

Marijuana: Neurochemistry & Physiology

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At the beginning of the 21st century, most headlines about marijuana contain the words medical marijuana.....hydroponically grown..... legalization..... Cannabis club..... or the name of the latest sports star to admit to using pot while technical journals describe endogenous cannabinoids..... anandamide..... THC..... CB1 receptors.....and nucleus accumbens- words and ideas that explain the changes in brain chemistry when marijuana is smoked.

Tashkin: “The purpose of this apparatus is to measure the manner in which he smokes the joint.”

After years of fierce emotional debate, increasing amounts of objective, non- judgmental research is available although it is made more difficult because of the complexity of the cannabis plant.

Dr. Stella: “The plant contains hundreds of different molecules but the Cannabis sativa, the Cannabis plant is able to synthesize these cannabinoid compounds which is a family of 60 molecules including the very well known compound THC.”

And even though the drug can affect so many physical functions of our body, it is the desire for the mental effects of marijuana that has caused it to be the most used illicit psychoactive drug in the world.

Pete: “When I first started smoking I thought I thought I had found the cure for everything about life that bothered me. I really loved the stuff!”

Jenny: “I just did it to get high. I just now . . . it made me tired and everything. I didn’t really care what I did. I wanted to sleep and eat.

Ryan: “You want to use it all the time. You want to be high, you want to hang out with the kids that are high so you get the same feeling or you are at the same level as them.”

Denise: “Marijuana puts me myself in a joyful, cheery , you know, everything’s funny”

Jerry: “It just mellows me down. I’m like; I’m always antsy you know, restless, moving around. But it just, I can slow down and kind of sit back and relax.”

Darryl Inaba, Pharm.D.: “It’s the mirror that magnifies. It has the ability to suppress your inhibitions; it has the ability to more open up your subconscious and things that you normally would inhibit yourself from doing or looking at, under the influence of marijuana you are more willing to do that.”

BOTANY

Cannabis has many street names: “pot,” “buds,” “herb,” “chronic,” “the kind,”and there are also hundreds of varieties that sound like brand names... . but presently, many botanists

believe there are just three species of *Cannabis* plants.

The most plentiful is *Cannabis sativa*, a tall plant that is grown throughout the world. It can be cultivated to produce large amounts of THC, the chemical that gives smokers the psychic effects they seek or it can be grown, as it has been for thousands of years as hemp, a source of fiber for rope and cloth. Hemp plants contain minimal amounts of THC.

Then there's *Cannabis indica*, a short smelly plant called skunk weed, with high concentrations of THC. It is especially plentiful in the India and the Mideast and lately in the United States. It is usually the source of hashish a highly concentrated form of the drug.

Finally there's *Cannabis ruderalis*, found mostly in Central Asia, but it has no use as a fiber and its psychic effects are minimal.

In an effort to increase the plant's potency, illegal growers of marijuana use the sinsemilla technique. This method prevents the female plants from being pollinated by the male plants thus increasing the concentration of THC. This is surveillance footage of several illegal grows on undeveloped land. Often, the water and fertilizer have to be carried in by hand. In contrast, these plants are being grown in the open by those with medical marijuana cards that allows them to grow a limited number of plants for their own prescribed use.

Nick: "The difference that I've noticed is the stronger potency of marijuana gets you higher with less amount of intake. Like you could take one or two puffs off of a pipe or bong rip and be very well off where a lower grade THC content of marijuana would take, per se, a bowl to three bowls to give you the same feeling."

Whether marijuana is grown illegally or with a permit, the substance can cause a smokers to experience déjà vu, increased awareness, and novelty, as well as a sense of being separated from their environment.

Nida: "You can't be there for people when you're not inside yourself. And when you get loaded you're not inside yourself. You remove, you know, it's like you remove yourself from your self and then you're another person."

Stronger varieties of marijuana can produce giddiness and distortions of time, color, and sound.

ZACK 34: "I have had illusions, not hallucinations of marijuana but just where different colors stand out, things move, different objects just little things that you never think twice about. It's just part of your high I guess."

BRAIN CHEMISTRY

As with other psychoactive drugs, marijuana affects a user because its botanical chemicals mimic neurochemicals that exist naturally in the human body, particularly the brain.

These internal brain chemicals are called endogenous cannabinoids or endocannabinoids. The first one discovered was anandamide followed by 2 arachidonylglycerol designated 2AG.

Dr. Cermak: “There are 10 times the amount of anandamides in our body, in our brain as there are the endorphins. So they’re involved in a huge range of functions most of which they are actually working to modulate, to modify, by either increasing or decreasing the sensitivity of our mind to certain things.”

Anandamides, like all neurotransmitters, help transmit messages from one nerve cell to receptor sites on an adjoining nerve cell.

This combination of electrical and chemical signals within the 100 billion cells that make up the central nervous system, helps the brain communicate with the outside world through its senses and within itself through memories, emotions, and thoughts.

So far, researchers have identified 2 types of receptor sites: the CB1 and CB2 receptors.

The CB1 receptors, are found primarily in the brain and their activation result in the psychoactive effects of marijuana. This is because THC mimics anandamide the endocannabinoid that naturally activates these receptors.

Cermak: “CB2’s are found throughout the rest of the body and they are much more involved with changing the pressure in our eyes, our heart rate, our blood pressure, also they are very involved in the spinal cord and the nervous system in terms of modulating the effect of pain and our sensitivity to pain.”

By understanding the neurochemical and physiological effects of marijuana, it is possible to make better judgments about the possible use of marijuana or refined cannabinoids for medical conditions.

Dr. Stella: “Unfortunately because giving marijuana to these patients will also provide THC, I think what we need to do in the next generation, hopefully sooner, is to be isolating these molecules from the marijuana plants and isolate only the ones that have the medicinal properties.”

Research on the possible medical uses of marijuana for glaucoma, multiple sclerosis, wasting diseases, and other conditions is not the subject of this video. Instead we wish to examine the latest research and information on the use of marijuana as a non-therapeutic drug.

NOVELTY

One part of the brain rich in endocannabinoid receptors is the amygdala, found in the brain’s emotional center

A crucial function of the amygdala is to signal a sense of novelty particularly when one encounters a new situation, idea, or even new surroundings.

Dr. Cermak: “Now if you increase the amount of stimulation, cannabinoid stimulation in the amygdala what you will do is you start creating that zing much more easily so that even mundane things that we have gotten used to and don’t pay attention to anymore will have a sense of freshness and novelty to them. I call it virtual novelty because it is pharmacologically or drug induced.”

As the amygdala is continually bombarded with THC, the CB1 receptors respond with delight.

But soon, particularly with excess use, these cells react to the overstimulation by retracting into the cell membrane and becoming inactive. This process is known as down regulation.

If marijuana is used chronically these receptors are even dismantled and their numbers can be reduced by up to 90%!

Dr. Cermak: “What that means when you get to that state if you stop smoking and just have your normal amount of anandamide in the amygdala but way fewer receptor sites is that even things that are novel truly new may not have that sense. You may not get that zing of novelty attached to something that is really new and so everything becomes very boring.”

Ryan: “School was boring to a point before I started weed but once I started smoking it more and more it just got even more boring. I didn’t want to go, I didn’t want to interact at school. I went there and skipped a lot of classes. Actually I skipped more than half the year.”

Darryl: “So, if you really aren’t interested in working; if you aren’t really interested in studying; if you aren’t interested in a relationship; if you aren’t interested in reading a book, then when you smoke marijuana /your primitive brain takes over and says, forget it, lets not do this.”

Once receptor sites are down regulated, it takes approximately two weeks for them to recover. But for really heavy smokers, it might take as long as 4-6 weeks for the receptors to be restored.

MEMORY

Zack: “I don’t remember the years that I did smoke I remember the most important things but the little details, Yep.”

Dr. Cermak: “One area where you find the highest concentration of cannabinoids in the body is the hippocampus. The hippocampus is shaped like a seahorse. /That part of the brain is very involved in short term memory and being able to boost anything in short term memory up into our long term memory.” /and what we know is that when we flood that with cannabinoid stimulation it actually cuts down on the amount of short term memory. Like a small cup.”

Clarence: “My only thing about short-term memory loss was, even though I’d been working that job for 8, or 10 years, or more at that point, from time to time I’d be doing the job and all of a sudden I’d look up and freeze and not know what to do.”

Dr. Stella: “Maybe our neurons produce endocannabinoids to shut off this memory and shut off this memory because we can not remember everything so what happens when people take a lot of THC is that they shut off their memory. They are mimicking what the normal function of the endocannabinoid is.”

In addition to short –term memory, the impairment of the frontal lobes which control the decision making is clouded . This makes differentiating between what is relevant and random much more difficult.

Clarence: “When I got high I thought I was the smartest person in the world. I knew I had the answer to everything and one day I sat down with the tape recorder and I started rattling off all this

brilliance that I had and the next day when I woke up in the morning and I played it back, it was almost like I wasn't even speaking English."

COORDINATION, VISUAL PERCEPTION, AND DECISIONS MAKING

Dr. Cermak: "A third area of the brain that has very high concentration of cannabinoids naturally is in the basal ganglia and the cerebellum.. /and both of them are very involved in controlling our motor activity./ It relaxes the muscles and it quells the amount of spontaneous activity."

Bill: "I have plenty of friends that smoke marijuana that become quiet, they can't speak, they become immobile. They're total veggies. You know, sitting around and cannot move. I become more active."

Overall marijuana decreases reaction time to situations and slows physical movements which may be vital for some response needs. Other visual effects compound the difficulties.

Darryl Inaba, Pharm.D.: "The ability to follow a moving object is greatly impaired by even small doses of marijuana. We have people who experienced what's called a trailing phenomenon, or seeing movements, not in an orderly, smooth fashion that you normally are accustomed to, ~~but seeing that movement broken up into sort of frames.~~"

These effects coupled with what is called "a temporal spatial disintegration" impairs the ability to carry out complex tasks such as programming a VCR or operating machinery when more is required than just getting from point A to point B.

"Ryan: "I drove a lot on it but I didn't want to drive because I thought, you know people were looking at me or I wouldn't. go to public places because everybody was just staring at you."

As the dosages increase, problems for the marijuana smokers increases.

Tracy: "My wife kept telling me I had a problem but I didn't think I have a problem but I had this truck accident. I smoked a joint a day before I got in this wreck."

REWARD/REINFORCEMENT CENTER

Another portion of the brain that has high levels of endocannabinoids and CB1 receptors is an area called the reward reinforcement pathway.

When it is stimulated normally by rewarding activities such as eating, exercise, or sexual gratification, a cascade effect bathes the core of this system, the nucleus accumbens, in dopamine, causing a feeling of accomplishment or gratification. The dopamine also encourages the individual to repeat the actions that produced this feeling

Marijuana and all other psychoactive drugs of abuse also have this effect on the reward pathway and can raise the amount of dopamine in the nucleus accumbens 10 to 15 times normal.

Denise: "You know, you could be depressed and not feeling your best or whatever and smoke a joint

and feel so much better about everything.”

When the dopamine receptors are overstimulated for a prolonged period of time, the urge to keep using more of the drug overpowers common sense or even the need to feel healthy.

Eric: “I would sit there with a nice little metal pipe and a nice sack of big chronic bud and try to see how much of it I could smoke and basically, I get to the point where I realize I’m laying on the floor. I’ve got the pipe in my hand; I can barely keep my eyes open and trying to light a lighter with a child-proof lighter just doesn’t work, so I pretty much assume that that’s as high as I’m going to get.”

PHYSIOLOGY

HUNGER

The body’s own endocannabinoids regulate appetite by the level of stimulation they cause in a set of CB1 receptors in the hypothalamus. By flooding the receptors with the THC in marijuana, appetite is greatly increased.

Michael: “Like if I’m sitting home and I smoke a joint and I know I got food in my ice box or whatever. Maybe about 10 minutes after I smoke that joint I’m in there fixin’ sandwiches this big you know.”

Research indicates that blocking selective CB1 receptor sites instead of stimulating them, causes a reduction in appetite and significant weight loss.

RESPIRATORY EFFECTS

Dr. Tashkin: “Marijuana smoking if it occurs on a regular basis leads to symptoms of acute and chronic bronchitis. Chronic bronchitis consists of chronic cough for most days for a few months out of the year / and marijuana smoke also depresses the bodies immune defenses against infection and probably increases the frequency of acute infectious respiratory illness.

Bill: “I’m sure I’ve done damage to my lungs. I mean, you can’t put that kind of tar down in your system, heated tar, going constantly into your system daily, for 23 years, and sit here and say there’s nothing wrong, and nothing had happened. Certainly something has happened.”

“This is a scanning electron microscope section of a normal airway lining. We see a lot of cilia, it looks like fields of wheat. This is a marijuana smoker, a lot of cilia are replaced by mucus secreting cells. This is a smoker of marijuana plus tobacco, all the ciliated cells are destroyed. It looks like a moonscape.”

.Tashkin: “Most of the smokers of marijuana also smoked tobacco suggesting some type of additive or synergistic effect between marijuana and tobacco.”

FETAL EFFECTS

Though more research has yet to be done, marijuana does cross the placental barrier between mother and fetus and does circulate in the baby's developing brain.

Nida: "Smoking marijuana during pregnancy, that was the big one.../"

The difficulty with assessing the impact of marijuana use on the developing fetus is that one is never sure if alcohol or other toxic substances were also used. In addition, it can take years for any drug induced changes to become apparent. Often we are only left with anecdotal stories and have to judge for ourselves.

Nida- "It has caused behavioral problems for my children. I think that it has affected their ability to learn and remember. I'm just supposing based on what I deal with today with them. I think those are pretty obvious ones. The behavioral problems and the inability to learn."

Nick: "Um, I think it has kind of put a stop to letting me um, what's the word for it, grow up kind of you know what I mean. I has kind of put a stop to me growing up mentally or physically."

TISSUE DEPENDENCE, TOLERANCE, WITHDRAWAL

The physiological and psychological processes that can lead some marijuana users into more than just casual use are: tissue dependence, tolerance, and withdrawal.

Tissue Dependence

Marijuana saturates the fat cells and remains in the body for an extended period of time, especially in regular or binge users.

Darryl Inaba, Pharm.D.: "Marijuana is a drug that persists in the body. We find it in brain cells actually in chronic smokers up to 6 months after they stopped smoking."

Tolerance

Jerry: "I think I have a very high tolerance. I can, I could smoke people under the table so to speak if I wanted to waste that much pot, but yeah, I think definitely there is a tolerance."

(retransfer) Eric: "Originally when we first got it we could smoke say 2 bong loads and be just totally stoned whereas we'd have to keep continuously smoking just to keep the high going."

Withdrawal

Darryl Inaba, Pharm.D.: "When a person especially these people who feel that marijuana is benign, they've been smoking for 5 years, they stop. They stop 1-2 days, 3 days even a week, they say, Wow, I feel great, marijuana's no problem. I have no withdrawal, it's nothing at all. Then they start up again. They never experience withdrawal. We see that withdrawal symptoms to marijuana are delayed sometimes for several weeks to a month after a person stops."

The withdrawal from marijuana is more drawn out because most of the THC has been retained in the fat cells and only after a period of abstinence will the withdrawal effects appear.

They include:
anger or irritability
aches, pains, chills
changes in appetite
headaches
depression
inability to concentrate
sleep disturbances
and craving for the drug.

Clarence: “ I sweated a lot, I could break into a sweat in the shower, I did break into a sweat in the shower. Focus, I could not focus, I couldn’t really maintain my concentration for about the first month or two. But remember, I was smoking a lot.”

Nida: “I couldn’t go to sleep without pot. I remember when I first got clean I couldn’t sleep. I went for days without sleeping, days.”

Not everyone will experience all of these effects but heavier users often mention craving.

Denise: “I would want it all the time. You know would have to have that joint in the morning in the afternoon, before you go to bed. During the course of the day so I guess it would be kind of a craving; not a craving to the point of crack of anything like that but it’s a craving also”

DRUG DEPENDENCE

Most people who use marijuana will not develop compulsion but for some craving can turn casual use into binge or daily use.

Zack: “My focus became because how I am going to get the money for my goodnight bowl, or my morning bowl, or my 10 minutes after my morning bowl; oh my gosh and that’s what my main outlook on life became.”

Tracy: “The more I smoked the finer marijuana where I was at, the more I wanted that taste. The more taste the more pot I wanted to consume. I’d get up to half ounce, three quarters of an ounce a day and put it in my small body.”

Dr. Inaba: “The main problem we’re dealing with today is the potent form of marijuana is causing a lot more problems than we saw in the 1960’s. I never treated a single marijuana self-admitted addict in the Clinic throughout the 1960’s nor the 1970’s and pretty much through the 1980’s but by the late 1980’s we started seeing people comin’ in, everyone of them on their own volition, on a volunteer basis saying “Help me” I want to stop smoking pot. It is causing me this problem. Causing me to have memory problems. It’s caused me to be too spaced out. Not to function in my work. I can’t complete tasks. It’s causing me to be sick in the morning and cough. I have withdrawal symptoms. I want to stop and I can’t stop. We now have at our program in San Francisco about 100 patients every month who are in treatment specific for marijuana addiction.”

Clarence: “Physical addiction aside you can have an emotionally addiction, it’s just incredible. It is almost, well, without help I couldn’t have stopped.”

Cermak; “ You can diagnosis a person with marijuana dependence without any physical addiction or any withdrawal being part of it. Have they lost control over its use. Are they using it compulsively. Have they begun to harm themselves in ways that they are not willing to acknowledge. Do they continue using it in the face of adverse consequences.

Clarence: “I thought I could control it because when I woke up in the morning I didn’t get high for the first hour or hour and a half. And I figured an hour and a half . . . that proves that I’m not hooked on this stuff because I don’t really need it.”

Dr. Cermak: “I have never seen anyone “Jonesing” in a gutter that needs their marijuana to get way from their physical withdrawal. I think that the really issue with marijuana is much more of its seductive qualities. People like what it does, like the way that it fits into their life; often times they like getting a sense of novelty in the world by puffing on a joint rather than doing the kind of work that is necessary in order to keep exposing themselves to truly novel things.”

SERIOUS PSYCHOLOGICAL EFFECTS

Paranoia

With marijuana there are two ways to look at paranoia. Marijuana is an illegal drug and one can be arrested for using or growing it. That is not being paranoid. The other side is that marijuana over stimulates the fright/flight center in the brain’s limbic system causing some users to be fearful of everyday events.

*Pete: “I’d keep smoking and keep smoking and keep smoking and get paranoid, AND FINALLY I’D HAVE to break off and leave.....CHANGE if you’re not relaxed and having fun, it seems really insane to keep doing it and I did keep doing it for a long time after I started developing fear. I kept thinking that it was going to go **away.**”*

Acute Anxiety Reaction

Darryl Inaba, Pharm.D.: “We’re seeing some severe emotional problems with marijuana. We’re seeing the same type of what we used to call acute anxiety reaction, a bum trip, a freakout./They begin to experience anxiety which then perpetuates or creates more anxiety than what they’re feeling and eventually, they have an acute break. They have a psychotic break. /Something now that medicine is calling a post-hallucinogenic drug perceptual disorder where people who after experiencing this, don’t come all the way back down to reality.”

Self Medication

In terms of mental health, some patients with a thought disorder or a mood disorder try to treat themselves with marijuana.

POLYDRUG USE

Michael: “The majority of people that I know that I hang around with if they ain’t smoking coke,

they smoking weed, or drinking. I'm not saying that they are bad people but that is just how it is."

Amanda: "I just saw everybody around me, including myself was just on drugs. And after smoking pot, pot wouldn't be enough and they would do harder and harder drugs."

Clarence: "Well, I've been in 12 steps for like about now a little over six years and I'm not going to say like 1 and 1 equal 2 but just about everybody I met in 12 steps started out with either marijuana or alcohol."

RECOVERY

Zack- "I was asking myself, Why am I here,, why am I doing I doing this to myself. I need to get out of this and then one day it just; something spoke to me and it was just like, You need to quit, you need to get your life together and get on, you are not even the same person you used to be."

Amanda: " And I believe that pot alters the way you think and feel and since I wanted a chance to think and feel my way and not have anything alter it then I came out and said I am not going to use any more. And I didn't use anymore."

Michael: "Well I'll put it like this. Everybody got their own like to lead.. like my niece and nephew if they did do it then it would be they choice but I would most definitely try to stop them from doing it. I would tell them, look, look at me for example. look. I'm smoking this stuff and it's not getting me nowhere so why would you want to be like this right now."

Peter: "I don't sit in judgment of people wanting to smoke pot. If something is a problem in your life deal with the problem. Deal with what's real What are the consequences? Is something costing you more money than you should be spending? Is it jeopardizing your job? Is it jeopardizing your relationship with your spouse or your lover or your children?"

Breaking the pattern of marijuana dependency can be difficult and might require entering a recovery program, going to counseling, and participating in 12 steps groups.

Clarence: "I started going to meetings and started meeting people. I started getting out and then I found out that all of a sudden I had a choice. Up until that point I could not conceive of the idea of not getting high. I would try it and I would try. I had tried every conceivable way of side stepping it, this that and the other. Anything I could not to and I couldn't conceive of a way I could stop smoking. All of a sudden I had a choice."

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