

Explaining Contemporary Patterns of Cannabis Teratology

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Abstract

Cannabis has been shown to be teratogenic in cells, animals and humans. Particular targets of prenatal exposure include brain, heart and blood vessels and chromosomal segregation. Three longitudinal clinical studies report concerning cortical dysfunction persisting into adolescence and beyond, which are pertinent to the autism epidemic. Increased rates of congenital heart defects, gastroschisis, anencephaly and others have been reported. The pattern of neuroteratology seen after cannabis exposure strongly suggests a spectrum of dysfunction from mild to moderate to very severe. Downs syndrome, atrial septal defect (secundum type), ventricular septal defect and anotia / microtia were noted to be more common in prenatally cannabis exposed children in a large US epidemiological study which would appear to have been confirmed by recent experience in Colorado and other USA states. Studies in cells, together with the above mentioned epidemiology, implicate cannabidiol, cannabichromene, cannabidivarin and other cannabinoids in significant genotoxicity and / or epigenotoxicity. Notch signalling has recently been shown to be altered by cannabinoids, which is highly pertinent to morphogenesis of the neuraxis and cardiovascular, and also to congenital and inheritable cancer induction. It is felt that subtle neurobehavioural psychosocial and educational deficits will likely be the most common expression of cannabinoid teratology at the population level. The far reaching implications of this wide spectrum of neuroteratological, pediatric cardiological and other defects and deficits should be carefully considered in increasingly liberal paradigms. Hence it is shown that the disparate presentations of cannabis teratology relate directly and closely to the distribution of CB1R's across the developing embryo and account for the polymorphous clinical presentations.

Keywords Cannabis; Gastroschisis; Pediatric Epidemiology; Congenital Heart Disease; Notch Signalling; Neurobehavioral Teratology

Introduction

At a time when up to 24% of Californian teenage mothers test positive for cannabis, it is of concern that the complex literature relating to the teratology of cannabis seems to have created mixed messages in both professional and popular fora, leading the teratogenic effects of cannabis to be overlooked and the impact of increasing cannabis consumption to be underestimated. It is therefore important to reiterate that a number of independent and well-designed studies have similarly indicated major teratogenic effects associated with both maternal and paternal cannabis use.

In reviewing the teratology of prenatal cannabis exposure (PCE) this paper will concisely consider neurobehavioural effects, cardiovascular effects including gastroschisis (which is thought to have a vascular aetiopathology), immune effects, chromosomal effects, genetic and epigenetic effects, mitochondrial effects, the effects of the various different exogenous cannabinoids, and notch signalling.

Neurobehavioural Teratology

Indeed, despite the existence of a conflicting literature on the teratogenic effects of cannabis, there is also a growing body of studies which indicate major teratogenic effects associated with prenatal cannabis exposure. Furthermore, since there is not always an established neurodevelopmental phenotype related to PCE, the

absence of an overt teratogenic effect does not exclude the existence of covert effects or vulnerabilities which become manifest during the postnatal development when individuals are in contact with various stressors. This can be explained by a vulnerability/stress model or again a double hit hypothesis [1-6]. Therefore, it becomes urgent to remind the profession of the latest findings suggesting major teratogenic effects in relation to PCE, especially in the context of a recent increase of cannabis consumption in many western countries. It therefore becomes important to note that the published literature shows a high degree of concordance that a variety of neurological effects are seen with increased frequency after prenatal cannabis exposure including: impairment of foetal development, elevated rates of prematurity, earlier births, smaller heads which have been shown to persist life long, and which necessarily includes smaller brain [7].

Such a pattern fits with the moderate to high concentration of cannabinoid type 1 receptors (CB1R) which has been shown to exist in the foetal brain from early in development including in the cerebral, cerebellar, orbitofrontal and hippocampal cortices, parts of the midbrain and the limbic system. The CB1R is the major cannabinoid receptor found throughout the body. Indeed two papers have issued from the Centres for Disease Control (CDC) births defects monitoring program the National Births Defects Prevention Network (NBDPN) which document rates of anencephaly elevated respectively to 1.7 (95% C.I. 0.9-3.4) and 1.9 (1.1-3.2) times above background [8].

The effects of PCE have been studied longitudinally in three major cohort studies from Canada (Ottawa), USA (Pittsburgh) and The Netherlands and there is again a remarkable level of concordance between the three showing impaired brain growth and development,

impaired intellectual acuity and academic ability, reduced attention span, and lower scores on a broad spectrum of school tests [1]. Many of these changes persisted and were detectable right throughout the schooling career through primary and secondary school and into their early twenties [7]. These findings of impaired executive and cognitive functioning are supported by other studies which have shown structural and functional damage including decreased frontal cortical thickness and a higher rate of disconnection of major white matter tracts of over 84% in key junctional nodal areas of the cerebral cortex (splenium to precuneus and in the fimbria of the fornix). Microcephaly has also been demonstrated in PCE neonates [9].

In this connection it is noteworthy that the largely supratentorial distribution of CB1R's in the foetal brain closely parallels the observed pattern of functional disability after PCE, which is largely restricted to the supratentorial brain. The pathology of anencephaly illustrates this feature particularly clearly wherein the brain stem is usually spared, and simultaneously has the lowest concentration of CB1R's whereas the other parts of the brain which are richer in CB1R's become effectively "chemically amputated".

Indeed further thought shows that the above mentioned neuroteratological manifestations of PCE including impaired cortical and destabilized affective function and an increased rate of drug dependency – which is mediated by the limbic system – also appear to closely follow the distribution of CB1R's across these structures. Indeed a clear sequence is documented by the extant literature from subtle forms of affective and intellectual impairment at one end to more severe impacts such as smaller heads, microcephaly and anencephaly at the other end of the spectrum. This spectrum of disorders can be further extended to include neurologically induced foetal loss both before and after birth including spontaneous and induced terminations of pregnancy.

Several exogenous agents are known to cause anencephaly including the anticonvulsant valproate, various serotonin uptake receptor antagonists and folic acid deficiency in addition to genetic disorders including ciliopathies and a prior history of an anencephalic pregnancy [10-17]. That cannabis can act to effectively amputate the forebrain strongly suggests a spectrum of neuroteratological cannabis related manifestations. In such a conceptual paradigm both the fact and the severity of cannabis neuroteratology is underscored by the inclusion of anencephaly within the cannabis-related neonatal-perinatal-pediatric disease spectrum. This important neuroteratological spectrum carries a major public health message which is not widely appreciated.

Implications of High Density Mitochondrial CB1R's

Importantly high density CB1R's together with their complete transduction machinery including intracellular cascades have been identified on mitochondria of many organs including the brain. Various major brain functions including memory, thinking, wakefulness and attention have been shown to be dependent on these mitochondrial activities [18]. Inhibition of the CB1R's on these brain mitochondria has been shown to be causally linked with a stimulation of the aging processes of the brain by impairing the metabolic crosstalk between mitochondria and nuclei, stimulation of the mitochondrial stress response, and impairment of mitochondrial and nuclear DNA repair [18,19]. Since these processes can also be expected to act in

utero the direct and profound implication is that molecular, neuronal and genetic aging is induced at the foetal stage, even prior to birth. Such a suggestion would be formally testable by investigating molecular and epigenetic biomarkers of aging from foetal and placental tissues.

Cardiovascular Pathologies

Cannabis use in adults has also been shown to be linked with significantly elevated rates of stroke, cardiac arrest, testicular cancer, chronic lung disease and hepatic fibrosis and cirrhosis [20-24]. Parts of the membranous interventricular septum and both the atrioventricular valves are derived from the endocardial cushions which are known to express high levels of CB1R's from as early as 9 weeks of gestation [25]. Perivascular CB1R also plays a key role in regulating the neurovascular coupling of the neural stem cell niche and is directly responsible for the elevated Blood Oxygen Level Dependent (BOLD) signal shown on MRI with increased local brain metabolism and neural activity. In 2007 American Academy of Paediatrics and the American Heart Association in a major position statement linked PCE to a doubled incidence of the two congenital heart defects ventricular septal defect (VSD) and Ebsteins anomaly and noted that the relationship was likely causal [26].

Increasing cannabis use in Colorado is the most obvious explanatory cause for the increased rates of Colorado: VSD by 35%, atrial septal defects by 262% and all major congenital defects by 70% from 2000-2013 (Figure 1) data cited April 2018, Colorado Respond to Children with Special Needs (CRCSN) program. Over this period drug use data from the National Survey of Drug Use and Health indicates that the use of other drugs in Colorado was falling and/or at very low levels likely too low to impact the population prevalence of these issues. It is noted en passant that the CRCSN Program have recently revised the totality of their birth defect data 2000-2013 in October 2018, for reasons which remain unclear at the time of writing. Data on selected defects including both the earlier data release and data subsequent to October 2018 is included in (Figures 2). From this Figure one notes a rise in several congenital anomalies in Colorado, all of which have been previously shown to be linked with PCE [9,26].

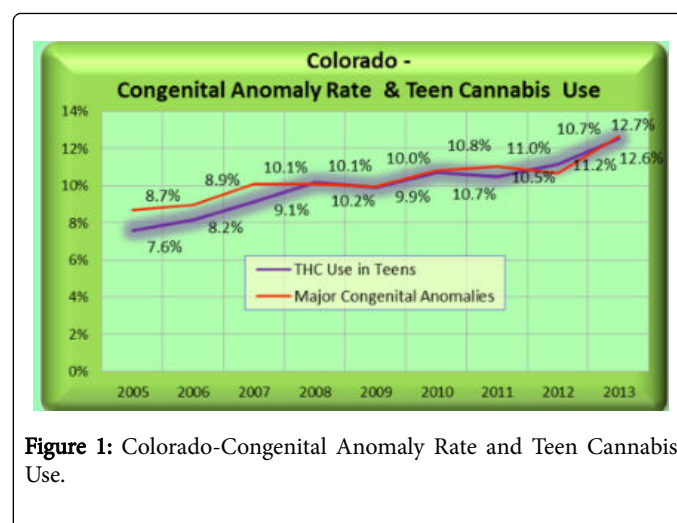


Figure 1: Colorado-Congenital Anomaly Rate and Teen Cannabis Use.

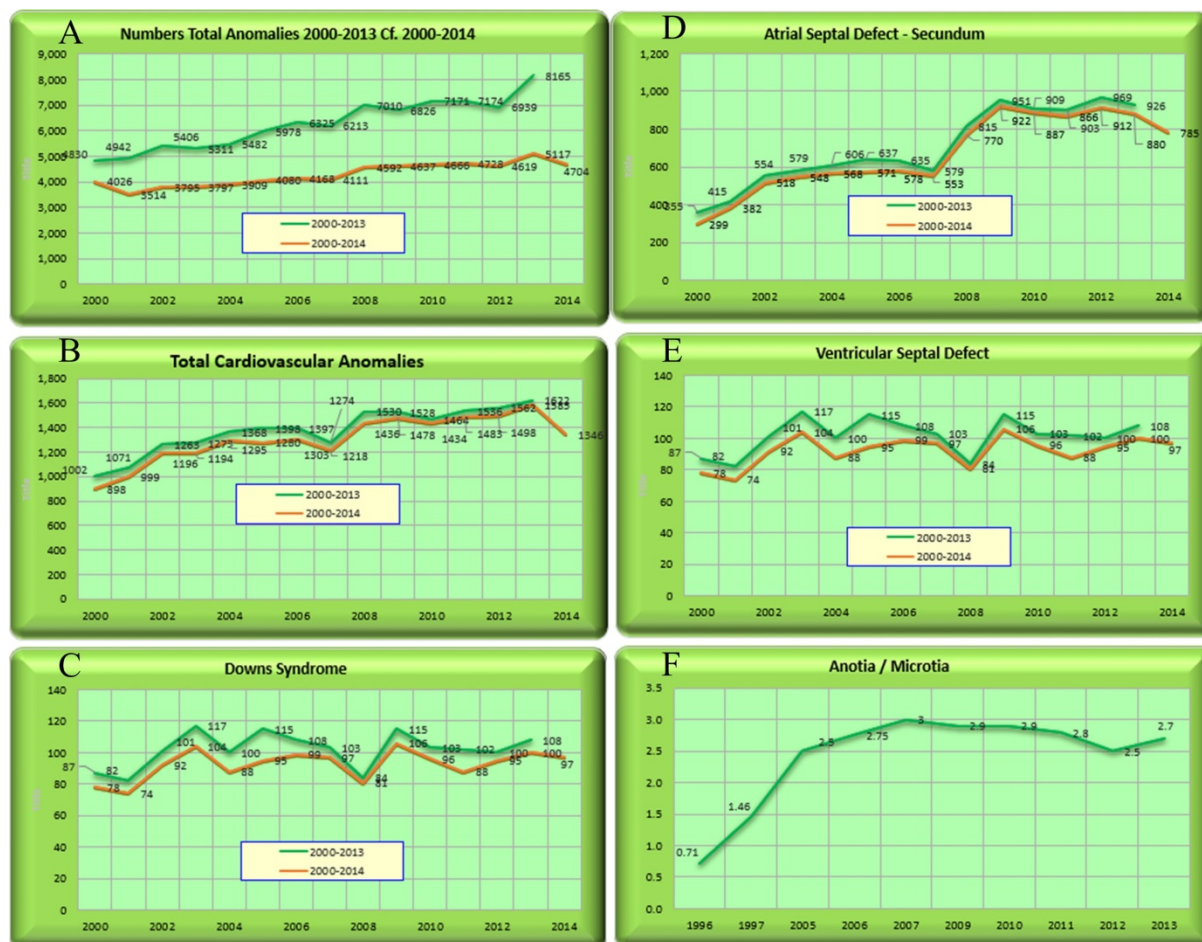


Figure 2: Congenital Anomaly Rates in Colorado.

Since cardiovascular structures are formed early in gestation they are particularly vulnerable to CBR-mediated effects. Early in pregnancy some women may not be aware that they are pregnant. Cannabinoids are lipid soluble and are known to have a very protracted half-life in fat stores, so that even immediate cessation in a regular cannabis consumer would not protect her foetus from exposure due to the residual effects of on board cannabinoids leaching out of her endogenous stores. Various studies also implicate paternal cannabis exposure in foetal teratogenesis. For some defects, for example for transposition of the great arteries, paternal exposure has shown to be more important than maternal exposure [27].

The rate of gastroschisis is known to have risen in areas where cannabis use has increased, such as Northern Canada, Mexico, Northern New South Wales in Australia, and North Carolina and Washington state in USA, and likely also reflects vasoactive cannabinoid exposure. CBRs are known to exist in high density on foetal arterial and venous vessels. Cannabinoids acting via CBRs have also been linked with both vasospasm and arteritis [25]. Concordant with this view one notes that seven studies uniformly document an increased incidence of gastroschisis after PCE and another two studies show increased severity of the deformity. Careful multivariate analyses from Canada have shown a three-fold elevation of gastroschisis risk after prenatal cannabis exposure. These findings also suggest that the

vasoactive properties of cannabis have not been widely appreciated as a potential cause of subsequent teratological malformations.

Immune Dysfunction

It is well established that cannabinoids play a large role as immunomodulators with CBRs most often up-regulating, and CB2Rs down-regulating immune responses [28-34]. Endocannabinoid receptors are widely distributed on all cell types of the immune system including endothelial cells and the microglia which are the macrophages of the brain. This is important as microglia play a direct role in synaptic pruning and the disposal of unwanted dendrites and sculpt the neural network for increased focus, attention and concentration. Deficits of such function have been linked with impaired memory, brain development and the onset of numerous major mental disorders including autism and schizophrenia [33]. PCE has been shown to result in activation of the microglia of the brain [33]. Moreover the demonstration that PCE can lead to alteration of the methylation state of DNA on immune cells has long lasting implications not only for immune development, but also for brain development and maturation, and has been linked with the subsequent development of opioid addiction in a rodent model [35].

Chromosomal Mis-segregation Disorders from Damage to the Mitotic Spindle

Δ^9 -Tetrahydrocannabinol has also been shown to interfere with the key elements of cytoskeletal framework including actin and tubulin polymerization [36]. Tubulin polymers form the microtubule "rails" of the mitotic spindle along which the chromosomes slide during cell division, and chromosomal mis-segregation is a major cause of serious genetic damage and anomalies of chromosomal ploidy. Hence it becomes important that Down's syndrome, which is one of the chromosomal mis-segregation disorders, has been previously linked with PCE by prior studies [9], and was recently found to be increased 35% in Colorado from 74 cases in 2001 to 100 in 2013 (October 2018 data release). Official Canadian Government reports demonstrate a clear association across Canadian provinces between cannabis use on the one hand [37] and elevated rates of total congenital defects, gastroschisis, orofacial clefts and cardiovascular defects on the other [38]. Similar data has also been published for eastern Australia [39].

Other Cannabinoids

Cannabidiol is the second most commonly occurring natural cannabinoid. Hence it would appear to be deeply implicated also in the above impressive series of epidemiological studies. One notes that cannabidiol at high concentration has also been shown by several investigators to bind CB1Rs [40-42], which further implicates cannabidiol in the above pathophysiological cascades. Cannabidiol has also been shown to have important interactions with PPAR γ (Peroxisome Proliferator Activated Receptor) which is a major nuclear receptor impacting metabolic, immune and adipose function on immune, adipose and hepatic cells in particular [43-46]. Cannabidiol, cannabinol, cannabivarin and cannabichromene have also been implicated in major genetic and epigenetic damage to cells in vitro [35,47-54].

Notch Signalling

It was also recently shown that endocannabinoids interact with the notch signalling system in many tissues [55-58], and indeed that reciprocal signalling occurs [59], opening the way for feed-forward information loops and relays. This is a profoundly important finding and highly relevant to foetal morphogenesis, as it is well established that notch is a major morphogen controlling body formation and involved in the cellular specification particularly of the brain and cardiovascular [60].

Notch is also an important signaling molecule involved in cancer induction. This is likely of particular relevance to the demonstrated links between PCE and the four pediatric cancers: acute lymphatic leukaemia, acute myelomonocytic leukaemia, neuroblastoma and rhabdomyosarcoma [36,61-66].

These considerations demonstrate that a careful consideration of the distribution of the major cannabinoid endoreceptor CB1R clearly explains much of the cardiovascular, neuropsychiatric and behavioural teratology which has been described in the extant literature as it relates to prenatal cannabinoid exposure from both paternal and maternal sources.

Higher concentration cannabis and systematic under-reporting in exclusively self-report studies consistently underestimate future trends [8]. Increased PCE consequent upon the intersection of elevated cannabis use prevalence, rising cannabis concentration and the

frequently asymptomatic cannabis genotoxicity dose-response relationships will result in predictable increases in brain and organ damage from which the child's recovery is likely permanently compromised.

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