Revista ARACÊ
ISSN: 2358-2472

EPIGENETIC EFFECTS OF THC EXPOSURE ON NEURODEVELOPMENT, A SYSTEMATIC REVIEW

https://doi.org/10.56238/arev7n3-129

Submitted on: 02/14/2025 **Publication date:** 03/14/2025

Nicolás Andre Aliaga Espinoza[1], María Jesús Acevedo de La Fuente[2], Rosa M. Zúñiga Bastías[3] and Luis E. Abarza Morales[4]

ABSTRACT

Introduction: The consumption of cannabis and THC has been increasing within the youth population at a national and global level. Perinatal THC consumption is a concern for its effects on neurodevelopment. Methodology. Se realizó una búsqueda de artículos siguiendo las directrices Prisma. Resultados: de 106 artículos iniciales sometidos a los filtros correspondientes, se seleccionaron 6. There is experimental evidence at the genetic level that relates THC consumption and its effect on the endocannabinoid system but epigenetic effects are caused as a consequence of gene methylations directly involved in neurodevelopment processes. Conclusions and Conclusions: Damage in the processes of maturation of nervous tissue, neuronal migration, neurite formation, and synaptogenesis are evident at the level of structural, physiological, and behavioral cries. It is necessary to follow the path of research in this line and design public policies that adviertan y protejan a la población sobre os efectos deletéreos que puede provoke el consumo de cannabis em la descendencia.

Palabras clave: Cannabis. THC. Neurodevelopment. Epigenetics.

[1] Medical Student
Faculty of Health Sciences
Universidad Autónoma de Chile
[2] Medical Student
Faculty of Health Sciences
Universidad Autónoma de Chile
[3] Cruz Roja Chilena Quilicura Branch
E-mail: r.z.bastias@gmail.cl
ORCID: https://orcid.org/0000-0003-1663-3956
[4] Universidad Autónoma de Chile
E-mail: labarzam@uautonoma.cl
ORCID: https://orcid.org/ 0000-0001-9583-4187

Revista ARACÊ
ISSN: 2358-2472

INTRODUCTION

Neurodevelopment is a complex and highly regulated process that begins a few days of gestation and is extended to mature in early adulthood, which is fundamental for the establishment of cognitive, emotional, and behavioral healthy functioning. (Föster, J. and López, I., 2022). Several investigations show that exposure to different substances, including marihuana, during critical stages of development can have lasting consequences on the structure and function of the brain, as well as in the behavior and mental health of the individual (Casavilca-Zambrano, 2019).

Cannabis is the most widely cultivated, trafficked, and abused illicit drug in the world, according to the WHO, with an estimated 147 million users globally (WHO, 2024). This increase in consumption has been especially notable among the youth population. In Chile, according to the 15th Drug Study in the General Population of the Chilean Drug Observatory, the prevalence of marihuana consumption in 2022 reached 10.9%, being 7.6% in women and 14.2% in men. Within the age groups, the 19 to 25 age group stands out, with a prevalence of 19.6%, followed by the 26 to 34 age group, with a 19% prevalence (SENDA, 2024). In another study conducted in Chile involving 166 university students, it was found that on average, 25.5% of them reported using cannabis at least three times a month (Cazenave, A. et al., 2017). Estos datos adquieren relevancia puesto que la edad promedio de inicio de la maternidad se establece alrededor de los 26 años (Díaz, M., 2023).element. On the other hand, an increase in the incidence of Autism Spectrum Disorder (ASD), Attention Deficit and Hyperactivity (ADHD) Disorder, and other learning disorders in children of cannabis-consuming mothers has been observed (Corsi, D., et al., 2020). There is evidence to suggest that changes in the expression of the enzyme DMNT1 (maintenance methyltransferase) and histone acetyltransferases, linked to epigenetic processes, could result in several alterations that are manifested in the offspring (Ge, Z. et al., 2015).

Epigenetic regulation and modulation of gene expression are key in human neurological development. DNA methylation, in response to exposure to various external substances, can trigger important genetic dysregulations that affect both cellular and tissue development at the organ level of the central nervous system (Casavilca-Zambrano, 2019).

En este contexto, la chromatin bivalente emerge como un concepto clave. This structure, present in the nucleus of embryonic and germinal mother cells, is marked by specific histone modifications associated with both promoter activation (H3K4me3) and

Revista ARACÊ
ISSN: 2358-2472

gene expression (H3K27me3) repression. This duality allows for precise regulation during development and cell differentiation (Sachs, M. et al., 2013). Epigenetic markers related to bivalent chromatin include DNA methylation and several modifications in histones, which act as "switches" to control DNA access and therefore gene transcription. The methylation of H3K4me3 promotes the active transcription to facilitate the regrowth of chromatin and histone acetyltransferase remodeling enzymes. In contrast, the methylation of H3K27me3 inhibits transcription by inducing a compact chromatin structure. This dynamic balance in bivalent chromatin plays a crucial role in the determination of cell fates and the specification of cell identity during embryonic and postnatal development (Bernstein, B. et al., 2006)element.

It is important to mention that cannabis contains ∆9-tetrahydrocannabinol (THC) as the main psychoactive component, which acts as an agonist of the CB1 and CB2 receptors of the endocannabinoid system. CB2 receptors are predominantly found in cells of the immune system, such as leukocytes, the bazo, and the tonsils (Liz, D. and Niuxia, A., 2023). On the other hand, CB1 cannabinoid receptors are distributed in high density in neurons located in areas such as the nucleus accumbens, the dorsal striatum, and the cerebellum, as well as in the hippocampus and the amygdala. In other brain areas, such as the neocortex, the superior colliculus, and the brain, the density of cannabinoid receptors is moderate. (Fernández-Espejo, E., & Núñez-Domínguez, L., 2022). This system plays a crucial role in several aspects of neurodevelopment, including neuronal migration and axonal enlargement, glial formation, proliferation and differentiation of neural mother cells, coordination of migration and axonal connectivity, and synaptogenesis. The CB1 receptor, central to this system, participates in fetal brain maturation and morphogenetic exchanges throughout the envelope in different brain regions. In humans, the CB1 receptor is present from the ninth week of gestation, maintaining a similar pattern of expression from mid-gestation to adulthood, where it reaches high levels. (Cayuelas Asensio, A. 2022). It has been proven that cannabinoids can cross the placental barrier, which reaches approximately 10% of the levels present in the maternal blood in fetuses. In addition, during lactation, cannabinoids are incorporated into the maternal leche, which exposes the offspring to this substance (Fernández-Espejo, E., & Núñez-Domínguez, L., 2022).

Addictive substances, such as marihuana, alter endocannabinoid-mediated synaptic neuroplasticity (eCB), both in its manifestation of cut duration and in perdurable (10). In this analysis, we will focus on neuroplasticity in a wide square, where the key phenomena

Revista ARACÊ
ISSN: 2358-2472

stand out: potentiation a largo plazo (LTP, por sus siglas en inglés) y la depresión a largo plazo (LTD). These processes are fundamental for the formation of memory and learning, and these substances alter the normal neurophysiology associated with them (Guadamuz, J. et al, 2022).

The eCB-mediated LTD appears after a transient increase in the activity of the neurotransmitter glutamate, which triggers a high production of eCB in the postsynaptic neuron. This overproduction of eCB leads to a prolonged reduction in glutamate release, thus contributing to LTD. In this way, it is associated with the prolonged activation of metabotropic glutamate receptors (mGluRs), which translates into a decrease in synaptic efficacy. This phenomenon has been observed in several brain structures, including the nucleus accumbens, the dorsal striatum, the prefrontal court, the amygdala, the hippocampus, and the ventral tegmental area (VTA). On the other hand, the activation of synapsis and coherence is converged in the base of potentiation a largo plazo (LTP) (Córdoba-Montoya, D. A. et al., 2010). LTP implies a lasting increase in the communication between neurons, which is produced immediately after the application of a high-frequency electrical stimulation train. This phenomenon is especially relevant in the hippocampus (Hernández, S., Mulas, F. and Mattos, L. 2004).

The interference of cannabis with epigenetic processes and synaptic neuroplasticity associated with it raises important questions about the effects of the consumption of this substance on neurodevelopment and cognitive function (Verdejo-García, A., 2011). Understanding how THC and other cannabinoids affect these fundamental processes can shed light on the underlying mechanisms of neurodevelopment disorders that are associated with cannabis use, as well as on potential strategies to mitigate these negative effects. Investigating the relationship between cannabis and its effect on neuroplasticity offers an important source of knowledge to advance the understanding of cannabis effects on the brain and thus be able to develop prevention and treatment strategies. The objective of our study is to explore the deleterious effects and not the loss of cannabis use by parents in the neurodevelopment of the offspring.

METHOD AND MATERIALS

A systematic review of the scientific literature following the PRISMA guidelines (Haddaway, N. R. et al., 2022) was carried out, and the continuation is detailed below.

Revista ARACÊ
ISSN: 2358-2472

The first searches were held in June 2023, for which we considered the terms ″Tetrahydrocannabinol", "THC", "Cannabis", "Neurodevelopment", "Perinatal exposure", "DNA methylation", "Maternal exposure", "Synthetic cannabinoids", in the Scopus, PubMed, Google Scholar databases. También se amplió la búsqueda con los operadores booleanos AND y OR combinando algunos de los términos señalados.

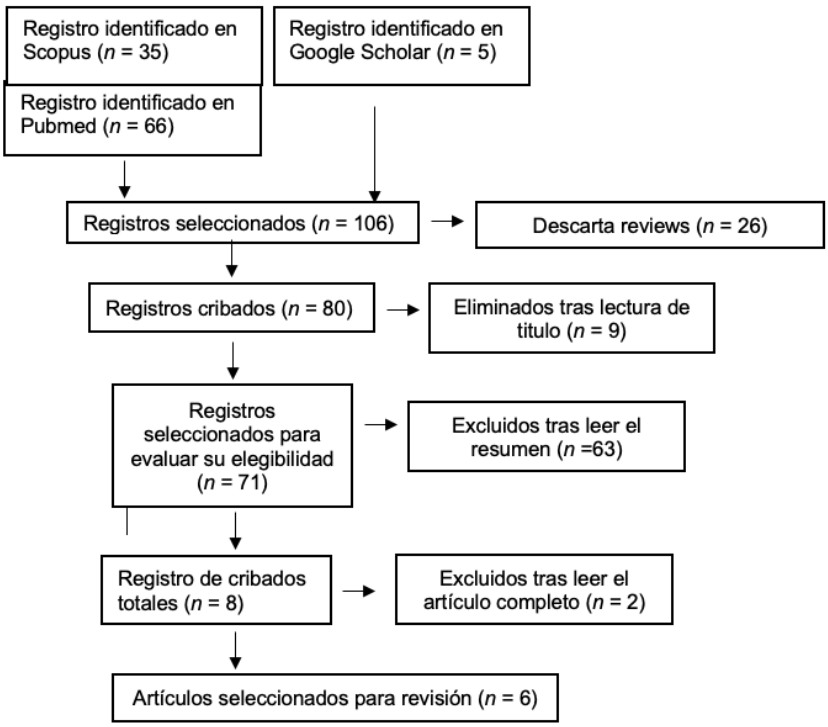
We found that there is a lot of literature related to cannabis consumption, however, few articles use an experimental methodology and imaging tools and histological procedures that verify the damage caused by THC and much less, if it is aligned with our study objective.

Finally, a total of 106 articles were registered, 66 in PubMed, 35 in Scopus and 5 in Google Scholar (Figure 1).

The search considered the following inclusion and exclusion criteria: articles written in English language, published between 2013 and 2024 inclusive, empirical investigations, results obtained through histological techniques or imaging and use as study specimens to different mammals. Se descartaron estudios as a result of other revisions.

In this way, 9 articles were discarded by title and other 63 were discarded by summaries and 2 were discarded by reading the complete article. No duplicate articles will be found. Finally, we list 6 selected articles.

Figure 1. Diagrama de flujo que resume la búsqueda y selección de artículos.



Revista ARACÊ
ISSN: 2358-2472

RESULTS

Los 6 artículos seleccionados se muestran en la tabla I. Tortoriello (2014) shows that the cries descending from hembras, exposed to THC, undergo structural and functional modifications in cortical circuits. Neuronal axones alter their cytoskeleton due to a decrease in the SCG10 protein that regulates growth and neuritic stability. On the other hand, CBR1+ buttons are increased in the radiated stratum of the CA1 subfield of the hippocampus, suggesting an erroneous orientation of synapsis. Beggiato (2016), obtained as a result after perinatal exposure to THC, that brain tissue evidences a decrease in CB1 receptor expression as well, a decrease in GABAergic activity.

Bara et al. (2018), analyzed the adult offspring exposed to intrauterine WIN and THC through histological sections of the pyramidal neurons of PCFm, demonstrating that eCB-LTD was absent in males exposed to THC and their social behavior was reduced about the hembras, which showed an indistinguishable behavior of the rats in the control group.

According to Schrott et al. (2020), 621 methylated genes were observed, of which there were enfasis in 7 (Dlg4, Shank1, Grid1, Nrxn1, Nrxn3, Syt3 and Lrrtm4), because they are genes implicated in neurodevelopment disorders and processes, with significant methylations (>10% in samples vs controls), in addition to this it is mentioned that they have been identified with previous Shank1 mutations, Nrxn1, Nrxn3 and Grid1 in individuals with ASD, as well as recognizance that Shank1 and Dlg4, both located in the postsynaptic density (PSD) of neurons, play a critical role in the regulation of synaptic escalation and plasticity. A process of solapamiento with epimutaciones associated with ASD was determined, and after abstinence, a superposition of 10 genes was found, among which this DLGAP2 was found. Among the strengths of the study, people who did not comply with the period of abstinence, as nicotine users and among their limitations were eliminated is the person who did not contemplate the route of administration, the potency of cannabis consumed as the presence of contaminants associated with pesticides or heavy metals. About DLGAP2, it is a gene associated with the generation of andamiaje proteins located in the postsynaptic density (PSD) of neurons, in turn its alteration is associated with schizophrenia and is the candidate gene for autism. The study concluded that in addition to generating hypomethylations in the CpG regions associated with this gene post exposure to THC, it was possible to detect hypomethylations in the nucleus accumbens of rats born of priests post exposure, which supports the concept of intergenerational inheritance.

Revista ARACÊ
ISSN: 2358-2472

Shorey (2023), to overcome the limitations of other studio models, conducts an investigation in sexually mature rhesus monkeys where she establishes controls (5) and exposures (5) to oral THC. Subsequently, a scheduled delivery by cesarean section was performed on day 155, performing an analysis of the placenta and fetal necropsy. 5 distinct tejides (placenta, cerebellum, ventricle derecho, prefrontal court, and lung) were analyzed, and methylations were found in all of them, but mainly in the placenta. The main differentially methylated CpGs in the placenta were associated with the MEGF10 gene (multiple EGF like domains 10), a highly expressed gene in the cerebral tejado, which is implicated in the synaptic function of the postnatal brain and also methylated regions differentially associated with PCDH genes (protocadherine genes), which were exposed to a large extent in the nervous system during its development. In the strengths of the study we find the overcoming of limitations that would occur in human groups exposed to cannabis as the son: the moment, duration, dosis, frequency, type and route of administration. Por otro lado, el estudio muestra similitud a la realidad pues los edibles de THC são consumidos por algunas embarazadas con el fin de mitigating nauseas

In Scheyer (2020), perinatal exposure to THC through lactation, increases social exploitation on the coast of discrimination between new and family social stimuli. Durante la primera prueba, si bien ambas ratas expuzararam una superior preferencia por la rata nueva al objeto nuevo, la descendencia expuesta al THC, según el tiempo que pasaron en los dos sitios (sprang on the sites), showed a more fuerte social preference. In the area of social memory, the rats exposed in simulated form showed the preference expected by a new rat over the family rat of the first period of prueba. However, the rats exposed to perinatal THC (lactation) did not show such a preference. Perinatal exposure to THC leads to a lasting deficit of eCB-LTD in PFC in adulthood. It was proven that mGlu2/3-mediated LTD is significantly higher in the rats exposed to THC than in the PFC. Además, se comprueba que niveles altos de 2-AG en la PFC restauran efectivamente el eCB-LTD en estas condiciones. Perinatal exposure to cannabinoids suppresses theta-burst-induced wide plachal potentiation (TBS-LTP) in the PFCs of adult male rats. In terms of the excitability parameters, through a more detailed experiment with current inyecciones, it was proven that in the progeny the THC exposure peaks of the action potential decreased, the comparison of the control group. The replacement membrane potential in the cambio in both, however, the rebase (minimum current required to provoke an action potential) was significantly increased in the progeny exposed to THC. En este trabajo no se observaron

Revista ARACÊ
ISSN: 2358-2472

diferencias en el sexo de la progenie. And if this studio presents some limiting, this refers to the calculation of THC doses transferred through maternal leche.

Table 1. Nómina de artículos seleccionados y sus principales resultados experimentales.

Author (año de publicación)	Title	Especimen de estudio	Controls	Exhibits	Findings
Tortoriello et al (2014)	*Miswiring the brain: D9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway*	Wistar	6	7	Behind the prenatal exposure, histological sections of cerebral cutsiness were analyzed in offspring of THC exposed to hembras, where a significant increase in CBR1+ buttons was observed in the radiate stratum of the CA1 subfield of the hippocampus, which suggests an erroneous orientation of the synapsis as a decrease in the depression at a large stage after the stimulation of the Shaffer collaterals, which can induce structural and functional modifications of the cortical circuit. In addition, a decrease in SCG10, a protein that regulates the growth and stability of microtubules at the axonal level, is observed.
Beggiato et al (2016)	*Lost-lasting alterations of hippocampal GABAergic neurotransmission in adults rats following perinatal Δ⁹-THC exposure*	Wistar	5	5	Histological sections of the brain tissue in the hippocampus of crias were analyzed after perinatal exposure, and a decrease in CB1 receptor expression and GA activity was found.
Bara et al (2018)	*Sex-dependent effects of in utero cannabinoid exposure on cortical function*	Wistar	6	4	The adult offspring were analyzed by exposing WIN and intrauterine THC by histological sections of the pyramidal neurons of PCFm, demonstrating that eCB-LTD was absent in males exposed to WIN and in THC exustations, as well as greater excitability of deep layers in rats exposed to WIN regardless of sex, y una disminución de la reobase en los machos expuestos al WIN. In addition, through behavioral practices, it was observed that males exposed to WIN had less social interaction in adult age than

Revista ARACÊ
ISSN: 2358-2472

					hembras.
Scheyer et al (2020)	Perinatal THC exposure via lactation inducing lasting alterations to social behavior and prefrontal cortex function in rats at adulthood	Wistar	23	18	Behind perinatal exposure, histological sections of medial prefrontal cutness (mPFC) were analyzed in adult offspring of exposed THC babes, where a significant long-term deficit of eCB-LTD is found in the medial pyramidal layer 5 behind the Theta Burst Simulation (TBS) protocol in adult age, as an increase in mGlu2/3-LTD. It was also observed that THC suppresses LTP in adult age and decreases the peak temperature of potential for action in the deep-cap pyramidal neurons of the PFC, as it increases the rebase in the expropriated offspring. In addition, changes were shown in the category "social focus" and "memory".
Schrott et al (2020)	*Sperm DNA methylation altered THC and nicotine: Vulnerability of neurodevelopmental genes whit bivalent chromatin*	Sprague Dawley	8	7	The sperm of the rats exposed to THC showed 4 genes active in neurological development and synaptic plasticity that were hypomethylated (Syt3, Lrrtm4, Nrxn1, Nrxn3) and 1 gen (Shank1) was significantly hypermethylated compared to controls. Al comparar con la base de Datos String se encuentra que 4 de estos genes esta asociados al autismo
Shorey-Kendrick et al (2023)	*Prenatal delta-9-tetrahydrocannabinol exposure is associated with changes in rhesus macaque DNA methylation enriched for autism genes*	Rhesus Monkeys	5	5	The following methylated genes were found in fetal brain tea: Cerebellum (SUPT3H, NSG1 and SLC12A8) and Prefrontal Cutness (SUPT3H and LRRC28). In addition, it compares with SFARI data base and finds 29 methylated autism candidate genes in THC expuestos with a $p<0.05$

DISCUSSION AND CONCLUSIONS

Prenatal and perinatal exposure to Δ⁹-tetrahydrocannabinol (THC) and other cannabinoids has been studied in several animal models, revealing a variety of neurobiological and behavioral changes. In general, these studies highlight how early exposure to cannabinoids can induce lasting changes in development and cortical function.

Revista ARACÊ
ISSN: 2358-2472

Changes in Neurotransmission and Synaptic Function: Tortoriello et al. (2014) demonstrated that prenatal exposure to THC in Wistar rats induces a significant increase in CBR1+ buttons in the radiate stratum of the CA1 subfield of the hippocampus, suggesting an erroneous orientation of synapsis and a decrease in depresión at a wide plazo. This could be related to structural and functional modifications of the cortical circuit, since a decrease in SCG10 was also observed, a protein crucial for the stability of microtubules at the axonal level.

Effects on GABAergic Neurotransmission: On the other hand, Beggiato et al. (2016) found that perinatal exposure to THC produces a decrease in CB1 receptor expression and GABAergic activity in the hippocampus of adult rats. These results suggest that early interference with the endocannabinoid system can have long-lasting consequences in neurotransmission inhibitory.

Sex Dependent Differences: Bara et al. (2018) reported that the effects of intrauterine exposure to cannabinoids are sex dependent. In particular, it was observed that eCB-LTD was absent in males exposed to THC, but the muscles did not present this effect. In addition, males exposed to THC showed less social interaction in adulthood, indicating a specific possible vulnerability of males to cannabinoid effects.

Behavioral Changes and Function of Prefrontal Court: Scheyer et al. (2020) found that perinatal exposure to THC through lactation induces lasting changes in social behavior and the function of medial prefrontal courtship in adult offspring. A significant deficit of eCB-LTD was observed in the pyramidal neurons of layer 5, together with an increase in mGlu2/3-LTD and suppression of LTP, which could explain the changes observed in the categories of "social focus" and "memory".

Effects on DNA Methylation: The studies of Schrott et al. (2020) and Shorey-Kendrick et al. (2023) provide evidence that exposure to THC can alter DNA methylation in genes critical for neurological development. In particular, Schrott et al. found changes in the methylation of genes associated with autism in Sprague Dawley rats, although Shorey-Kendrick et al. reported similar changes in rhesus monkeys, suggesting that the epigenetic effects of prenatal exposure to THC could be conserved across species.

Overall, these studies underestimate the importance of considering the effects of prenatal and perinatal exposure to cannabinoids in neurological development. The alteration of neurotransmission, synaptic function and methylation of proteins associated with DNA suggests that the use of cannabinoids during the embarrassment may have

Revista ARACÊ
ISSN: 2358-2472

lasting consequences in the offspring, with potential implications for the development of neuropsychiatric disorders. These hallazgos highlight the need to propose public health policies that warn about the risk of consuming cannabinoids during the embarrassment and lactation due to the neurological damage that these cause. In addition, it suggests future directions for research, including longitudinal studies in humans to confirm these effects and to investigate in depth the molecular and cellular mechanisms subyacentes.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

Revista ARACÊ
ISSN: 2358-2472

REFERENCES

1. Bara, A., Manduca, A., Bernabéu, A., Borsoi., M., Serviado, M., Lasalle, O., Murphy, M., Wager, J., Mackie, K., Pelissier, A., Trezza, V. & Manzoni, O. (2018). *Sex-dependent effects of in utero cannabinoid exposure on cortical function*. 11(7); 36234. Https://doi.org/ 10.7554/eLife.36234

2. Beggiato, S., Borelli, A., Tomasini, M., Morgano, L., Antonelli, T., Tanganelli, S., Cuomo, V., Ferraro, L. (2017). *Long-lasting alterations of hippocampal GABAergic neurotransmission in adult rats following perinatal Δ9-THC exposure.* Neurobiol Learn Mem. 139; 135-143. https://doi.org/10.1016/j.nlm.2016.12.023.

3. Bernstein, B., Mikkelsen, T., Xie, X., Kamal, M., Huebert, D., Puño, J., Fry, B., Meissner, A., Wernig, M., Plath, K., Jaenisch, R., Wagschal, A., Fell, R., Schreiber, S. & Lander, E. (2006). *A Bivalent Chromatin Structure Marks Key Developmental Genes in Embryonic Stem Cells. Cell. 125 (2);* 315-326 https://doi.org/10.1016/j.cell.2006.02.041

4. Casavilca, S., Cancino, K., Jaramillo-Valverde, L. y Guio, H. (2019). *Epigenetics: the relationship of the environment with the genome and its influence on mental health*. Journal of Neuro-Psychiatry. 82(4); Ep 266-273. https://doi.org/10.20453/mp.v82i4.3648

5. Cayuelas, A. (2022). *Changes produced in the fetus and in the child due to cannabis use in pregnancy and lactation.* http://dspace.umh.es/bitstream/11000/28347/1/Cayuelas%20Asensio%20Ana.pdf

6. Cazenave, A., Saavedra, W., Huerta, P., Mendoza, C., and Aguirre, C. (2017). *Consumption of marihuana in university youth: Percepción de los padres. Science and Nursing*, *23*(1); 15-24. https://doi.org/10.4067/S0717-95532017000100015

7. Corsi, D., Donelle, J., Sucha, E., Hawken, S., Hsu, H., El Chaâ, D., Bisnaire, L., Fell, D., Wen, S. & Walker, M. (2020). *Maternal cannabis use in pregnancy and child neurodevelopmental outcomes.* Nature Medicine 26; 1536–1540 https://doi.org/10.1038/s41591-020-1002-5

8. Díaz, M. (2023). *The postponement of maternity in Chile: between autonomy and precariousness.* Universum 38 (2). 2023 38(2):591-616. https://www.scielo.cl/scielo.php?pid=S0718-23762023000200591&script=sci_arttext

9. Diaz, L. y Alonso, N. (2023). *Mechanisms of action of phytocannabinoids on the human endocannabinoid system.* Adicciones. 34 (19) https://cedro.sld.cu/index.php/adicciones/2023/paper/view/34/19

10. Fernández, E. & Núñez, L. (2022). Endocannabinoid-mediated synaptic plasticity and substance use disorders. Neurology. *37*(6); 459–465. https://doi.org/10.1016/j.nrl.2018.12.004

Revista ARACÊ
ISSN: 2358-2472

11. Föster, J. and López, I. (2022). *Human neurodevelopment: a continuous exchange process of an open and context-sensitive system*. Las Condes Clinical Journal. 33(4); 338-346 https://doi.org/10.1016/j.rmclc.2022.06.001

12. Ge, Z., Schatten, H., Zhang, Zhang, C. & Qing-Yuan, S. (2015). *Oocyte ageing and epigenetics.* Society for Reproduction and Fertillity 149(3); 103–114. https://doi.org/10.1530/REP-14-0242

13. Guadamuz, J., Miranda, M. y Mora, N. (2022). *Update on brain neuroplasticity*. Sinergia Medical Journal. 7 (6); 829. https://doi.org/10.31434/rms.v7l6.829

14. Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2022). PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. *Campbell Systematic Reviews*, *18*(2), e1230. https://doi.org/https://doi.org/10.1002/cl2.1230

15. Hernández, S., Mulas, F. and Mattos, L. (2004). *Functional neuronal plasticity.* Journal of Neurology, 38(1); Nos. 58-68. https://www.neurologia.com/38/Suplemento%201/10.33588/rn.38S1.2004073

16. López, S., Córdoba D., & Albert, J. (2010). *Potenciación a largo plazo en la corteza humana.* Journal of Neurology*, 51(6), 367-74. https://dialnet.unirioja.es/servlet/articulo?codigo=4500910*

17. Sachs, M., Onodera, C., Blaschke, K., Ebata, K., Song, J. & Ramalho, M. (2013). *Bivalent chromatin marks developmental regulatory genes in the mouse embryonic germline in vivo. Cell reports*, *3*(6); 1777–1784. https://doi.org/10.1016/j.celrep.2013.04.032

18. Scheyer, A., Borsoi, M., Pelissier, A. & Manzoni, O. (2020). *Perinatal THC exposure via lactation induces lasting alterations to social behavior and prefrontal cortex function in rats at adulthood.* Neuropsychopharmacology. 45(11); 1826-1833. https:// doi.org/10.1038/s41386-020-0716-x

19. Schrott, R., Rajavel, M., Acharya, K., Huang, Z., Acharya, Ch., Hawkwy, A., Pippen, E., Lyerly, H., Levin, E. & Murphy, S. (2020). *Sperm DNA methylation altered by THC and nicotine: Vulnerability of neurodevelopmental genes with bivalent chromatin. Sci. Rep. 10(1); 16022. https://doi.org/* 10.1038/S41598-020-72783-0

20. National Service for the Prevention and Rehabilitation of Drug and Alcohol Consumption (SENDA). (2023). Chilean Drug Observatory*. Main results of the 15th Estudio de Drogas en Población General*.. https://www.senda.gob.cl/senda-presenta-principales-resultados-del-15-estudio-de-drogas-en-poblacion-general/

21. Shorey, L., Roberts, V., D'Mello, R., Sullivan, E., Murphy, S., Mccarty, O., Schust, D., Hedges, J., Mitchell, A., D'Terrobias, J., Easley, Ch., Spindel, E. & Lo, J. (2023*). Prenatal delta-9-tetrahydrocannabinol exposure is associated with changes in rhesus macaque DNA methylation enriched for autism genes. Clin. Epigenetics. 15(1); 104*

Revista ARACÊ
ISSN: 2358-2472

https://doi.org/10.1186/s13148-023-01519-4

22. Tortoriello, G., Morris, C., Alpar, A., Fuzik, J., Shirran, S., Calvigioni, D., Keimpema, E., Botting, C., Reinecke, K., Herdegen, T., Courtney, M., Hurd, Y. & Harkany, T. (2014). *Miswiring the brain: Δ9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway.* The Embo Journal 33(7);668-685. https://doi.org/10.1002/embj.201386035.

23. Verdejo, A. (2011). *Neuropsychological effects of cannabis use. Addictive Disorders.*13 (3); 97-101

24. World Health Organization. *Cannabis*. Retrieved on May 24, 2024, https://www.who.int/teams/mental-health-and-substance-use/alcohol-drugs-and-addictive-behaviours/drugs-psychoactive/cannabis.