Sports Pharmacy

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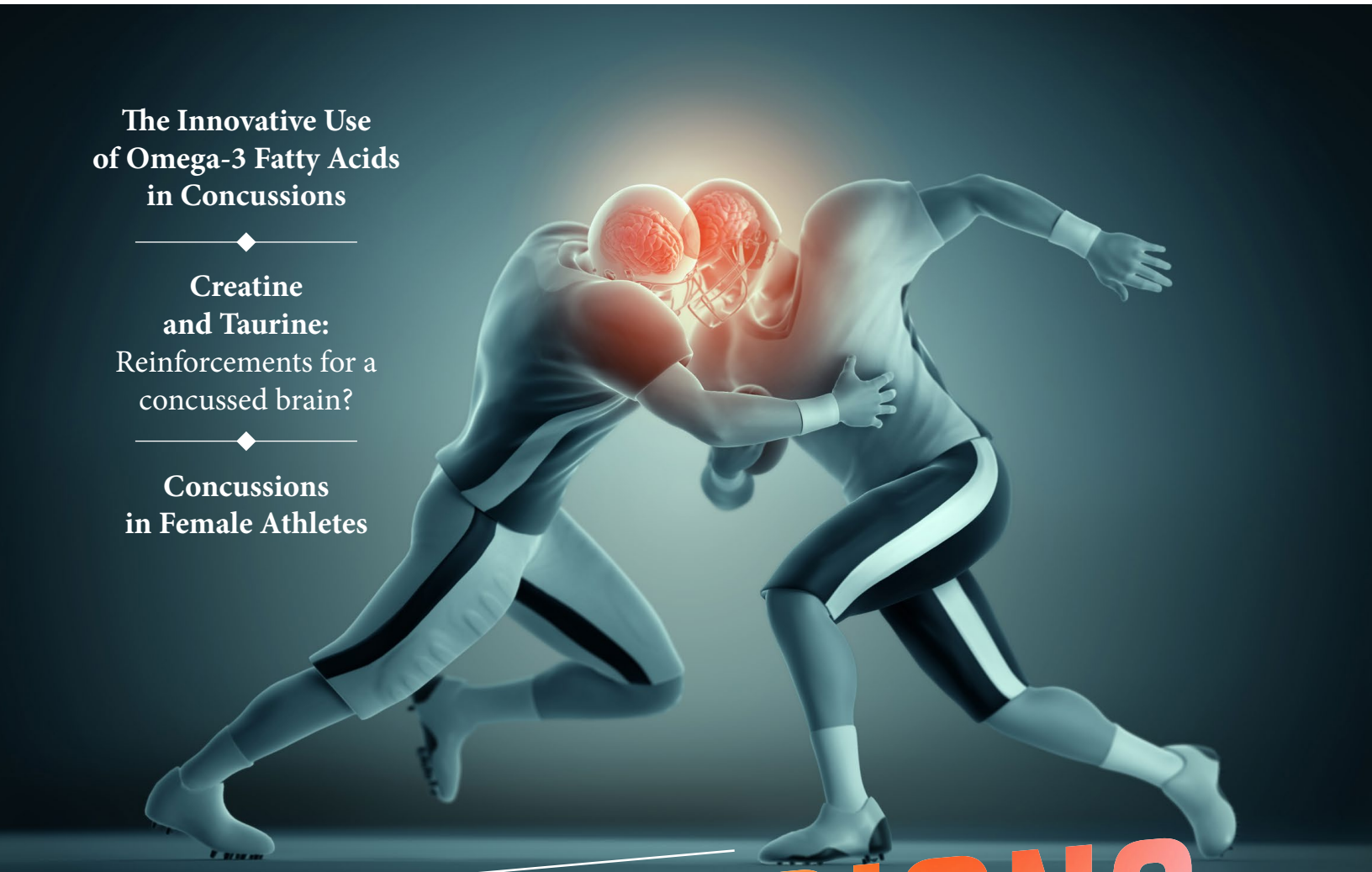
The Innovative Use of Omega-3 Fatty Acids in Concussions

Creatine and Taurine: Reinforcements for a concussed brain?

Concussions in Female Athletes



CONCUSSIONS

SPORTSRXNEWS
DECODING THE SCIENCE OF ELITE HUMAN PERFORMANCE

Pharmacist Athlete Contributors

MISSION STATEMENT

THE PURPOSE

Brandon K. Welch, Pharm.D.
Founder of Pharmacy Athlete

The Sports Pharmacy magazine exists to empower a community of pharmacist professionals to optimize their impact through disseminating evidence-based knowledge and applied science on sports performance supplements and nutrition. Pharmacists can be pivotal players in the arena of sports. They are poised to help intersect biochemistry with biomechanics and real-life science with athletic performance. Our patient athletes rely on results and we are here to deliver them in real-time.

> Where Pharmacists unlock biochemistry to intersect with biomechanics to optimize patient-athlete performance
>
> Brandon K. Welch, PharmD.

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Brandon Welch, PharmD
NASM-CWC (Expected December 2022)

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The Innovative Use of Omega-3 Fatty Acids in Concussions

By Dr. Brandon Welch, Pharm.D., M.S.(c)
Human Performance Specialist

AUTHOR BIO:

Dr. Brandon K. Welch is an experienced licensed wellness pharmacist that holds his doctorate in pharmacy from the University of South Florida and his bachelor degree in biomedical sciences with a focus in biochemistry. He is the wellness pharmacist for Baptist Health where he works collaboratively with the Miami Dolphin's and Florida Panther's team physician to help enhance athletic performance and reduce risk of illness. His passion in performance training led him to pursue his Master's degree in physiology and kinesiology with a concentration in human performance and athletic development. His expertise lies in functional training, sports nutrition, sports medicine, genetic counseling, and sleep therapy. He utilizes science based medicine and literature to help maximize his clients training performance and daily lifestyle. He's worked with several clients, helping them lose weight, improve performance, improve their sleep cycle, muscle building, and appropriate nutrient supplementing.

More than 3.5 million known traumatic brain injuries (TBIs) occur each year, accounting for more than 300,000 hospitalizations and around 52,000 deaths.[1] When considering the importance of the brain and its role in every conscious and unconscious action taken by the body, it is clear why TBI is a significant clinical challenge that needs addressing.

TBIs are a common occurrence in sports medicine due to the increasing probability for athletes to experience a bump, jolt, or blow to the head, disrupting the brain's normal function. These injuries are categorized as mild, moderate, or severe, with most cases falling into the "mild" category and labeled as a concussion.[1] However, even mild TBIs have prolonged secondary pathogenesis and diverse complexities that make it difficult to find an effective treatment strategy.

The Two Phases of TBI

TBI is classically described as occurring in two phases. The first phase constitutes the primary or initial injury, which occurs as a direct result of the traumatic event. However, the damage to the brain does not end there, with the secondary injury occurring for days or weeks following the initial injury as a result of multiple neuropathologic processes. These processes lead to prolonged cell death and worsening damage to the brain beyond what occurred with the initial injury.[2]

Elements of the secondary phase include:

- excitotoxicity, ischemia, and intracellular biochemical cascades
- cerebral edema
- axonal injury
- inflammation and regeneration

This secondary phase, and its impact on brain health, has gained increasing awareness as a target for therapeutic interventions. Still, an effective treatment strategy must combine neuroinflammation control, neuroprotection, and neuroregeneration,[3] and while clinical trials have yet to identify a treatment strategy that accomplishes these three tasks, emerging research on omega-3s shows promise.

In *Concussions, Traumatic Brain Injury, and the Innovative Use of Omega-3s*[2], Michael D. Lewis reviewed the evidence supporting the capability of omega-3 supplementation to target the secondary phase of TBI and promote healing in the brain.

Understanding Omega-3s

Omega-3 polyunsaturated fatty acids, more commonly shortened to omega-3s, are a structural component of cell membranes. One type of omega-3 fat in particular, docosahexaenoic acid (DHA), is highly concentrated in the brain and retina. Knowing this role of omega-3s, research has long established that they are essential for proper neurodevelopment and function.

Despite their crucial role in the body, omega-3s are not produced by the body. As such, their concentration within the body relies entirely on dietary consumption, and research shows that the composition of neuronal cell membranes

directly correlates to the dietary intake of omega-3s and omega-6s.[4] Even more, the ratio of omega-6 fatty acids and omega-3 fatty acids impacts the physiological function of the brain and alters synaptic membrane fluidity and cell permeability, which then significantly influences neurotransmitter activity.[5]

This influence of the fatty acid ratio on brain function demonstrates the need for a proper balance, with a traditional ratio between omega-6s and omega-3s of 1:1.[5] However, the Western diet places a greater emphasis on omega-6s, leading to a deficiency in omega-3s due to their inverse relationship. Current insights now suggest an omega-6 to omega-3 ratio of 22-25:1, showing the immense domination of omega-6s in the Western diet.[6]

On a cellular level, this imbalance between omega-6s and omega-3s results in the displacement of DHA from membrane phospholipids, impeding brain recovery and proper functioning.[7] A proper balance between the two fatty acid types is also crucial because of the respective inflammatory and anti-inflammatory properties of omega-6 and omega-3 fats, with adequate dietary consumption of omega-3s needed to inhibit the inflammatory nature of omega-6s.[8]

Omega-3s and Concussions

The ideal TBI treatment will offer three advantages, neuroprotection, neuroinflammation control, and neuroregeneration promotion. Omega-3s offer all of these advantages, which allows them to influence the primary mechanisms of the secondary injury phase of TBI. Additionally, omega-3s have the additional benefit of being able to be administered to patients during the first phase of the injury (or even before the injury) and then continued throughout the entire rehabilitation process. Animal models regarding omega 3s show immense promise in their ability to improve TBI outcomes, stroke, and spinal cord injuries.[9, 10, 11, 12]

Various case studies have also shown the promise of omega-3s in treating severe cases. One involves a teenager who was in a motor vehicle accident and sustained a severe TBI with diffuse axonal injury. The attending neurosurgeon believed the injury was likely lethal, and the patient would remain in a permanent vegetative state. However, 21 days after beginning omega-3 supplementation, doctors could wean the patient off the ventilator, and four months after the injury, he was able to go home.[13]

Despite the potential for omega-3s in cases of TBI, as evident in the above case report, the complexity of TBIs and lack of clinical trial evidence currently hinder the ability to definitively conclude that omega-3 supplementation will help in a particular TBI case. However, growing evidence observed by multiple providers is that the brain requires high doses of omega-3s in order to heal and, as such, a lack of high omega-3 doses decreases the brain's ability to heal. Some patients may respond better to omega 3s than others, but there is no reported downside to providing optimal nutrition levels to patients recovering from a concussion to promote the best possible healing environment and functional outcomes.[2]

> Omega-3 supplementation offers a way for sports pharmacy to target this secondary phase of concussion injury by supplementing the body with DHA, a vital component of neuronal cell membranes.

Omega-3 Dosing for Concussion Cases

Dosage amounts and methods of ingestion vary amongst the various reports and case studies regarding omega-3s. For example, one case may use a concentrated liquid in a feeding tube, while another may use a fish oil capsule or liquid equivalent. The method of ingestion utilized is highly reliant upon the patient's ability to swallow for themselves, with those who have concussions typically able to take a fish oil capsule.

Regarding the dosage, the Brain Health Education and Research Institute recommends 5,000 mg of fish oil (which equates to 3,000 mg of omega-3s) given three times a day for at least one week before decreasing to twice a day and then once a day.[14] For the best results, though, it is recommended to analyze the omega-6 to omega-3 ratio weekly, looking for the desired 1:1 ratio. The dosage can be increased or decreased if necessary to meet this ratio.[15]

Omega-3s for Concussions

Concussions and other forms of traumatic brain injuries pose a significant problem to the world of sports medicine due to their complexity and differences from patient to patient. Even more, concussions often have two parts to their injury: the initial damage and the continued injury to the brain in the days and, potentially, weeks following the initial injury.

Omega-3 supplementation offers a way for sports pharmacy to target this secondary phase of concussion injury by supplementing the body with DHA, a vital component of neuronal cell membranes. Emerging research regarding omega-3s for concussion treatment shows promise, although it still consists of individualized results with outcomes and reaction intensity varying by patient. With no reported side effects of omega-3 supplementation in clinical trials, though, there is no harm in adding this supplement to an athlete's treatment plan to give them a greater chance of functional recovery.

For more information, contact Dr. Brandon Welch, Human Performance Specialist.

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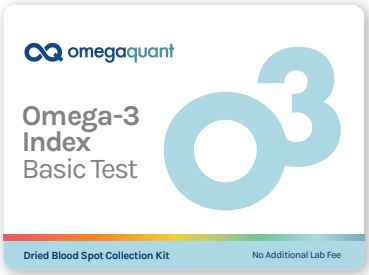

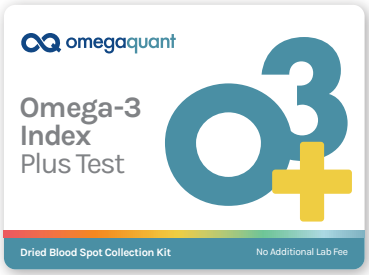

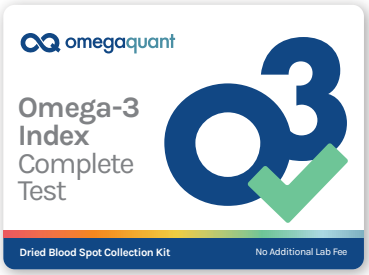

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Creatine and Taurine

Reinforcements for a concussed brain?

By Sean Casey, RD, CSCS

AUTHORS BIO:

Sean Casey RD CSCS is a registered dietitian, movement coach and member of the Evolve Wellness Science Team at Hometown Pharmacy of Wisconsin. He specializes in sports nutrition, nutraceuticals, and proactive care.

Quick Hit Summary

Creatine and taurine are well known for their ergogenic role in muscle function. Emerging evidence also suggests that they may also have restorative effects on cognitive function following a traumatic brain injury (TBI). Creatine in doses of ~0.18 gr/lb/d for 6 months and taurine in doses of 13 mg/lb/d for 14 days has improved clinical outcomes in those with TBIs. Theoretically speaking, for athletes at risk for experiencing concussions, one may want to consider taking 10-20g of creatine and 2-4g of taurine prophylactically.

A Historical Look at Creatine and Taurine

There are many nutraceutical supplements on the market today which are marketed for their physical performance enhancing benefits. Two widely recognized compounds that fit this bill are creatine and taurine.

Outside of potentially caffeine, creatine is one of the most widely researched ergogenic supplements. Its impact on strength, power and speed as well as safety are well documented in scientific literature; with earliest reports of use in elite level sport dating back >50 years ago.[1-3]

For instance, a look into the potential ergogenic role of creatine in elite athletic performance was taken up by the USSR during the 1970's and 80's.[3] Creatine gained even more attention on a worldwide basis in 1992. Following the Barcelona Olympics that summer, various high profile British sprint and power athletes stated that creatine supplementation helped their performance.[4] Additionally, a research team led by Roger C. Harris, performed the as first contemporary study on creatine supplementation in western literature.[5]

Although its ergogenic track record doesn't extend as far back of creatine, research on the semi essential amino acid, taurine, has indicated taurine to have positive benefits on muscle damage/recovery, VO2Max, anaerobic performance and other performance variables.[6]

Although both creatine and taurine are best recognized for their musculoskeletal roles, emerging research has identified another potential benefit for both – Brain health! More specifically, mitigating the negative effects of Traumatic Brain Injuries (TBIs).

In this article, we will examine the physiological phases of a traumatic brain injury followed by a discussion on the potential therapeutic role of both these ergogenic compounds in protecting brain health in the event of a TBI.

Phases of a Traumatic Brain Injury (TBI)

A traumatic brain injury (TBI) is characterized by two distinct injury phases known as the primary and secondary phase.[7] The primary phase occurs at the time of the incident; it's characterized by the actual mechanical force which leads to the stretching, compressing, and tearing of cells upon impact and lasts microseconds to seconds. For example, this is what occurs when one's head hits his or her head on an athletic court floor or in the case of American football, a helmet-to-helmet collision.

This secondary injury phase takes place during the minutes to weeks that follow a traumatic brain injury.[7] It's at this time were inflammation, mitochondrial dysfunction, excitotoxicity, impaired glucose metabolism

> Due to limited downside with potential upside, athletes at risk of concussions should consider using creatine and taurine prophylactically to support bioenergetic and inflammatory processes in the event of experiencing a TBI.

as well as additional biochemical change take place within the brain, leading to a post traumatic energy crisis and neuropathologies within the brain.

It's during this secondary phase of injury where creatine and taurine hold potential in minimizing damage and speeding up recovery following a TBI.

Creatine & TBI Research

Various animal and in-vitro studies have examined the effects of creatine supplementation on TBI. For example, Sullivan et al. found that injecting mice with 3 mg/g/d (**HED* = 110 mg/lb), for 3-5 days leading up to a controlled cortical contusion reduced cortical damage by 21 and 36% vs. placebo 7 days post injury.[8] Additionally, their research team found that feeding rats a creatine enriched diet for 1 month following a TBI reduced cortical damage by 50%! It was hypothesized that these positive outcomes were related to creatine's role in supporting mitochondrial bioenergetics and membrane potential.

To date, only one research study has been conducted in humans examining the impacts of creatine on recovery following a traumatic brain injury. In a 2006 explorative study conducted by Sakellaris et al, 39 adolescents between the ages of 1-18 years old were assigned to a control group which received standard care or the creatine group which received ~0.18g of creatine per day for 6 months following traumatic brain injury.[9]

Upon conclusion of the study, Sakellaris et al found that those receiving creatine experienced better outcomes as it related to both short term outcomes (post traumatic amnesia, ICU Stay) as well as long term outcomes (cognitive functions, personality/ behavior and communication).[9]

** Human equivalent doses (HEDs) are used when extrapolating doses used in animal studies to humans. Due to metabolic differences, rats and mice need higher doses of a given substance to have same theoretical effect of what's seen in humans. NOTE – HEDs are meant to be best available estimates.*[10]

Taurine & TBI Research

Similar to creatine, most of the research to date on taurine has been completed in animal studies. In their 2014 study, Gu et al found that giving rats 50 mg/kg of taurine (HED = ~ 3.7mg/lb) intravenously both 30 minutes and 4 hours post brain injury reduced brain damage in the corpus callosum and neuronal cell death in the hippocampus vs. control group.[11] The taurine group also saw improved neurological functions 7 days post head injury.

Similar positive effects of taurine on brain recovery were observed by Wang et al who gave rats a taurine dose of 200mg/kg/d (HED = 14.7mg/lb) for 7 days following a TBI like event.[12] In this particular study, Wang et al noted improved blood flow as well as mitochondrial activity in the group of rats receiving taurine.

The positive benefits seen in animal studies have also been supported in human research. In a recently published double blind randomized controlled trial, Vahdat et al randomly assigned 32 patients with TBI to either a control or taurine group which received ~14 mg taurine/lb of bodyweight for a period of 14 days. Those receiving creatine experienced reduced levels of IL-6, a marker of inflammation, and enhanced clinical outcomes.[13]

Prophylactic Dosing of Creatine & Taurine

Although it has not been formally studied, based on theoretical rationale, one may be able to 'armor' their brain in advance of experiencing a TBI by increasing the number of first line defenders present (i.e. creatine and taurine) prior to suffering an event. Thus, limiting the negative consequences one experiences following a traumatic brain injury.

There are still a lot of unknowns as it relates to creatine dosing to saturate brain tissue levels. Based on current research, aiming for a creatine doses of between 10-20g/day may be prudent for brain health; especially for those participating in events at higher risk of TBI's.[14]

A practical prophylactic dose of taurine to support brain health, may be in the ~ 2-4g/day range.

Wrapping Things Up

To date, there are few nutraceuticals which have shown promise in situations of TBI. That said, although more research is needed, it appears that both creatine and taurine may hold promise to enhance recovery from TBI. Due to limited downside with potential upside, athletes at risk of concussions should consider using creatine and taurine prophylactically to support bioenergetic and inflammatory processes in the event of experiencing a TBI.

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Concussions in Female Athletes

By Dr. Jessica Beal-Stahl, Pharm.D.

AUTHOR BIO:

Jessica Beal-Stahl, PharmD, is the founder of The Athlete's Pharmacist company, tying her passions of athletics and pharmacy together where she works privately with clients to improve their performance in sport and life. She received her Doctorate of Pharmacy from Mercer University in 2009 and has been practicing as a Director of Clinical Services at Hobbs Pharmacy in Merritt Island, Florida, since graduation. Jessica also knows what it's like to be a high-level athlete, having played D1 volleyball, medaled internationally in Olympic weightlifting, and set at 41 years old a world record in Olympic Weighting for snatch in her age/weight class. She holds additional certifications in Integrative Medicine, Nutrigenomics, and Sports Nutrition.

Female athletes are twice as likely as males to get concussed and have prolonged symptoms and more severe effects. Possible factors that put female athletes at a higher risk for concussions include biomechanical, anatomical, and hormonal differences. More research is required to determine when and how such injuries are sustained and whether treatment should be different in female athletes to effectively prevent, diagnose, and treat concussions in female athletes.

There has been increased awareness and media coverage surrounding concussions, and rightfully so. In the United States, 1.6 to 3.8 million sports and recreational concussions occur annually.[1] In a 2017 CDC survey, 2.5 million high school students – 15% of all high school students nationwide – reported having experienced a concussion in the previous year. More than 40% of those students were girls.[2]

Shockingly, studies show that female athletes are 1.9 times more likely to develop a sports-related concussion than their male contemporaries in comparable sports and the effects are often more severe. [3,4]

Outside of football, no high school sport causes concussions at a higher rate than girls' soccer. Women's soccer, softball, and basketball have higher incidence rates of concussion than male-equivalent sports.[5,6,7] Concussions account for nearly 15% of athletic injuries among high school athletes and 6.2% of reported injuries among NCAA athletes.[6] Even with intentional bodychecking prohibited in women's ice hockey and permitted in male ice hockey, female hockey players sustain nearly equivalent rates of concussion relative to male hockey players.[5,6,7] Additionally, female-dominated sports, such as cheerleading, have high rates of concussion, with cheerleading having the most of any sport in practice.[8]

A review of 25 studies of sport-related concussions suggests that female athletes are not only more susceptible to concussion than males, but also sustain more-severe concussions.[9] Females also demonstrated higher post-concussive symptom scores, had slower reaction times than baseline, exhibited greater cognitive decline, and took longer to return to play compared to males playing comparable sports.[10]

The question many female athletes have is, "Why? Why did that impact affect me that way, yet you watch guys take hard hits every Sunday on TV, and they're fine?"

Research demonstrates that traumatic brain injuries (TBI), including concussions, affect women differently.

Concussions are a type of traumatic brain injury caused by a bump, blow, or jolt to the head or by a hit to the body. This external force causes the head and brain to move rapidly back and forth. As a visual, think of your brain in your skull like jelly preserved tightly in a Mason jar. The jelly can't move much within the jar while tightly vacuum-packed. The brain is situated the same way within the skull, with only a thin film of fluid surrounding the brain and filling up any spaces.

After an impact, the head rapidly decelerates, causing the brain to undergo significant shearing forces causing physical damage to the brain tissue. The damage causes swelling and reduced blood flow temporarily,

which contains glucose and oxygen, starving nerve cells of fluid. The shear force can also cause a momentary release of various neurotransmitters throwing the brain's signal out of balance.

Males and females will likely report different symptoms in the following days and weeks. In contrast, male concussions are more likely to be followed by amnesia, while females often report prolonged headaches, mental fatigue, difficulties with concentration, and mood changes. Female athletes also seem to require more time for symptoms to subside and disappear.

Understanding why females are more susceptible to concussions is essential if we reduce those risks. There are three main theories about why females experience concussions more than males. In reality, it is probably a bit of each. The three theories are:'

1. Anatomical – small difference within the brain inside
2. Structural – female necks tend to be slimmer and have less shoulder/neck muscular mass than males.
3. Hormonal – risks change based on varying hormone levels within the menstrual cycle.

Every neuron has a major fiber called an axon which transmits electrical signals from cell to cell. Damage to the axon due to the shear forces is thought to be the main reason concussions occur. Once an axon is damaged, it is gone forever. Think of your brain like silly putty; when gently stretched or moved, it deforms and relaxes back into shape. But when yanked or force applied, the putty would always snap apart; this is like your axons.

Within this topic of anatomical difference, there are a few areas of thought:

Females' axon fibers, which connect neurons together in the brain, are slimmer than those of males.[11] Smaller and slimmer axons make for increased risks of damage from sheer forces.

Also, it has been shown that females have slower nerve signals while males have faster nerve impulses in their brains, which could lead to quicker healing.

Female brains are thought to have slightly faster metabolisms than males, with greater blood flow to the head. And if a head injury momentarily disrupts that supply of glucose and oxygen, it could cause greater damage.

Looking structurally at male vs. female necks, several studies have reported that shorter neck dimensions, less head mass, and narrower neck girth result in less neck strength in females than male athletes, which predisposes girls and women to greater head-neck acceleration during impacts. One study showed that female players' necks were 47% weaker than males.[12]

Looking at soccer, the sport with the highest rate of concussions for females. One reason believed is that females have a smaller "ball-to-head size ratio," or smaller heads compared with the ball, and thus a greater transmission of forces occurring. Female players also had significantly greater head-neck angular acceleration," which is a type of biomechanical measure of head impact and head displacement, than male soccer players. Angular acceleration is considered damaging to people's brains and causes brain injury.[13]

Additionally, most female athletes are less heavily muscled up in the shoulder girdle and neck areas which decreases absorption capability making it easier for the head to move when struck by a blow. This is also the reason children are more susceptible to concussions because they have thinner and weaker necks compared with fully grown adults.

Not everyone agrees, however, that neck strength or anatomical differences are the problems or the answer. Some researchers favor the idea that concussions are aggravated by the hormones that govern the female menstrual cycle.

Researchers found that women who were injured during the last two weeks of the menstrual cycle, when progesterone was at its highest (luteal phase), had worse post-concussion symptoms compared with women injured during the first two weeks when progesterone was low (follicular phase), and with those who were taking contraceptive pills.

The levels of sex hormones, such as progesterone which is known to have a calming effect and can improve cognition, memory, and mood, can change after a concussion, especially during the second half of the menstrual cycle (luteal phase). When a concussion happens during this time and progesterone levels drop due to the natural hormones cycle, the brain injury causes progesterone levels to abruptly plummet [(I),] creating a sense of withdrawal and making concussion symptoms, such as headache, dizziness, and nausea, worse. This is known as the "withdrawal hypothesis," coined by Jeffery Bazarian, MD, MPH.[14] In the follicular phase, by contrast, progesterone levels are already lower and would not drop so dramatically – meaning the resultant symptoms are less severe.[14]

Interestingly various studies have found that females taking contraceptive pills are also less likely to suffer severe symptoms following a concussion because oral contraceptives work by regulating the levels of sex hormones in the body, so you don't have the hormonal surges and drips of the course of the month.[14]

Research is discovering that not only does the menstrual cycle have an impact on concussion, but conversely, head injuries can affect the menstrual cycle and other aspects of reproductive function by interfering with the brain regions that help to control levels of estrogen and progesterone.

A recent study evaluated females aged 12 to 21 years diagnosed with a concussion. The researchers did a follow-up four months after the head injury and found that ~ ¼ of patients who had a concussion experienced two or more abnormal menstrual periods. Compared with females who had sustained a non-head injury, patients who had a concussion were more than five times as likely to have had more than one abnormal menstrual cycle. These findings suggest that brain injuries, such as concussions, may affect the hormonal processes. The investigators concluded that young women are at an increased risk for abnormal menstrual patterns after a concussion and that menstrual patterns should be monitored.[15]

Is progesterone causing all the problems in concussions? No, but it's probably taking the problems from a typical concussion and making them worse.

Complicating matters even more, the surges in estrogen and progesterone during the luteal phase might also influence dopamine signaling. Dopamine is implicated in many of the brain's functions that are influenced by concussion, including motivation, mood, memory, and concentration, making it a good contender for a potential mechanism.[16]

There have been strides in how concussions and other TBIs are treated, but it's important to study the long-term effects of these injuries to know how to treat each sex differently.

Many agree on the need for more research about women who sustain head injuries. Treatment protocols, recovery experience, and the return to play protocols at all levels are changing to try to prevent injury. Still, there needs to be a difference in treatment between females and males. Better awareness of these differences between sexes could ultimately lead to better care before and after a concussive event. We must focus on the rest of their lives and healthy aging.

For more information on why concussions might affect women differently than men, download "Women & Concussions," developed by NORA and the non-profit group PINK Concussions.

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Ketone Supplements to Support Recovery from Traumatic Brain Injury

A theoretical look

By Sean Casey, RD, CSCS

AUTHORS BIO:

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Quick Hit Summary

Upon suffering physical trauma, the human brain undergoes many metabolic changes while simultaneously experiencing a state of elevated oxidative stress. Collectively these changes reduce the brain's ability to metabolize glucose for energy. A potential alternative fuel source for the brain during this time period is ketones. In addition to providing energy, ketones may also support brain recovery by reducing oxidative stress, improving blood flow and limiting neuronal cell death. Although a mechanistic benefit has been established, more research is needed to objectively assess the impacts of ketone supplements and/or diets on recovery from traumatic brain injuries.

Feeding the brain!

The human brain – it's pretty dang important! As we've learned from primary grades on up, the brain regulates the rest of the rest of the body. It dictates every action of your body. This high workload does not go unnoticed as it relates to caloric expenditure.

Despite accounting for only 2% of one's total body weight on average, it burns through ~ 20% of one's daily caloric expenditure![1] In short, relative to caloric demands and size, one's brain is an extremely expensive piece of caloric real estate.

As it relates to macronutrients, for most athletes participating in high intensity sports, glucose is not only their muscle's primary source of energy, but also the preferred fuel of the working brain. It's only under circumstances of a low carbohydrate availability, such as a ketogenic diet, where this balance shifts under normal physiological conditions.

However, in the event of a traumatic brain injury (TBI), the brain is no longer operating under normal physiological conditions. Thus, the question must be asked - is there a better fuel source for the brain during these traumatic events?

Changes in Brain Metabolism during a TBI

As aforementioned, the primary source of energy for the brain for most athletes under normal physiological conditions is glucose.

However, during a TBI, a cascade of events takes place, limiting the brain's supply and ability to metabolize glucose including:[2]

1. Slowing down of enzymes along the glycolytic pathway
2. Impairment along the electron transport chain, reducing it's ability to produce ATP
3. Deceased cerebral blood flow, limiting both glucose and oxygen delivery to the brain
4. Production of free radicals and resulting oxidative stress

The net effect of all these 4 factors – a state of hypometabolism and potential for deleterious acute and chronic effects on brain function.

Mechanistic Metabolic Efficiency Benefits of Ketones During TBI

Due to the brain's inefficient use of carbohydrates during TBI, researchers have examined alternative sources of fuel for the brain. One potential candidate of promise is ketones. There are three main ketones of note – acetoacetate, B-hydroxybutyrate and acetone. Of these, b-hydroxybutyrate is the body's main ketone.[2]

The use of ketones during TBI's hold many physiological

advantages as it relates to supplying energy within the brain.[2] This includes a reduced number of steps to enter the TCA cycle; most notably it bypasses many of the glycolytic enzymes, such as pyruvate dehydrogenase complex which is inhibited during TBI.[3]

Additional Physiological Benefits of Ketones during TBI

In addition to their metabolic efficiencies relative to glucose utilization, ketones may also hold additional physiological benefits during concussions.

For instance, ketones have been shown to reduce oxidative stress, modulate inflammation, improve cerebral blood flow and limit neuronal cell death. [4-6] Taking collectively, ketones have the ability to not only supply the brain with a more efficient source of energy vs. carbohydrates but also, speed up the brain's ability to recover from TBI's via different physiological mechanisms.

Ketones & TBI – From Theory to Application

To date, beyond mechanistic studies, few research trials have investigated the potential use of ketone supplements or use of the ketogenic diet following a TBI.

On the supplemental side of the equation, key issues that still need to be examined include what is the most ideal form of ketones to supplement with – ketone esters vs. ketone salts. The former appear more effective at increasing circulating ketone levels. However, they also are metabolized quickly and taste poor.[2] On the other hand, although taste may be slightly more palatable with ketone salts, they can also cause GI disturbances when consumed in higher doses.

Additionally, research is still needed to determine what ideal levels of circulating ketones look like in order to optimally support TBI recovery.

Although research regarding ketones and TBI is still in its infancy, additional support for their use is seen by examining clinical trials in patients with similar brain pathophysiological conditions. For instance, similar to what's seen in TBI's, altered glucose metabolism is a hallmark symptom of Alzheimer's Disease. Here, the use of a ketogenic diet has been shown to improve brain metabolism & reduce neuronal cell death in Alzheimer's.[7,8] Similar positive effects of a ketogenic diet on brain pathologies has been observed in Parkinson's disease, migraines and epilepsy.[9-11]

Wrapping Things Up

Research surrounding the use of ketones to optimize recovery from TBI events is intriguing. Not only does it supply a metabolically efficient source of energy but also, may enhance overall brain recovery through a variety of physiological mechanisms.

Although promising, more research is needed to assess both dosing, timing and net effects of ketone supplementation and/or a ketogenic diet in assisting recovery from a TBI.

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Understanding the Endocannabinoid System

An Athlete's approach

By Dr. Kristal Potter, Capt, USAF, BSC, PharmD.

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Dr. Kristal Potter is an assistant professor at the Larkin University College of Pharmacy. She received her Bachelor of Science in Neuroscience from Florida Atlantic University and her PharmD from the University of South Florida Taneja College of Pharmacy. After graduating she served as a pharmacist in the United States Air Force. During her time serving at Cannon Air Force Base she was the Pharmacy and Therapeutics Committee Chair and championed several patient education programs. Dr. Potter is passionate about holistic approaches to healthcare inspiring the next generation of pharmacy leaders.

Intro

Walking into my neighborhood Publix the other day for a coffee run I was surprised to see a stand fully stocked with cannabidiol (CBD) products. Fixed atop the stand was a banner proudly stating "CBD Topical Products Have Arrived. Have questions about CBD? Talk with one of our pharmacists." Athletes like Megan Rapinoe (USWNT) have endorsed cannabis recovery products, and others like Conor McGregor (UFC) have even launched their own lines of cannabis-based recovery products. So, if a patient does want to talk about these novel recovery products, are you ready to answer their questions? Hopefully you'll feel more confident after reading this.

The Endocannabinoid System

The endocannabinoid system is a neuromodulatory system with unique receptors and activity.[1] This system may regulate many functions in our body including learning, mood, addiction, pain modulation, and cardiovascular functions.

The best-characterized cannabinoid (CB) receptors are CB1 and CB2 receptors. These are G-protein-coupled receptors (GPCRs) that primarily couple to inhibitory G proteins. The interesting thing about the CB1 receptor is its diversity in signaling, which is enhanced by its ability to cross-talk with other GCPRs such as dopamine, serotonin, and opioid receptors.[1,2] CB1 receptors are found in abundance on GABAergic interneurons, but are also found on a variety of other neurons in the brain including glutamatergic, cholinergic, glycinergic, serotonergic, etc. In neurons, CB1 receptors are particularly concentrated on synaptic terminals, indicating their role in modulating synaptic transmission.[1]

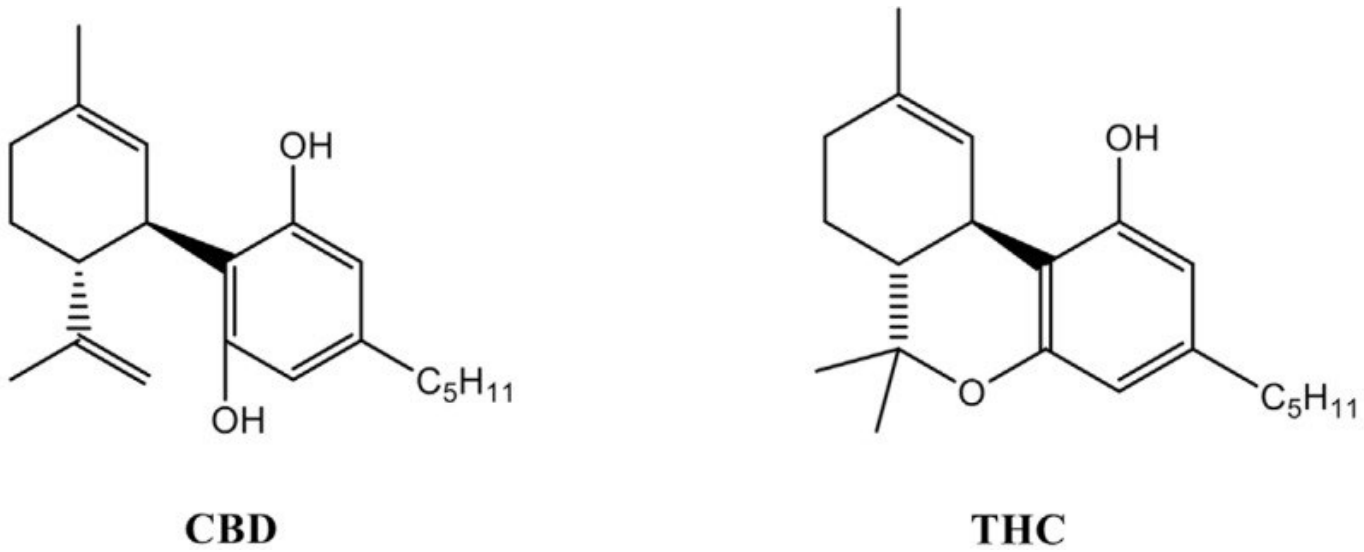
CB2 receptors are mainly found in cells of immune origin, such as microglia. They may also be expressed in neurons, but to a lesser extent. Microglial CB2 receptor activation generally has anti-inflammatory action. Due to its limited role in functions related to athletic performance/recovery, we will primarily be discussing CB1 receptors in the realm of sports pharmacy.

Endogenous Cannabinoids

Endogenous cannabinoids are naturally occurring ligands that bind to the receptors of the endocannabinoid system.[2] For example, anadamide (also known as N-arachidonoylethanolamine) is a neurotransmitter that binds to both CB1 and CB2 receptors. Anadamide may play a role in hunger, sleep, and pain modulation. Another well-known endogenous cannabinoid is 2-arachidonoyl glycerol, which is the primary ligand for CB2 receptors. Both of these endogenous cannabinoids are synthesized by the body and work in different ways to modulate various CNS functions, including the processing of pain.

Cannabis Plant

Cannabinoids extracted from plants are known as phytocannabinoids.[2] While there are about 100 cannabinoids that can be isolated from the cannabis plant, the main psychoactive one is *-trans*-19-tetrahydrocannabinol (THC).



Wiley JL, Gourdet CK, Thomas BF. Cannabidiol: Science, Marketing, and Legal Perspectives [Internet]. Research Triangle Park (NC): RTI Press; 2020 Apr. Figure 2, Chemical structures of cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC)

The amount of THC content can vary from 5% (marijuana) to 80% (hashish oil). THC binds to CB1 and CB2 receptors in the same way endogenous anandamide does. Almost all of the pharmacological affects of cannabis such as analgesia, bronchodilation, and muscle relaxation can be attributed to THC. It is also responsible for the psychoactive actions of cannabis.

On the other hand, CBD is considered the non-psychoactive analog of THC. CBD is theorized to have more significant analgesic, anti-inflammatory, anti-convulsant, and anxiolytic affects. It is also proposed to play a role in reducing the likelihood of the psychoactive effects, thus increasing the tolerability and safety of THC. CBD does this by acting as a non-competitive allosteric modulator on the CB1 receptor. While CBD does not have as high a binding affinity for CB1 as THC, it can regulate the perception of pain via other non-cannabinoid GPCR and ion channel targets.

Synthetic Cannabinoids

Briefly worth mentioning are the two synthetic cannabinoids currently on the market, dronabinol and nabilone. Dronabinol is the synthetic form of THC (Marinol), and its oral dosage form is approved for chemotherapy-associated nausea and vomiting. It is also approved for anorexia associated with human immunodeficiency virus. Nabilone is the structural analog of THC (Cesamet), and its oral dosage form is also approved for chemotherapy-associated nausea and vomiting.[2] Their limited use for increasing appetite and weight gain in cancer and HIV patients precludes them from being further discussed in relation to sports pharmacy.

Cannabinoids and Pain

Studies show that cannabinoids can act on multiple pain targets simultaneously.[3] CB1 receptors are found in high concentrations around areas of the brain and spinal cord that process pain. They are also found on primary afferent neurons involved in nociceptive pathways. Studies have shown that stimulation of these receptors can produce antinociception. As mentioned earlier, there is also evidence of crosstalk between the endocannabinoid system and other receptors (e.g., opioid, serotonin). Some studies also propose the analgesic effects of cannabinoids is through anti-inflammatory actions. With all the ways the endocannabinoid system is involved in nociception, the system became a noteworthy target for pain management.

Animal studies have shown that the endocannabinoid system may be a valuable therapeutic target for managing chronic pain.[2] Synthetic or plant-derived cannabinoid receptor agonists or ligands were also effective in managing acute pain in animal models. This efficacy has been replicated in animal models of neuropathic, inflammatory, and cancer pain. Recent findings have also shown that cannabinoids may have a beneficial effect on the emotional and

cognitive aspects of pain as well. This is an important area of research as there are multiple emotional and cognitive factors that influence both the perception and experience of pain in humans. The success of CBD for analgesia in animal models still needs further research to be translated into clinical practice. Most studies in human demonstrate the effective use of CBD for chronic pain in conditions such as neuropathy and fibromyalgia.[4] Randomized placebo-controlled clinical trials should be conducted to elucidate the role CBD can play in the athletic population for acute pain and recovery.

Cannabinoids and Sleep

Another area where CBD can have a positive impact for athletes' recovery is in sleep. A systematic review of randomized controlled trials found that cannabinoids can improve secondary outcomes such as sleep, muscle stiffness, and spasticity.[5] Melatonin is also an endogenous compound produced by the body that can be supplemented to help with sleep. Some patients prefer taking natural therapeutics with better safety profile than sedatives to manage insomnia or trouble sleeping. It could be argued that cannabinoids may also make a suitable sleep aid for patients wanting to take more natural products. Cannabis use has demonstrated success in helping athlete's sleep time and recovery.[6]

Safety and Tolerability of Cannabinoids

It's also important to discuss the safety and tolerability of CBD products. Most studies have found that cannabinoids are well tolerated. The most frequently reported adverse effects are fatigue and dizziness, ranging from mild to moderate severity.[5]

Something else to consider is the relative safety of CBD compared to current pain management medications. The opioid crisis in America continues and it has raised awareness about the challenges for treating opioid use disorder. CBD products have been studied as a potential treatment of opioid use disorder. A study found that administering CBD (400 mg or 800 mg) reduced cue-induced drug-seeking behavior and anxiety, with its effects being maintained for weeks following the administration of CBD. This study also found no serious adverse events in association with CBS administration, with the most frequently reported side effect being fatigue.[7]

Cannabis Prohibition in Sports

The World Anti-Doping Agency (WADA) added cannabis to its list of prohibited substances in 2004. The list bans marijuana and other cannabinoids, including synthetic versions in competition. In 2011, WADA published a paper in *Sports Medicine* citing 3 reasons for its prohibition:[8]

1. Potential to enhance sports performance
2. Risk it poses to athlete's health
3. Violation of spirit of sport

This policy was relaxed in 2013 when WADA increased the threshold level of THC metabolite allowed in urine from 15 ng/mL to 150 ng/mL. This created a marked decrease in the number of athletes failing drug tests, from 9.0% (2012) to 2.4% (2014). The policy was further relaxed in 2019 when WADA made a surprising exception for cannabidiol. The US Anti-Doping Agency (USADA) followed suit and provided athletes with a clear cut "Marijuana FAQ" page for clarification of the changes.[9]

The disqualification of Sha'Carri Richardson from the 2021 Summer Olympics following a positive marijuana test reignited a fierce debate on cannabis use in the athletic world. The World Anti-Doping Agency was even asked to review the status of THC after her case. In September 2022, WADA announced its decision to continue to list cannabis as a prohibited substance citing that it is "against the spirit of sport" and to maintain conscientious alignment with international regulatory laws and policies. The silver lining for athletes who hoped for a change to policy is that WADA also affirmed plans to continue research in this area.[10]

Athletes and Cannabis

Despite its prohibition, the number of athletes who endorse CBD products, use it themselves, support legalization, or even invest in companies producing CBD recovery products is growing rapidly. Sports Health published a study in 2020 found that 23.4% of athletes reported using cannabis. This percentage was higher than anticipated, especially for a study relying on self-reporting where we would normally expected underreporting. For example, another study in Germany using self-reporting found that 0 athletes (N=719) reported cannabis use, but when drug tested 9.8% of urine samples detected THC levels that indicated use within the past 24 hours.[11]

The National Collegiate Athletic Association (NCAA) also conducts a Student-Athlete Drug Use Survey every 4 years since 1985. Their studies have shown a trend of increasing use in the student-athlete population, with significantly higher percentages in students who live in a state where it is legal for recreational or medical use.[12]

Impacts on Performance

Studies have not demonstrated that cannabis has any performance-enhancing effects for athletes.[6] When comparing marijuana users with nonusers, no significant between-group differences were found in cardiovascular function or performance. Studies have also found no changes in aerobic performance or physical work capacity.[11]

Sports Pharmacy does not endorse the use of CBD products, but this highlights that many athletes may already be self-medicating or at least using cannabis recreationally. For this reason, it's important to understand the basics of the endocannabinoid system, as well as the mechanisms and pathways involved in its various pharmacological actions.

Future Implications

More anecdotal evidence exists to support the use of CBD in athletes for recovery than clinical evidence, but this may not be the case in a couple years as this field of research grows. Perceptions of cannabis in sport are evolving and we are poised to be the drug experts on this novel usage of a compound that dates back at least 5,000 years. CBD products may provide some benefits for athletes looking for an alternative medicine for pain management or insomnia. As with any new medication, patients should speak with their doctor or pharmacist to discuss the best recommendations for their unique needs.

Photo credit: Kristal Potter

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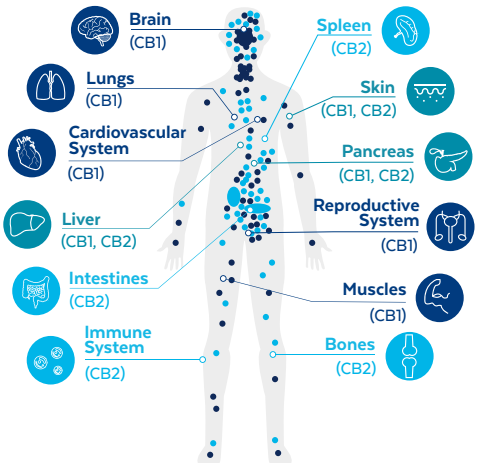
Endocannabinoid system (ECS)

CB1 — Areas Impacted by CB1 Receptors

- Mood
- Memory
- Inflammation
- Stress response
- Blood pressure

CB2 — Areas Impacted by CB2 Receptors

- Inflammation
- Immune system
- Bone and skin health
- Cardiovascular system
- Liver and kidney function



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