function in at-risk pregnancies. Comparative studies assessing the effect size and longitudinal severity of Δ^9-THC relative to synthetic agonists (e.g., WIN55,212-2), CBD and other modulators of the ECS are also essential to refine risk estimates and guide clinical decision-making.

Ultimately, understanding how prenatal cannabinoids reshape respiratory and homeostatic circuits across the lifespan will be key to identifying therapeutic leverage points. These insights should inform public health policies and regulatory discussions, emphasising that the use of cannabinoid-based substances during pregnancy, whether recreational or therapeutic, carries measurable neurodevelopmental risks that warrant careful and evidence-based consideration.

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Additional information

Competing interests

The authors declare no competing interests.

Author contributions

L.G.A.P. and L.H.G. provided critical and intellectual input during manuscript preparation. Both authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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