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EFFECT OF N-ACETYL-PARA-AMINOPHENOL (PARACETAMOL) AND HEAVY CANNABIS USE ON EXERCISE PERFORMANCE, METABOLIC PARAMETERS AND NEURO-COGNITIVE FUNCTION IN HUMANS

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ABSTRACT
The notion that N-acetyl-para-aminophenol may be a key player in the neurocognitive arena and enhances the actions of cannabinoids is very recent and still evolving. Paracetamol exhibits this effect through its metabolite, N-arachidonylphenolamine, an endogenous cannabinoid which blocks fatty acid amide hydrolase-(FAAH)-like anandamide transporter (FLAT) in the brain to inhibit anandamide uptake. A down-stream effect is that it may also target the cysteine proteases for algogenic cytokines. CB1 cannabinoid receptors are well represented in the dorsal striatum, a region of the brain that regulates memory, attention and executive functioning. Many workers have reported that there is increased inflammatory response during exercise, the inflammatory response of exercise (IRE), which may be responsive to the combined effects of paracetamol and cannabinoids. Both paracetamol and cannabinoids are involved in analgesia and dampening inflammation. Present study examined the effect of paracetamol and heavy cannabis use on neurocognitive function, pain, metabolic parameters and exercise performance in 20 volunteers compared to controls. The mini-mental status examination (MMSE), walking distance or time of onset of fatigue, BMI, cholesterol and fasting blood sugar of the test volunteers were compared to the controls. Chronic heavy cannabis use (more significantly) and paracetamol decreased sugar and cholesterol levels. The lowest MMSE score was in the test group on heavy cannabis ($P < 0.05$). This group also had the most significant increase in walking distance. The group on cannabis + paracetamol had less errors at work compared to the group on cannabis alone. This may be due to the previously documented reports that paracetamol may rescue the distorted upregulation of 5-HT2A serotonin receptor signalling by cannabinoid CBI receptor signalling responsible for neuropsychiatric disorders. Present evidence indicates that the nootropic, paracetamol, increases neurocognitive functioning and has salutary effect on glucose homeostasis.

KEYWORDS: Cannabis, Paracetamol, Time-to-Fatigue, Neuro-Cognitive.

INTRODUCTION
Cannabinoid CB1,CB2 receptor agonists and CB1/CB2 receptor dual agonists activate AMPK[1][2][3] though CB2 agonists appear more specific.[4] Thus CB2 receptor signalling more specifically enhance AMPK-Akt-eNOS-SIRT-PGC1-alpha-ER alpha- peroxisome proliferator-activated-receptor-alpha (PPAR-alpha) signalling to increase lipid oxidation and mitochondrial biogenesis.[5][6][7] This enhancement of mitochondrial function has a redox control of MMPs and the inflammatory state.[8][9] High fat diet promotes mitochondrial dysfunction[10] and enhances CB1 receptor signalling which may increase lipogenesis.[11] In contrast to calorie restriction, high fat diet decreases CB2 receptor signalling and PPAR-alpha gene transcription.[6] Cannabinoids such as 2-oleoyl-glycerol acting via GPCR-119 increase GLP-1 to promote pancreatic beta-cell neogenesis.[12]

Both CB1 and CB2 receptor activation may be important for neuroprotection.[13] However, workers have recently reported that chronic cannabis use, especially before the age of 15, is associated with impairments in highly integrated cognitive functions such as memory, attention and executive functioning[14] [15] and lead to more non-perseverative[16] and perseverative errors[17] in the Wisconsin Card Sorting Test (WCST) and A-not B task. There is also evidence for striatal hyperactivity in adolescent cannabis-using boys.[18] This overly sensitive motivational brain circuitry in cannabis users causes imbalance between reward and inhibitory control. Chronic CB1 (HU-210) administration has been shown to downregulate 5-HTIA and upregulate 5-HT2A, similar to what is observed in depression[19] and neuropsychiatric disorders. Cannabinoid CB1 and CB2 have opposing roles in long-term potentiation (LTP), with CB1 agonists decreasing LTP and CB2 agonists increasing LTP.[20][21]

Depression and pain share the same biological pathways and neurotransmitters (depression and pain co-morbidity).[22][23] There is deficit in striatal dopamine release in cannabis dependence which also leads to deficits in working memory, impulse control and attention.[24] D2 dopamine receptors and BDNF are involved in the actions of endocannabinoids (eCB).[25][26] While BDNF in dopamine neurons regulates eCB responses, D2 dopamine receptor activation facilitates endocannabinoid-mediated long-term synaptic depression of GABAergic synaptic transmission in midbrain dopamine neurons via cAMP-PKA signalling.

In mammals, stress elicits a stereotyped endocrine response that requires an increase in the activity of hypothalamic parvocellular neuroendocrine neurons. The output of these cells is normally constrained by powerful GABA-mediated synaptic inhibition. Acute restraint stress in rats releases this system from inhibitory synaptic control drive in-vivo by downreguating the transmembrane anion transporter KCC2, rendering GABA inputs largely ineffective.[27] Also, synaptic inhibition of GABA by CB1 signaling is reduced after stress. This effect is rescued by psychostimulants with rewarding properties. Social defeat stress paradigm is able to induce anxiety-like behaviour by causing a dramatic re-arrangement of CB1 receptor-mediated control of GABA transcription in the dorsal striatum, a region of the neuraxis involved in complex neurocognitive functions.[28] Also, this impairment of endocannabinoid signalling is associated with inability to adapt to chronic stress and in progressive development of maladaptive behaviours.[29][30][31] For example, chronic caffeine sensitises GABAergic synapses to the presynaptic effect of CB1 stimulation and attenuates the downregulation of CB1 receptor-mediated responses after social defeat stress.[28]

The mechanism of action of the common pain-killer, paracetamol (or acetaminophen or N-acetyl-para-aminophemol), has recently become clearer. Paracetamol, which does not active AMPK,[32] inhibits COX-I, COX-2 and COX-3 by acting as a reducing co-substrate on the peroxidase site of PGHS and lessens availability of the ferrylprotoporphyrin IX radical cation. This results in inhibition of phenoxyl radical formation from a critical tyrosine residue essential for the cyclooxygenase activity of COX-I and COX-2 and prostaglandin synthesis especially at low levels of arachidonic acid and peroxides. Thus, although paracetamol does not inhibit severe inflammation; it is useful in lesser inflammation. The inhibition also of myeloperoxidase decreases formation of halogenating oxidants that may be associated with multiple inflammatory pathologies such as atherosclerosis and rheumatoid diseases. The central analgesic effect is also mediated by descending serotonergic 5-HT7 receptor pathways. Paracetamol also blocks spinal hyperalgesia induced by NMDA and substance P. The analgesic effect of paracetamol is reduced by inhibitors of serotonin, opioid and cannabinoid systems.[33][34][35][36][37][38] The analgesic effect is also reduced by the hydroperoxide-generating lipoxygenase enzymes (peroxide tone) and swamping of the peroxidase (POX) site of PGHS with a substrate such as PGGG2 (unstable) and this explains lack of peripheral analgesic, platelet and anti-inflammatory effect.[33] The metabolism of arachidonic follows multiple pathways that may involve the release of nociceptive mediators such as bradykinin, histamine, serotonin and cytokines.[39]

Paracetamol is an indirect activator of CB1 receptors.[40] It is deacetylated to the primary amine, para-aminophenol, which is conjugated with arachidonic acid to form N-arachidonylphenolamine, an endogenous cannabinoid. The enzyme involved is fatty acid amide hydrolase (FAAH) which is an agonist at TRPVI receptors and an inhibitor of anandamide uptake by blocking FAAH-like anandamide transporter (FLAT). CBI antagonist prevents the analgesic effect of paracetamol which are i) minimal COX-3 inhibition; ii) central COX-2 inhibition;[41] iii) CBI agonism; iv) Analgesic activity via N-acetyl-p-benzoquinoneimine (NAPQ), a metabolite of APAP) which exhibits spinal level analgesic activity at the transient receptor potential vanilloid-I (TRPVI) receptor[42] or at the transient receptor Ankyrin-I (TRPAI).[43] There is co-expression of TRPVI and TRPAI receptors on a subpopulation of nociceptive spinal sensory neurons. Activation of TRPAI by N-acetyl-para-benzoquinoneimine, an oxidative metabolite of APAP or by the tetrahydrocannabinol, delta-9 tetrahydrocannabiorcol (non-CB1 and non-CB2 cannabinoid) inhibits ion (sodium and calcium) currents in dorsal root ganglion (DRG) neurons.[43] iv) Sodium channel inhibition in DRG may activate eNOS.[44] v) Overall, the target of NAPQI may be the thiol group of cysteine proteases that take part in processing of cytokines such as IL-I, IL-6 and IL-I beta.[45] Already, cannabinoids have been found synergistic with acetaminophen in rats with neuropathic spinal cord injury.[46]

Paracetamol displays 5-HT agonism in the frontal cortex.[47] The potentiation of analgesic activity of paracetamol plus morphine involves the serotonergic system in rat brain.[48][49] Paracetamol enhances serotonergic and non-adrenergic neurotransmission in prefrontal cortex, hypothalamus and striatum and thus LTP;[50] and decreases neuronal inflammation.[51] This may underlie the nootropic effect of acetaminophen[52][53] and indirectly, the attenuation of other neuropsychiatric disorders such as migraine by serotonin 5-HT IF receptor agonists.[54] Upregulation of serotonin signalling enhances BDNF release which is beneficial in cardiometabolic and neuropsychiatric disorders.[55] Depletion of spinal 5-HT totally abolished the anti-nociceptive and anti-algogenic effects of paracetamol.[38] By decreasing CBI-receptor mediated inhibition of 5-HT(IA), paracetamol could attenuate the imbalance in serotonin 5-HT IA/ 5-HT-2A receptor signalling caused

by CBI receptor signalling and its attendant consequences. This explains paracetamol's differential enhancement of social behaviour in inbred mice.[47] Acetaminophen blunts evaluation sensitivity to both negative and positive stimuli, attenuates evaluative processing of errors and also reduces the pain of decision-making.[56] [57] The decrease of empathy and decrease of risky decision-making by participants under paracetamol may due to the blunting of affect and of evaluative processing for negative and positive consequences (ruminations).[58] It may also explain paracetamol's attenuation of social and physical pain; and its reduction of emotional dread (existential anxiety). Paracetamol's reduction of empathy for pain helps regulate prosocial and anti-social behaviour.[59]

Low serotonergic signalling, which is rescued by paracetamol, is implicated in increased empathy and appetite, disturbed social behaviour, lack of impulse control and the relative subjective value of the risky option.[60] [61] Serotonergic signalling is implicated in glucose homeostasis[62] and attenuation of Alzheimer;s disease biomarkers[63] and may explain reports of decreased glucose levels with paracetamol.[64] Increased arachidonic acid levels is also implicated in pain catastophising (increased sensitivity to ill-effects of pain) which mediates the relation between self-reported measures of strenuous exercise and pain pathways[65] and low glucose levels.[66] Inhibition of cyclooxygenase activity may lead to increased free arachidonic acid levels[67] and this free arachidonic acid may increase cAMP levels and inhibit adipocyte differentiation.[68]

There is inflammatory response to strenuous exercise in man, the inflammatory response of exercise. (IRE). In the acute phase, there is leucocytosis, leucocyte activation for which muscle or connective tissue damage and endotoxaemia are triggering factors. Tissue damage, cellular infiltration produce free radical activation of complement, coagulation factors and fibrinolytic activity. It is orchestrated by release of inflammatory mediators and arachidonic acid.[69] The anti-oxidant, paracetamol, inhibits TNF alpha, IL-I, macrophage inflammatory protein alpha and RANTES. It also increases the anti-apoptotic Bcl-2 to decrease neuronal inflammation.[51]

Over 90% of ingested paracetamol is metabolised by glucuronidation and sulphation to non-toxic metabolites. 5% is metabolised to NAPQI which is extremely hepatotoxic and this agent may account for the low therapeutic range of paracetamol. It may require drug monitoring to achieve therapeutic levels and minimise toxicity (Wikipedia.org). Generation of NAPQI is increased if reduced glutathione levels are low. Risk factors for acute toxicity of paracetamol include factors which cause NAPQI over-production or cause decrease in reduced glutathione (GSH) levels such as i) chronic alcoholism, ii) malnutrition, iii) concomitant administration of drugs that are inducers of liver microsomal enzyme CYP2EI, such as isoniazid and phenytoin. Causes of chronic toxicity of paracetamol include repeated supratherapeutic ingestion resulting in a dosage > 4 g/day, now 3 g/day. In pregnant women, acetaminophen may be contra-indicated. Neurodevelopmental problems have been reported in children born to mothers who were on regular acetaminophen. FDA has recommended that the pills of acetaminophen should not contain more than 325 mg per pill.[70]

High hepatotoxic doses of paracetamol may produce generalised convulsions in rats. This can be counteracted with the stable form of gastric pentadecapeptide BPC 157.[71]

Aim of the study

The aim of the study was to investigate the effects of paracetamol and cannabis, alone and in combination on neurocognitive function, pain, metabolic parameters and exercise performance

Method

Study was done in Oriaifo Clinic Complex, Edo- Central Senatorial Area, in 2001 and repeated in 2015-2016. 20 healthy males (aged 20-30) who were heavy cannabis users were used. The effect was compared to controls who were non-cannabis users. Effect of paracetamol alone, cannabis + paracetamol use was also compared in 20 control volunteers. Blood glucose and cholesterol levels were measured in Clinical Chemistry Department of the University Hospital affiliated to the department of Pharmacology and Therapeutics. Study was approved by the College Ethical Committee. Exclusion Criteria: Obese subjects and subjects with cardiopulmonary, renal and thyroid diseases were excluded. Dose of paracetamol: 500 mg tablets were given twice a day (I gm per day) for three months before the evaluations. Participants under heavy cannabis smoke (more than15-20 wraps per day) would have had this habit for at least 3 years.

The Mini-Mental Status Examination

Any score greater than or equal to 25 points (out of 30) is effectively normal (intact). Below this, scores can indicate severe (≤9 points), moderate (10-20 points), or mild (21-24 points) cognitive defect.

STATISTICAL ANALYSIS

Paired Student's t-test was used,[72] and one-way Analysis of Variance (ANOVA) applied to compare only two samples (t-test) or more than two samples (one-way ANOVA) followed by Duncan Multiple Range test (DMR) or the Tukey-Kramer Multiple Comparison Test as post-hoc tests. Data are presented as mean ± standard error of mean (S. E. M.); number of subjects used for each experiment (n) = 20). The difference was considered to be significant at $P < 0.05$.

RESULTS

Parameters	Control	Paracetamol	Cannabis	Cannabis+ Paracetamol
BM1	24.95 ± 1.73	18.40± 1.60*	18. 38± 2.20**	18.36± 2.20***
MMSE	28.50 ±2.00	25.01 ± 3.60**	21.50 ± 3.58***	28.45 ± 4.60*
Cholesterol	185.20 ± 6.50	160.40 ± 3.6*	155.70 ± 4.20**	154.22±2.00***
FBS	98. 50 ± 2.80	75.62 ± 8.00*	74.21± 6.30**	73 .21± 8.00***
Walking distance	450.50 ±118.70	532. 60.00± 145.70*	608.72± 215.20***	604.60±112.20**
Pain score	severe	moderate	mild	mild- to- nil***
No. of accident at work	1.00 ±0.60- 0.73	2.00±0.01-0.35	5.40±1.92-3.61***	2.00±0.2-0.7

Figure I: Effect of paracetamol and cannabis on exercise performance, metabolic parameters and neurocognitive function in humans
* level of significance.

CONCLUSION

1. Heavy use of cannabis+ paracetamol was most significant ($P < 0.05$) in decreasing BMI(M/KG^2), cholesterol levels (mg/dl); Fasting blood sugar (FBS in mg/dl); and pain. Intensity score of pain: mild, moderate and severe
2. Heavy cannabis use alone had the most significant walking distance before fatigue
3. Heavy cannabis use alone was associated with most significant number of accidents at work due to errors.
4. Heavy cannabis use alone was most significant in decreasing MMSE score reflecting greatest negative impact on neurocognitive function. Paracetamol + cannabis group had near-normal MMSE score.

Compared to heavy cannabis use alone, the addition of paracetamol to cannabis rescued the cannabis-induced cognitive deficits.

DISCUSSION

The use of N-acetyl-para-aminophenol APAP impacts the cannabinoid system most of all non-steroidal anti-inflammatory drugs.[76] The word "system" or acetaminophen, discovered in 1877, is popular in most areas of the world including the US. It is on the WHO List of Essential Medicines for the relief of pain and fever. In our locality, a lot of farmers, strenuous workers such as bakers and artisans take it for pain relief after the day's work. In the same vein, a lot of men doing very strenuous labour such as timber workers and bakers illegally take cannabis, often-times heavily. The anti-oxidant, acetaminophen attenuates pain and inflammatory response of strenuous exercise (IRE).[69] In most countries, back-pain accounts for the largest proportion of lost working days of all musculo-skeletal disorders. (*Bevan: the work foundation.com*) Present study extends this observation to the use of acetaminophen for the relief of emotional pain. This was the rationale and impetus for this work; in the quest for patient-friendly drugs with metformin-like effects that may positively impact eNOS- peroxisome proliferator-activated receptor-alpha (PPAR-alpha) signaling. PPAR-alpha is critical for mitochondrial biogenesis, cholesterol metabolism, neuroprotection and down-grading of inflammatory mediators. APAP decreases compulsive worry over the pros and cons of a situation (rumination) since it blunts affect,[58] reduces empathy for pain[59] and evaluation sensitivity to both negative and positive stimuli.[56] It may have a major role here since it enhances serotonergic signalling. Subjects can be helped to build up their exercise tolerance with the aid of APAP[73] [74] and APAP can help with the depression of chronic exercises. Depression and pain share biological pathways and neurotransmission.[75]

APAP impacts the cannabinoid most of all non-steroidal anti-inflammatory drugs.[76] Some NSAIDs have additional influences on the cannabinoid system either by inhibiting fatty acid amide hydrolase (FAAH) or by inhibiting FLAT. All the NSAIDs that inhibit COX2 can influence the cannabinoid system because of a possible important degradative pathway for anandamide and 2–arachidonoyl glycerol might involve COX 2.[76] For example, aspirin and R-flurbiprofen might also have some effect on CBI and CB2 receptor signaling.[77] [78] Results (Figure I) also show that APAP in combination with cannabis attenuated the errors at work more than cannabis used alone. Cannabis is known to increase perseverative and non-perseverative errors probably due to the fact that chronic cannabis use decreases D2 dopamine receptor signalling in striatum[24] which leads to deficits in working memory and attention. It also downregulates serotonin 5-HTIA and upregulate 5-HT2A signalling.[19] APAP may increase BDNF release since it enhances serotonergic signalling by decreasing cannabinoid CBI receptor-mediated inhibition of 5-HTIA mechanisms.[47] [46] The results implicate APAP as a drug that may attenuate the neuropsychiatric side-effects of cannabis consumption with the caveat that APAP may alone can cause decrease in error evaluation.[58] In children, sleep disruption and proprioceptive delirium has been reported after APAP.[79] which has also been associated with developmental problems and autism in children[40] when used during measles, mumps and rubella (MMR) immunisation. Although routine rubella vaccination is not available in the country, on-going determinations may elucidate whether a similar problem may exist occultyly in our locality. In the meantime, we report that no sign-post has been detected.

Cannabis is reported to be useful for chronic pain[37] and could synergise with APAP in this respect. Endocannabinoids are also released during exercises and account for the runner's- high.[80] [81] Hippocampal

neurogenesis is enhanced by exercises and this is via CBI cannabinoid receptor signalling although chronic stress impairs endocannabinoid signalling in the dorsal raphe nucleus,[82] so marijuana use has to be considered individually.[74] Marijuana administration may prevent the decreased regulation of plasticity of glutamate synapses by endocannabinoids and the cAMP/PKA pathway in midbrain dopamine neurons.

Cannabinod CB2 receptor signaling is associated with weight reduction and beta-cell protein in the obese rat model while CBI receptor signalling is associated with weight gain.[11] But there may be a reversible and regionally selective downregulation of brain cannabinoid CBI receptors in chronic daily cannabis smokers[82] and this may lead to increase signalling by CB2 receptors. There is a regulatory role of the cannabinoid CB2 receptor in stress-induced inflammation[83] and in upregulating beta-endorphin release[84] while the cannabinoid CBI receptor inverse agonist AM 251 possesses anti-depressant-like effects in mice.[85] Cannabidiol, a non-psychactive cannabis constituent protects against myocardial ischaemic reperfusion injury.[86] Cannabis decreases BMI most significantly from results (Figure I) and its consumption is useful for obesity in young adults[87] confirming our previous and present reports.[88] APAP may synergise with cannabis for weight reduction since it increases serotonergic signalling that induce BDNF. APAP may inhibit voltage-gated sodium channels in the DRG and increase eNOS signalling which is a down-stream effector of AMPK-induced molecular signalling.[55] APAP also may lead to increase in levels of free arachidonic acid that helps with glucoregulation, and this may be mediated by the increased cAMP levels.

Cannabis increases walking distance significantly and so may appear under the list of ergogenic herbal adaptogens (Lagano L: healthyorganicwoman,com) and World Anti-doping Agency has raised the threshold for it to be considered a banned substance from 15 ng/ml to 150 ng/ml (www.usatoday, 2013). Chronic use of cannabis may infact be ergolytic because of CBI receptor-induced inhibition of serotonergic 5HTIA receptor signalling. It may increase heart rate, interfere with reaction time and psychomotor performance.[89] Cannabis use is associated with neurocognitive dysfunction[14] and present results (Figure I) confirm this where it most significantly reduced MMSE scores. Results also show that paracetamol may rescue the low MMSE scores caused by cannabis abuse. Chronic stress is deleterious for cannabinoid control of GABAergic transmission in the dorsal striatum which leads to increased anxiety.[28] Endocannabinoids and cannabinoid CB2 receptor agonists promote neural progenitor cell proliferation.[90] The cannabinoid CB2 receptor axis through AMPK activaton is also cardioprotective[91][92] though it has been reported that a CBI/CB2 dual agonist with limited brain penetration, CB-13, was more efficacious.[3] Thus, chronic cannabis administration may be implicated in reducing the incidence of stroke during exercises in subjects with deficient exercise training. It may also be added, from the phytomedicinal angle, that cannabidiol, a non-psychoactive component of the cannabis plant, may enhance fracture healing by stimulating lysyl hydroxylase activity in osteoblasts[93] and the prospect seems heart-warming for the elderly, sports-men and sports-women.

CONCLUSION

Present results illustrate that the nootropic, APAP, enhances exercise performance and, in combination, attenuates the neuropsychiatric side-effect of cannabis consumption.

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