***Cannabis – better 'con' than 'pro'***
***Part 2: Cannabis and the central nervous system***

***Biological evidence proves that cannabis by no means is a 'safe drug.' All efforts should be made to avoid harm to children, adolescents, pregnant women, and their children.***

The 'gateway hypothesis' seems not only valid for cannabis. The 'zeitgeist' that made cannabis an accepted drug in many countries is now focusing on psychedelic drugs such as ecstasy. A feature in a November (2023) issue of Nature expects that 'with the regulatory landscape shifting,' legal research in psychedelic substances is becoming easier for neuroscientists, psychiatrists, pharmacologists, and biochemists. Prof. Dr. David Olson from the University of California thinks that 'from the clinical perspective, understanding how the drug works might not matter. You don't need to know the mechanism of the drug to have a very effective therapy' (1, 2).

The Public Health viewpoint might be completely different! Similar to the first wave of endorsement of cannabis, California was at the forefront; again, a state in the USA (Oregon) is the forerunner, allowing the use of psilocybin, approved by the FDA, for the treatment of post-traumatic stress disorders (3). Hopefully, but probably in vain, the initiative remains on the level of therapeutic approaches for psychiatric diseases and doesn't become a controversial public health issue like marihuana. Let alone psychedelic drugs, even the use of cannabis, a generally thought 'safe drug,' results in alarming consequences for the central nervous system, as the newest research results show.

<u>Adolescents and the fetus</u>

The most vulnerable group to damaging side effects are adolescents and the developing brain of the fetus (4). In the USA, it was found that smoking the drug was more common than resorting to tobacco, which was especially the case for adolescent males. Exposure to smoking and eating, let alone taking concentrated Δ9-tetrahydrocannabinol (THC), affects certain regions of the brain. Even after cannabis users stopped the habit for 28 days, functional magnetic resonance imaging showed higher brain activity compared with non-users (5). Adolescent users risk developing psychic alterations in later life, such as being easily afraid, being depressed, and showing deficits in one or the other intellectual ability and addiction (6).

Most neurodevelopmental processes of the brain during gestation are initiated but not completed. The culmination process of the different stages during the development of the encephalon for most parents is a most challenging time with their teenage offspring ('I hate you, mother,' as a response to the effort to talk some sense into the teenage daughter as far as the dress selection for an evening out is concerned). Cannabis can harm the developing brain and cause the risks of mental health problems in later life (7, 8).

Behavioral dysfunctions similar to what is observed in humans go along with THC-caused changes in the brains of laboratory rats (9). Chronic cannabis use gives rise to risky decision-making (strategy favoring exploration instead of long-term gains), elevated "reward learning'

(seeking pleasure and avoiding pain), and cognitive impairment leading to confusion and memory loss.‘ THC affects the cortex for cognition (10), the cerebellum for motor coordination (11), the hippocampus for memory (12), and the amygdala (13) for emotional regulation (4). What could be detected in the brain of laboratory animals was also found in the brain of human fetuses, which displayed an ‘abnormal amygdala dopamine D2 gene.‘ The investigation was made possible with human fetal specimens during the 18$^{th}$ to the 22$^{nd}$ week (14).

The observed reactions to Δ9-THC in the brain intensify with the increasing potency of the compound of the drug (9, 15). In effect, this means in the course of legislation and decriminalization, the potency of the compounds used by youngsters also increases significantly (16, 17), and the risk for cannabis use disorder will rise likewise (18, 19).

The normal functions of the brain

To convincingly demonstrate the harm cannabis is causing, it is necessary to understand how the brain is working. That requires a basic knowledge of recent developments in genetics. Not only are monogenetic diseases important, but likewise, part of omics previously thought to be biological ‘junk’ are key points in gene regulation. Genetic variants affect diseases and have significant roles in gene function (20, 21). The brain functions because of ‘neural connections, linked by complex circuits for working together’ (22).

<u>The effect of THC</u>

The most surveyed component influencing the effect of cannabis on the psyche of humans and laboratory animals is Δ9-tetrahydrocannabinol (THC). THC mainly influences the neural network, which is called the G protein-coupled receptor (GPCR) family with the cannabinoid receptor 1 (CB1R) and 2 (CB2R) (23). The entire endogenous cannabinoid system (eCB) and CB1R and CB2R are involved in the neurotransmission (24, 25). The detailed exploration into the depth of brain function leaves no dough about dangerous effects, not only on adolescents in later life but on the developing brain of the child during pregnancy and breastfeeding, while the mother is on cannabis (26).

<u>Pregnancy outcome, the fetus, and cannabis</u>

Pregnant women take cannabis, among other reasons, against stress, fear, and ‘morning sickness’ and don’t realize that together with the breastmilk, the baby is taking in THC as well. In a cohort study in Canada, a country that is one of the hotspots in cannabis use, the prevalence of its use was about 2% (27). In the USA, cannabis use among pregnancies varies between 3 to 16% (28, 29).

The drug use increased the risk for preterm birth (OR 1.37), either spontaneous (OR 1.80) or medically induced (OR 1.94), low birth weight (OR 1.90), small-for-gestational-age (OR 1.21), large for gestational age (OR 1.06), congenital anomaly (OR 1.71) cesarean section (OR 1.13) and gestational diabetes (OR 1,32) (all 95% CI was statistically significant) (27). The Canadian study only confirmed what had already been found years before, in that fetal growth restriction, low birth weight, and preterm could be the consequence of maternal cannabis use (mCB) (30-

32). Additional stress factors in the environment could increase the harmful influence of cannabis on gestational development. An investigation making use of an Atlantic hurricane called Superstorm Sandy, which devasted the Caribbean islands up to New York in 2012, assessed the long-term consequences of multiple stress factors during pregnancy and the implications for the children.

Those mothers who lived through the superstorm and were under cannabis had a 31-fold increased risk for ‘disruptive behavioral disorders (DBDs) compared with children from those mothers who were not affected by the storm. It means that multi-early life ‘adverse exposers,’ here Superstorm Sandy as well cannabis use by the mothers, synergistically added to the risk for mental health problems of the children (33).

THC and the placenta

THC in pregnant women's blood freely enters the placenta barriers (34). Recently, the effects of maternal drug use on newborns and babies were investigated in more detail by conducting a longitudinal study from a total cohort of 322 mothers with their neonates (35). Besides demographics, the physical functions of growth, development, energy metabolism, and homeostasis were measured by steroid hormone analysis from hair samples (36), the neurobehavioral profile in early childhood (37), the parasympathetic nervous system through heart rate variability, the mCB use and placental transcriptome by RNA sequencing (20). Variables assessed of 71 mCB users with their children were compared with 251 non-cannabis-taking mothers and their young children by statistical means.

Mothers and their spouses in the mCB group were slightly younger than the controls. More mCBs were single mothers who smoked cigarettes and showed depression and anxiety. The largest group within the different races of the cohort belonged to African Americans, followed by Caucasians and Asians. Confounders were adjusted for, but there was no difference between races as far as mBC versus non-CB for perinatal health and pregnancy complications were concerned. Increased cortisol levels in mCB children revealed their systematic stress situation. The neurobehavior profile of mCB offspring showed increased anxiety, aggression, and hyperactivity. Clinical intervention for abnormal behavior was more often necessary for the mCB children. Also, the heart rate variability was more often abnormal for the mCB group of newborns, indicating a more stressed parasympathetic nervous system (35).

RNA sequencing (RNA-seq) was processed from placental biopsies at the mean gestational age of 39 weeks. Differential expression analysis (DEA) resulted in 480 genes, of which 359 decreased and 121 increased. The results obtained by the DEA technique compared those from mBC RNA-seq with the control specimens. Genes of particular interest were proinflammatory cytokines and chemokines reduced in mCB, such as IL1B (interleukin 1 beta) and CXCL8 (IL8 protein). The important CB receptor 1 (CNR1) was reduced with significantly increased mCB. All in all, immune-related gene expression was reduced for mCB. The network of the proinflammatory cytokines IL1B and CXCL8 was significantly related to hyperactivity levels. In summary, it was found that ‘mCB’ is associated with anxiety-related traits during early childhood in addition to altered stress hormone levels and psychophysiological activity’ (35).

Sex differences in cannabis use

Considering that statistics is a major tool of public health and that statistics is 'the science of age and sex breakdown,' a major concern should be the different influences of THC on females compared to males. The understanding seems to be that mainly adolescent males are affected. An example from North America shows that male priority might not necessarily be true. After legalizing cannabis in Connecticut, the proportion of female cannabis smokers increased abruptly. A company selling the drug experienced an increase of 55%, with 48% of new customers being female. Females, more than males, seem to resort to the drug to relieve pain, anxiety, depression, nausea, and spasticity (38). For animal experiences with THC, usually, sex differences are not mentioned, or male animals are selectively chosen (15, 39).

An extensive study of gene expression mainly investigated sex differences in mice exposed to cannabis and related the findings in rats to human cannabis use disorder (CUD) (40). Compared to others of its kind, the paper is not so difficult to understand, especially when referring to the figures. Specimens from THC-exposed rats were compared with those from controls using statistical means. Remarkable sex differences in THC exposure were observed. Cognitive behavior in rats relates to object recognition, memory, social interaction, and anxiety. THC-treated females, not males, were less interested in new objects, while social interaction was reduced in both sexes without significant differences.

Behavioral differences between males and females might not be alarming, but selecting six different brain regions and finding that the transcriptomes (total of mRNA expressed from the genes) are extensively different from one brain region to the other for both sexes meaning that the still largely unknown consequences of THC exposure and cannabis use disorder (CUD) to the brain differs between boys and girls significantly.

For females, three central brain regions are important in connection to cannabis use while examining differentially expressed genes (DEGs) compared with control regions. For males, just one is predominantly affected by cannabis. The outstanding brain structure involved for females is the amygdala (Ami), one in each cerebral hemisphere. The structure involves emotional responses, mainly acting as a 'threat-detector' and generating fear in general (13). Five hundred forty-nine DEGs accounted for Amy for females but only twenty-two to the nucleus accumbens (NAc) for males. The latter has an impact on depression and drug addiction (41).

However, most genes don't act alone but interact in signal transduction or metabolic pathways. Sets of co-expressed gens can be identified as complex modules to which different 'pathways terms' can be identified. The terms are metabolic pathways for enzymatic processes within a cell or tissue. In female rats, there are numerous pathways from different brain regions to cognitive disorders such as Alzheimer's disease. Other pathways hint at developmental or metabolic processes, such as lipid kinase activity regulation, phospholipid metabolic processes, and negative regulation of cartilage development. A particular module included some pathways related to the immunological system. The male NAc module was linked with pathways related to chemical synapses, calcium signaling pathway, integration of the energy metabolism, and oxytocin, a hormone related to trust, sexual arousal, and relationship building.

How does what is found in rats relate to humans?

Several methods are used in genetics to identify key driver genes in humans. The process is called a Mergeomics pipeline and visualizes a Bayesian network (42).

Following the 'Mergeonomic pipeline' method, cannabis-use -disorder (CUD)-associated modules are likely to be indirectly affected by THC. THC and CUD overlapping modules in males and females were specific for brain regions and sex. From NAc, four key drivers were identified. The key driver analysis revealed that in the respective models, the expression of the numerous genes followed either the sex of the males or females. The subnetworks of the key driver genes followed eight pathway terms, among them nicotine addiction, glycosphingolipid biosynthesis, nervous system development, and morphine addiction. The results are also similar to observations in humans in that marijuana use by females leads to structural abnormalities in Amy and NAc brain regions, resulting in psychiatric abnormalities in mood and anxiety as well as neurological disorders (43). Follow-up studies with humans must validate the role of key drivers, and hypotheses need to be confirmed.

Cannabis use alters the brain's DNA

Recently published results (December 2023) described the epigenetic effects of lifetime cannabis users. A meta-analysis was conducted from seven cohort studies from various countries, including sister and twin studies and parent-child pairs. Out of 9.436 participants, 4.190 were cannabis users, and 5.246 never used the drug.

When adjusting for smoking, there are five epigenetic sites in the DNA of those using cannabis. The epigenetic mark, i.e., the DNA methylation, is recognized in the CpG islands (where cytosine and guanine are separated only by one phosphate molecule) (44). The nearest genes to the CpGs identified are LINCO1132, ADGRF1, ADAM12, ACTN1, and APOBR (45).

The epigenetic effect could not always be assumed to be harmful. Those who use cannabis had lower methylated DNA compared to the controls for the following genes: LINCO1132 is an oncogene related to hepatocellular carcinoma (HCC), and blogging that gene is an attempt to fight ovarian cancer. ACTNT is related to three rare genetic diseases: osteoporosis, lupus erythematous, and worsened COVID-19 infection. APOBR binds to triglyceride-rich lipoproteins, obesity, bladder cancer, pneumonia, and allergy.

Assuming that cannabis use has a beneficial effect on various serious diseases might be pretty short sides. Other genes are positively associated with cannabis use: Overexpression of ADGRF1 relates to breast cancer. ADM12 upregulates various tumor cells and could be used as a biomarker for cancer. Additionally, it is associated with multiple sclerosis and Alzheimer's disease. (Numerous references for the function of the genes mentioned are given in the publication indicated above and are not repeated here (45)).

Additional research is necessary to find out whether the data about gene expression has a causal link towards risks or benefits of lifetime cannabis users compared to those who never used the drug. For instance, 'cigarette smoking is a strong confounder for cannabis use.' In adjusting for

smoking, the CpG for cannabis use decreased strongly. Besides smoking, other confounders are LDL, educational performance, and alcohol use.

Is there a drug against addiction in the future?

A shimmer of hope to have medicaments against addiction in the future ironically is due to the chemical structure of THC and CBD, which are almost identical and bind to the same receptor. Both compounds are considered safe and widely used in several countries by the food and health industry (46). An opposing yin/yang effect is accounted for Δ9-THC and CBD. While the first compound increases reward and drug seeking, anxiety, and 'sensitivity to other drugs of abuse, CBD decreases it (47).

CBD interacts with CB1 receptors from the eCB system, yet the mechanism of action is not fully understood. So far, attempts are still underway to test CBG in preclinical studies for `treatment against schizophrenia, depression, anxiety, inflammation, and cancer. Of primary interest is the effect of CBD against addiction to opioids, psychostimulants, cannabis, and nicotine (48).

For instance, in an animal study testing CBD administration, repeated heroin seeking was inhibited (49). From a case report, it was shown that a 19-year-old female, after treatment for ten days with CBD, showed withdrawal symptoms from cannabis addiction, and the treatment was also promising to inhibit the relapse phase (50). Healthy individuals tolerated intravenous fentanyl administration without respiratory depression and cardiovascular complications in a double-blind, placebo-controlled phase 1 study (51). Despite this short, promising outline, significant additional research is needed before CBD can be claimed to be a drug against addiction.

Conclusion

What is the relevance of everything described about cannabis so far for Thailand? The decision to increase the accessibility of cannabis most probably was not a wise one. Given the overall drug problem, one might think about The Sorcerer's Apprentice (52).

From 19 districts in 10 provinces, 90% of cannabis users started to do so after the 'legal amendment process' in 2018 (53). An investigation reported that most users obtained cannabis from illicit suppliers during the first year 'after the regulatory transition' (54). An investigation conducted in the northeast of Thailand discovered that over 75% out of 1.273 individuals questioned 'has the intention to use medical cannabis.' While the health literacy of the participants was assessed as being sufficient to excellent, they had a low and average level of 'knowledge concerning medical cannabis use' (55). A 'positive expectation from the outcome and need' for medical cannabis for cancer patients, in particular, for breast cancer patients treated in the North of Thailand, was observed (56, 57).

To take the lid off cannabis use by opening its consumption for 'recreational' purposes probably cannot be reversed. Whatever revision in the attempt to revise the preceding legislation for cannabis will succeed in passing parliament will not bring back the former hesitancy to use the drug. To limit the harm caused, public health has to resort to influencing parents and caretakers

to persuade adolescents to refrain from taking cannabis and other drugs as well. Exceptional attention should be given to mothers and child health care to prevent the harmful effects of cannabis on the brain of the fetus.

Finally, a word to the wise. Before you fly to Singapore, carefully check your bags and belongings to make sure that you don't carry any cannabis products with you. Missing to do so might be life-threatening.

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