

Registrazione riunione- _INES Winter School (Blended Intensive Programme)- Principles of toxicokinetics and toxicodynamics applied to drugs of abuse-20240125_170001

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 **Fernando Remião (U.Porto)** 4:43
OK.

Good afternoon, everyone.

Uh, Stefano, I don't know if I can start.

Anyway, I'm going to share my screen with you the PowerPoint.

Please confirm that you are able to see it.

Let's see if I can chat.

Fresh off I tried before and it worked.

Please confirm that you are.

Able to see my PowerPoint.

 **Tiago Alexandre Ferreira Goncalves - tiago.ferreira@studio.unibo.it** 5:28

Yes, we can see it, professor.

 **Fernando Remião (U.Porto)** 5:30

Yes, thank you very much.

Now I'm going to put it in a way that it will be easier to me explain to you.
OK.

So thank you very much to be with us.

I think I'm the 1st and sharing our knowledge about drugs of abuse in this seminar and what I'm going to show you is some concept channel concepts about topical phonetics and toxicodynamics is something that, umm, I think most of your farm of you already know.

But I realize that some of the students are not in this area and can have some difficulties to understand.

So I'm going to share with you some general concepts and also found more specific conflicts and uh. Anyway it's.

I'm also explained to some experiments that can be done and that we did it in our lab and it's a way to share with your son of experiments and some studies that can be done in these areas, specifically in toxicology.



Bárbara Silva si è unito alla riunione

FR

Fernando Remião (U.Porto) 6:57

OK, this PowerPoint and this presentation is prepared by me and also by Barbara.



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Fernando Remião (U.Porto) 7:04

Barbara Silva is a researcher.

She she finished her PhD two or three years ago and catching on.

So since that getting on and some of the results that I'm going to share with you are from are teaching sofa and OK, uh, I'm from University of port, the Faculty of Pharmacy.

So I'm off.

Students are also our master student, so they are also there and some of the things are very, very easy to understand.

But anyway, we can think about what the mean toxic mean, and there is a general concept that is saying that is any substance that can cause severe injury or death at the end as a result of physical can contraction with a living tissue.

Well, in fact, we know and it's just something that we say anytime toxicology that all substances are toxic.

At the doses makes the difference, but anyway, there are some some exceptions to this, but there are not the drugs of abuse.

When we are talking about toxicokinetic, what?

What they're talking about?

Well, in fact.

Umm, we have five this part of flight is important is that I think you can

understand it anyway by the the the words and the scheme, but we can we can think about what happened in her body, what happened to the dryer in our body after absorption and it we can absorb a compound by different ways and all of you actually know that.

Are you OK?

The track, this is Steve, is very prepared way to protect us and in fact this is the main.

Therefore, for the most of the compounds, the Lang is another way to observe.

So we have also a lot of compound that we have served by this way.

It's also more or less protected because we can where can metabolize in the land also, but it's not so efficient as it happens in the label.

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 **Fernando Remião (U.Porto)** 9:40

And what happened with the compound that are served by this way?

They they hire most of the time they are Transformers and metabolized, and there are the metabolites that going to be distributed to the army.

But it's compounds are absorbed by skin or by injection, and they can very easily be distributed in our body without any chemical modification.

And because that there are more toxic or their effect are stronger or are more important because in fact we don't have the opportunity in our body to transform the compounds in something that could have less effect.

OK.

Well, so most of the time the topic of phonetic we we have overall profit that include absorption, distribution, metabolism and the metabolism can happen before distribution, uh or after?

It depends more or less.

How about the pathways by which the compound is absurd and at the end we tried to eliminate compound most of the time by reading, but also by the buyer, and that attends dinner level.

But anyway, the RDM here are something that happens for all compounds and it's very steady phenomena.

We can have also tea.

You can find that in the literature and it can have two different means.

It can mean transport because compounds in order to enter itself, they need to be able to to path along the membrane, and sometimes the only way to do it, they need some transporters, transporters, we call that the fees feel where the compounds enter in cell and phase three, when compounds go out of cell.

Most of the time it is a metabolite of the process of metabolic process that

have two phases, one and two.

Most of them they have two phases is not it doesn't.

Doesn't happen anyway every time, but it's a skin that is very confident, very general.

So the importance is to understand.

Uh, what happened to our body or what happened to compounds of drug abuse in these mechanisms?

So social distribution, metabolism and description and at the end we are going offer to discuss some toxicodynamics.

So out compounds can induce toxicity, which are the main mechanisms.

If you have any question or something that you I was not so clear pleasing to help me, OK we can do that this in a more dynamic way and so it would be easier to me and perhaps to you also.

So for the direct, not only for drugs or five years, but also for for my set for drugs, there are all always, uh, a parameter that you need to be aware we call that bio availability in fact an injection intravenous injection.

We have 100% of their availability.

What is this?

Is it compound that is administrated and it is in the blood?

So if you administrative directly in the blood old compound are in the blood, so we say that it is in the bio availability is 100%.

When we observe when we ingest a compound, well, until you reach the blood, he needs to be observed.

It can happen that intestinal level E it's a we have a lot of ways to modify the compound because we have microbiome that can already transform compound compound needs to be observed, go to the liver.

We are.

We have also the metabolism and only after that you will be in the system in systemic circulation.

So of umm.

Lots of compounds don't doesn't have 100% of bioavailability when they are interested, so they are less than 100% and this is an important because for the drug of abuse, yeah, we have a process that is very effective in transforming that in transform the compounds and to reduce the bioavailability of them.



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Fernando Remião (U.Porto) 14:52

OK.

We when we when we think about hearing why people doesn't take doesn't initiative in because in fact the airline is destroyed in this process. So the bioavailability of heroin by orange action is very low.



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FR

Fernando Remião (U.Porto) 15:09

So he's not effective, and because that people inject directly in the blood. OK.

So when you think about geography, because we need to be to think about the bioavailability of the compounds by the different pathways that they can be observed, observed.

So.

So this is important for drugs of abuse and this explain why the people are different ways to contact with these terms of of this drugs.

So also another phenomenon is not only the absorption, also the distribution distribution of compounds.

It depends a lot of characters of the organs, so the division to the brain is completely different as the tribulation to the kidney or to the Lang.

OK, our brain is very well protected for the most of you already know that we have a blood brain barrier that is very impermeable.

So the compounds need to be very lipophilic and also need to be not as substrate of our transporters, the face free that I'll talk to you before.

So this transporters that we moved the compounds from the brain and this limits the effect of the compounds.

In fact, lot of pharmaceutical drugs doesn't are able to cross our BBB or blood brain barrier and because that they are not effective.

One example, antibiotics, antibiotics, are not effective at the vine because they cannot cross the BBB, and because that is so dangerous when we have an infection in brain because we are not able to use any antibiotic to combat this, do you think faction well when you are talking about kidneys opposite kidney are very permeable so compounds can wish.

The key thing very easily so we can easily have an effect of giving but.

But when we are talking about drugs of abuse, of course we want all the people want that they have an effect in the brain.

So the compounds need to have some chemical characteristics in order to achieve new neurons, and because that the compounds need to have some, uh, chemical and physical characteristics that we know that they need to be lipophilic.

So they need to be more soluble.

Lipid size.

They cannot be very, very big.

They they need to be small miracles in order to be easily to cross the BBB and in in fact if they are highly bound to plasma proteins, they have also difficulties to to cross the BBB because the proteins are not crossing and I will removing the free compound that can cross so.

What I would like to share with you is this.

We need to be aware if the way by which the compound is observed, can

this can make the destruction of the compound and this will be crucial to determine the bio availability after the compound being in the blood and when we are talking about drugs of abuse, we need to be you see the characteristic chemical physical characteristics of the compound in order to shift compound her hable to cross the DVD in order to achieve our brain and to have an effect.

Well, as I said before, our level is a specialized in metabolized compound. So it's a way to transform the compounds.

Usually it compounds are perfect in order to be observed and so deliver most of the time.

What you did it does is to transform a compound as it is lipophilic in a compound that is water soluble.

So it profilic in order to be eliminated in urine.

So it's something that is a general concept.

It doesn't happen always, but in a general concept it's something that happens for all compounds.

They are transformed from lipophilic to either philic in process most of the time the compounds are detoxified so they they became in inactive in a biological way.

Uh, it doesn't happen always.

Of course, that's most of the time is the aim of our live liver is to transform the compound.

That is not active.

There are logical active and it will be easier to eliminate and because that, as I said before, you need one and offered.

The example is very well very easily transform it in this inactive compounds that can be eliminated without any effect.

And because that we cannot receive all, we cannot commiserate everything by oral ingestion in a way to obtain an effect.

Description and most of the time compounds they are eliminated by by the urine.

In fact, our our kidneys are very, very effective in doing that.

And if you compounds are very big and sometimes we do that because in the metabolisms we increase the the weight of the compounds by conservation process of chemical delights like a stamp, a chemical stamp, we put the compound bound to our channel biotic to our driver of abuse and it becomes speaker.

Uh dolphin, more it prophetic and we try to eliminate by you.

But if they are very big in the river, we don't eliminate to the blood in order to go to the kidney.

But in laminate to the bill and by the bill, it's going to do at the end and to the instance will eliminate it.

It's compound, of course.

Is volatile.

It can be eliminated by the link.

So what kind of effects can happen through the compound E uh, we can

have a local effect.

Yeah, inside of a partial cough.

But for drugs after because we are more concerned with systemic effects. So something that happened with different kind of organs were compound can achieve, especially in the buying.

We can have a acute toxicity.

It's very dangerous when we have overdose.

It's an example, so it's something that happens in the next hours after ingestion and we can have a chronic toxicity which also happens with drugs of hippies and along with the time, as most of you already know.

Well, now I'm going to talk to NPS.

With what kind of new SQL gives substances that can talk about?

Well, most of the time they can be thinking about free big types of compounds are more like and some of them are very well related with uh. OK, OK.

With amphetamine side in the middle and.

I suppose you know what it is.

And this kind of tablets are very useful by the young people in, in parties and in in the way that they think that they're not very, very dangerous.

But most of the time they don't know very much what they are taking. OK.

And also we have compound that traumatize cannabinoids.

That cannabis so it can have is in no what it is and we have the synthetic cannabinoids.

They are going to talk.

We are going to talk about this and in fact they are quite similar in a way.

They try to act in the same receptors or biological receptors to these compounds and their, but they are stronger in this effects and also some of compounds are trying to minimize talking.

Well, these three big groups, OK, compounds that tried many ties, cannabinoids affect amines and cocaine.

They are coining new pepper active substances.

In fact, they're not same of this compound that we already know, because they have much stronger and much more potent in this effect.

And they also have some strange effects that you are not expecting for the other drugs.

It's only they are in the market.

Uh, they are calling legal highs.

They were legal some years ago.

In fact, he had in both not only in Portugal, some shops that were OK.

The people who went there and they could buy this kind of compounds, but we started to have a big problem with them with this and yeah, the covenant private.

Now they are not legal at all.

But anyway, the people can buy it.

At St level, dealers in the Internet and head shops anyway, and they

usually are selling not for human consumption.

But we know that if not the objective that they use it, but you know consumption.

Uh, OK, I I have.

Uh, of course.

Much more slides, but I'd like to know if you understood what I was saying in the office.

You have any doubts about this?

What are you?

I was trying to explain to you.

Everything OK?

I will remove this.

OK.

Sorry.

Therefore, expand that any doubt, some some of you would like to ask something.

No, no question, I'm so clear.

OK.

And what I'm going to show you now is report from 2052.

And different part is showing the number of substances monitoring by the U early warning system and it it belongs to European Monitoring Centre for drugs and Drugs of Addiction and we can see the number of NPS for each kind of compounds.

So we have cannabinoids and you can see that you had more than 200 different kinds of synthetic cannabinoids.

Why not have a big group?

Is catching on the synthetic catching on.

So when at 6:52 and the first group that you have is similar filaments, so they are the freebie girl groups in this kind of in TS.

OK.

We have also some other substance.

It's not not so big in number of them, but anyway they are also concerned.

People think that student that work with this because these things there are a lot of pharmaceutical drugs that are things that there's some difference with that tip.

The means styles of some compounds that have this kind of effects.

Opioids.

Uh, OK, you have one that is now is very popular and very, very big concern.

Fentanyl.

OK, it's a very important component.

Can heat easily with very small who pawned them so big?

Blonde.

Gets very different, very difficult to to those write to those in order to have doesn't have a fatal effect.

Well, but we are going to talk about this three groups, OK?

And I'm going to show you some main concepts and ideas about them and also some studies that we did it in our lives in order that you can understand what kind of effect this compound can have and how we can study.

So I'm going to start it with synthetic cathinone and think that getting hands are compounds that are trying to minimize when compound that is catching on.

So they're not, they are different of catching on, they they they change the molecule in order to have a different kind of effect.

But anyway, the catching on came from cat.

Cat is a plant that you have some figures here and it's very easy sharing that people sharing this plant, especially in this countries.

So it's in Africa and on the top part of Africa, Ethiopia student, Kenya, Somalia, Yemen.

So these countries is very is used to to sharing these these plants and is a strange thing because OK, they are always sharing and we know that to the effect is a stimulant.

So it's like taking caffeine.

So for them showing this and showing one other military grams, 100 grams of this, if it is, it's more or less like this taking a coffee.

OK.

But anyway.

Is something that.

Sometimes it's the people takes a lot.

They can have a bigger effect and we have here some of the fact that we can feel sorry for you, increase your self esteem, increased ability to concentrate the creation of ideas and communications.

So as I said, it's more or less for them.

Like caffeine? No.

However, uh, what happened in the the war is we are changing this catching on in order to have a more potent compound and not only more potent but the the problem of getting on is it it is it decorated very easily.

OK, the plant degradate very, very easily to getting on.

So they try to export the plant and it's not easy because after some hours the plant we came not useful for the fact that they want.

So the syntactical cathinone they change the cathinone in order to have a compound that they can, uh, produce and sell that for the effects piccoli.

Effects that the people want we have here the general structure of this compounds the chemical structure and they have four classes of time.

Well, it's interesting to know that because and when you are going to deal with this, even at legal way, we are going to see that most of the time this kind of change that we can see are not only related with a different kind of effect, but it's related with fact if they modify the compound we are talking about the compound that can be illegal to sell because it doesn't exist in the least soft compounds that are are forbidden.

OK.

But but we have four big groups, these ones, as you can see where we have some changes in this substitutes and we changed by initial group with a chemical simple group that have to to make some difference and miracles from theoretical drives.

It's fine.

Another group have this methylenedioxy group is we have two oxygens and also caravan here and this is a kind of compounds methydone. I put you on at you on that is a group of compounds with very similar effects.

We have to another group that is uh.

It has a parallel in chemical group.

This hand with 1234 carbons and cyclic carbons and so this is a paladin group and we have a mix.

So they have the methylenedioxy group and also the philogene and namely PV is one example of getting on that I'm going to show you results MDP.

So there are some of them.

So all of them are synthetic getting nodes, but they are organizing different kind of structures.

And as I told you, sometimes they have a little bit different effects and the potential difference, but the the important or in having so different compounds and the producer of soti different compounds, it is a way that the the dealers try to produce compounds that are not forbidden because they didn't exist in the list of the following compounds.

There are cell like this.

Uh.

Very.

A.

A mutant way and people are by that.

And they don't know very well what is inside of this kind of packet.

But anyway, they know that the kind of effect that they have are more or less the same, and this is like a psychoactive because a psychostimulant they they became like amphetamine effect.

They became more easily to have fun when they take this anyway.

The big issue with this compound test is we cannot predict very well the side effects and toxicity, and this is a concern because in 10 people, perhaps eight or nine people doesn't have a bad effect.

But one or two can have a very toxic effect and they can have also that life in danger.

And because that these compounds usually are forbidden in most of the countries, but the legislation is not the same for all of them and the people still easily obtain these here via the Internet, and each time the substance we came legal controller, new structural modification nodes are introduced into legal market and because that we have so many compounds as I've explained before.

All these compounds are interactive, as I told you.

We tried.

They tried to ingest compounds, you know, way that compounds can achieve our brain without a metabolizing process.

So some of them can be ingested because in fact the yes, our our liver are not able to transform very quickly the compound in a way that the fact doesn't happen or they use the nasal insufflation that is a way that it compounds can more easily achieve the brain.

The doses consuming the very, very depending on deliberative in question, depending on its potency according to hotel.

Certainly stration.

So it depends on and then yeah.

Well, now I'm going to talk a bit a a little bit about something that it's very dark.

It's main force of toxicology.

So the metabolism, OK, uh, I I'm not going to explain in the telling.

This is not our hand.

And what I want to know what what I'd like to show you.

Yeah.

And I like that you could know that is the we.

We always have a different ways to metabolize compounds, so we don't have only one way and this makes a difference about the facts because we we are not so, so equal between us in a way that we metabolize compounds.

The metabolization depends of many, many characteristics of the persons. Is the nutrition of the persons if the person have or not have a liver disease.

If they are either dated so there are a lot of factors that can modify the metabolization of the compounds, and if it if you are not able to metabolize for one of the reasons we are going to have a problem because company can achieve higher consideration without the detoxification process.

Well, some of the chemical with the reaction that happens in the metabolization, uh.

I'm sorry for the student that doesn't understand this chemical structure, but anyway, what can I say is with please the compounds is one thing that we do in metabolization we clean and so we remove parts of the of the the structure.

Look here we do an end mutilation.

So the and the mutilation.

So we we move this material from this this nitrogen atom.

So you can see that here it remove it.

It's away.

So we are cleaning compounds.

It's a way to to to make.

Uh metabolization another way that it's very, very common is a process we called ethoxylation.

Well, what happens in?

In the documentation we put it through fill either way, to put something that hydrophilic you don't feel you're feeling OK, so here we put 8 roxhill here in this carbon.

So as I told before, our river tried to increase the literal philic.

Uh, Connectwise called compound.

So we do it oscillation.

It's a way of oxidation.

Here we have an increase of this oxidation.

You have 1/2 it here, but anyway it's a way of oxidation, so it's still very, very common to our component.

We we can cleave, we can also oxidize, and all of these reactions, we call that phase one reactions.

OK, so the important thing that you know is that what we try to do and now at least to these drugs of abuse and just getting on is try to put this compounds in a way that data 35, the desktop 5 phone in a way that can they harm or easily aminated because they are more it prophetic and in a way that they decrease the effect if this is the overall uh prophets.

We are going to see after that sometimes the thing I've not so so clear and we can have not the process of detoxification, but also a process of bioactivation.

So the metabolite is more toxic than the than the parent compound.

All compounds induce the catamount in this and in fact.

OK.

Well, they they act as the nervous system.

As I told you before and in order to induce any fat in our nervous system, usually they they are related with neurotransmission neurotransmitters.

What?

What it is is compounds that are uh, E liberated by Juan Europe and this compounds go to this area.

The synap are you and going to act in the another neuron passing that around.

So we are passing at neuron a passionate in neuron and we have family setters here and they are neurotransmitters.

We can see that they are delivered from here to here, where in synaptic they can achieve the receptors where they are going to stimulate neuron after.

Well, this is a very complicated process.

I'm not going to explain that in very detailed, but the the the the issue that most of the drivers abuse.

So work are a teaser real because when we we you have these neurotransmitters here we need to remove that.

OK, they have an effect and after that we need to remove and we have different ways to remove the neurotransmitters from these area.

I suppose you are seeing my laser.

OK, wow.

OK.

So neurotransmitters are here and we need to be.

Uh, sure that there is no transmitter are removed after the effect, and one way to remove it it the uptake of the neurotransmitters for to the presynaptic neurons.

So we can see we have here transported that taking this and compounds are removed from the synaptic vendor.

Well, well, well.

These neurotransmitters.

This blue.

Uh, dots.

Uh, in the presence of synthetic cathinones are not remove it and we call that the cooking like dirt.

Because monoamine, we're taking a bitter and inhibition of this kind of they cannot remove the dopamine and northern online from the final finatic they're not uptake it.



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Fernando Remião (U.Porto) 44:04

So we still have a very high level of these compounds and they can continue to stimulate the parsing attic neuron.

So we increase the fact of neurotransmitters and this is a way by which cocaine act, OK, we have a overstimulation of some of certain parts of our brain.

The amphetamine not only.

A block the the uptake of the compound to the.

Presynaptic neuron, but also we need more, you know transmitters.

So it's something that it happened in two mechanisms blocks the remote, the remotion of the neurotransmitter from sender schematic and they increase the levels of this neurotransmitter.

So we have higher effect.

So what happens with this compound?

We, uh, increase the stimulation of of our neurons, so we are more activated at near and part of our brand.

The big issue is that desktop and in the same way in all the brain it it depends where it compounds can achieve and this is made all the difference because they are part of our brain that if they achieve, they repress us.

So we go down because these neuron are going to depress us, but other parts they are increased are overstimulation us and the way that compounds can go around a long our brain they can achieve different part of our brain and they can have different kind of effects.

And if for most of us, the way our the part of our brain that compound can achieve are quite similar for some of us, they are not the same.

And because that is the fact that these people have are different, and this is the way that you can understand why the people doesn't have all the same effect, because the the toxic coffee netic the the distribution of compound in the brain are not similar for old people, OK.

OK, go now.

I'm going inside of the the cells and explain what can happen in the toxic E pathways and we have here a set of examines OK cathinones and they can have an effect, a toxic effect at mitochondria.

Mitochondria is organelle that we have is very important to produce energy, ATP and even the people that are not in this area know that the TPP's energy.

So we need an energy from mitochondria and these they are this function. Of course, we need to quiz.

Never soft energy.

And this is something that is not a good, very good effect for ourselves.

We can increase also stress activity and effective stress.

OK.

So we produce, we generate more reactive oxygen species and we have an effect in very important effect in our antioxidants.

One of them is very important, so the time it's depleted or oxidated and we can use.

Also apoptosis, in a way it's a way of soldiers controlled cell death.

Usually you can see that by aiming increase of spaces and in fact we have.

I'm going to show you some results with this and also.

We can also have out of fashion, so it's a way that the cells try to clean some of our organelles.

So if you have an organelle inside of cells, it's not working well, it's damage.

We try to clean it and out of it is also different thing.

Important mechanism of cell regulation.

The physical stimuli and there are no effects of this.

Synthetic genomes are white, female or to other NPS, so they're not so different they they have neurological psychiatric effects, agitation, safety, cognitive disorder, delusions, OK.

Kind of a splash expanding Potention personality player gas engine on the back of them.

Now pain.

No, the images increase the transferases.

OK.

Final or in the kidney increase serum getting in so damage of kidney.

Emmett Logic or medkova?

OK, we have some and we all even.

If it's a very important thing because it's damaged not only the Moscow but also damage the kidney, because at the end it's kidney that is damaged and we also this is the patients, something that happened a lot

with amphetamines.

The people, the laugh, a lot of water and they need to take water and sometimes they take so much water they they have problem with that. At the end we can have a multi organ failure and death.

Summary Thoughts that you have in our lives, so I'm not going to be in detail, but I'm going to show you what kind of studies we can do so we can we can work.

So we have some here, some experiment with time and write better flights.

So we isolate the cells from the level of right and we expose the cells to different kind of getting ones.

And this is one of getting out.

We exposed the DMC uh from the first group to dial.

I show you and what happened is that we use not only the exposition to this getting on, but also to any better of the metabolites.

So this is our the enzymes that do the the reaction to metabolites to degradate this checking on and what is so is that when we inhibit the metabolism we did we did squeeze the toxic the toxicity of compound.

If we decrease toxicity of compound, we see that the metabolism are creating compounds more toxic, so we have a bioactivation look.

This is an important result because what they are saying is that our live liver take the compound and transform the compound to something that is more dangerous down the parent compound.

This happened for this one for the next one. It was the opposite.

So the metabolism is protecting us.

So now we can understand why it happened.

Different kind of effects because you go to a party and we we take one of this compound and nothing happened to you.

But in the other day, you'll go there and you take another catching on and you think the fact is the same and is not in one way your liver.

It is the perfect time.

The compound in the other way delivery bioactivation the compound.

Another effect that you have here are we studied is the cell death OK?

Apoptosis.

And you can see that well, you can see the compounds these two, two cathinones and you can easily see by this that quiz of caspases.

I told you before, caspases are very important mediators to induce apoptosis.

It's a way of cell death and important way.

Out there, another example of studies that we did, it is to to to measure, to evaluate the oxidative stress we have here results related to production of and reactive species.

So this reactive species you can see that when you're increasing the concentration of these cathinones and like this is amphetamine and MDMA, one type of amphetamine exist.



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ha lasciato la riunione



Fernando Remião (U.Porto) 53:05

But might you know one endpoint you are increasing the labels of reactive oxygen species.

So I'm pleasing this test, the oxidative stress, uh and in the opposite way you are reducing the level of good audience, something that's protecting or or a body is important way to reduce successive stresses to have a higher level, soft reducing good that I am and not only is reduced but also it is oxidized.

So what?

I think I can show you when we did with office that these compounds have a fact that we know that this permission and bad effect that inside of self and we are talking about it but outside.

So these compounds have bad effect at our level.



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Fernando Remião (U.Porto) 53:57

Now we have fell from neural neural neural cell lines.

So there are there are cells from neurons from the brain, and the effects also oxidative stress induction.

We can see from different kind of technology that we have here, OK.

And what can you see happening?

Quiz.

Not so big, but we have an increase of reactive oxygen species and you have a reduction of the level of good time.

So we have a reduction of level of our protective compounds.

Uh, So what?

We saw at the liver level with a thing also at the brain level.

Other study that we did it and it was Barbara that it this kind of study doing PhD we tried to understand what happened for an effect that's important effect phenomena that happened in chemical if we call in antiemetic effect.

Well, I'm going to try to spend that, you know, while this is not so much complicated, but these two compounds seem seems very similar.

It's like our hands.

OK, they are very similar but they are opposite one to the other.

In fact, what we can do in the with our left hand is not saying that we can do in our with our wife and and all of you, all of you know that well, it happened.

Same with this chemical compound.

They they are not equal.

They are like our hands.

So in our body, they don't have the same fact.

They seem equal.

They have the same name that only a little difference.

Look, we have here pentadrone at one of them and we have plus and minus.

In fact, if like left and right, OK, and you can see that the effects are different from the left to the right.

So when we are talking about this kind of trash, we are dealing not only with different kinds of compounds, but we are dealing also with compounds that they seem to be equal but they are not equal most of the time they are 50/50% but sometimes we cannot.

We can have only one of them.

We can have only the left hand or the right hand, and Barbara tried to understand if the effects are different, sort of both.

We call that enantioselectivity.

This is an important issue for us from a theoretical drug, so we know that Sam from a theoretical drug only let's hand works.

So we need to take the left hand and sometimes only the left hand works on the right and have a toxic effect.

So we did this kind of studies with this drug abuse.

We have the same studies.

This is related to transport, but that's OK.

The idea is to show you that and the.

We've made studies also with the with the intestinal level cells, where we also observe in terms of selectivity, OK.

And we did studies concerning the metabolism of this compound, where we saw also in terms of like the studies were done in 3D about the facts.

So E it was fairly satisfied.

This is a model of our more developed model to make studies.

OK, so before going to the synthetic cannabinoids, I would like to ask you if you have any question concerning this part.

If I was too complicated.

Too much complicated.

Still there.

OK, OK.

So I'm going to continue.

Synthetic cannabinoids.

So synthetic cannabinoids, our components are trying to simulate cannabis, but they are not the same well, they are smoked, they can see here some packets with the with the compounds and usually they are smoked which leads to a rapid absorption by all valley.

So they can achieve very easily the brain and alphanan Sheffeld tea?

Not very common, which is popular friend.

Buying consistent, consistent absorption like the problem that I explained

before so they are markets as incense often label others not intended for human consumption, but it is not a.

It's not the fact.

So as I show you before, we have a lot of time.

Can we know it's in that can we notes in the market more than 200 at this time and here we have structures.

OK, I'm not going to explain this to you anyway.

We have here the feet of cannabinoids and one of them is that eight or cannabinol, and if most famous of that because it's the compound that is present, the main compound present in cannabis.

So when people smoke cannabis, they are having the effect of this cannabinoid and uh, amazing.

We have fam and open every night.

What I'm trying to tell you is that we have cannot cannot be knowledge in our body.

It's something that we have and they are important mediators.

You know our system nervous system and they have a physiological effect.

Uh, two of them are here, described, and then the meeting is one of the main more important of them.

So at the end of gonna be nice and there are a lot of synthetic.

Can be nice.

Yeah, you have here.

Some of these symbols of time OK.

So when when you are talking about this, we can think though we have we know about it endocannabinoids they have an effect.

We can take it from the plants or cannabis and we take you taking the take either gonna be null and.



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Fernando Remião (U.Porto) 1:01:16

The dealers I produce a lot of synthetic ones in order to use that.

The substitute the feet of Anarita gonna be notes and to stimulate the same receptors that our endocannabinoid system light but in a more potent way.

So they are highly prophetic.

So because it is an important because they need to be lipophilic to to to be distributed to the our brain and they suffer metabolism, phase one and phase two and they are metabolites in neutrophilic compounds and most of them are configured.

So fight and it's time that we put in the compound in order to take it very little of philic primate in the evening.

OK.

Always happens.

Well, these compounds work in a different way, and in fact they they they are acting.

They are acting in in a way they they reduce the liberation of neurotransmitters.

It's a.

It's a strange thing because it's the opposite of getting on, so the getting owns are increasing the levels of neurotransmitters in synaptic vendor.

The cannabinoids reduce it and reduce it.

Why?

Because they activate these receptors that are in the presynaptic terminal, they decrease the chemical stability of the membrane.

I'm not going to explain that that are stopping this signal is stopping the liberation of the neurotransmitters and so we have less activation of the postsynaptic uh receptors and we call that the receptors of cannabis gonna be now it's.



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FR

Fernando Remião (U.Porto) 1:03:27

So there are five, one and CB2.

They're more important, except that that we know that in effect, so this effect to synthetic cannabinoids are not activating our brain there.

Reducing these activation.

OK, you know, another scheme that is showing the same.

OK, that anyway as you can see, uh, the facts are sequel, so they they they try to modulate but at the end we have a slowdown of our brain.

So what happened to people that detectives, they they have a relection so because they are not selective at the fella, so they are more they are.

If you are strategy, we can less stressed call and you can divine a bit because your brain is more able to be permeable to everything.

OK, in sometimes it happen.

You fornica it's opposite.

If you need to understand that in the same way that I explained you before, these compounds go to the brain and they go to different part of the brain.

They don't doesn't go to the same way in in all time that we take the drug and it depends of the people.

And if you go to some part of the our brain, they slow down our inhibition.

If if they slow down our inhibition, we became more echoic, it might more or less like alcohol.

Hopeful is ethanol is going slow down our inhibition system, so it's slow down inhibition will be more euphoric.

OK, it takes care and the best.

OK.

But in fact that the pricing process so, but it's depressing our inhibition.

We have some studies.

I'm not going to complicate it because the time is going very fast.
We do the same study that we did before.
Moralize we have 3 examples here of synthetic cannabinoids, OK, and what I'm going to show you is an effect at my documents.
OK, my phone is a very special organ.
Now that we have it, it's like another Organism.
In fact, it was another Organism that was taken by.
Itself, but it has also a potential the membrane.
It's very important for their effect and we study these potential membrane with this kind of technical path.
But what we realize is that the membrane became less, uh thoughts or more chars, and for these compounds they are more sharks and usually we have.
When you have our mitochondria with membrane more charges and they produce more ATP, OK?
And this is what we saw.
So we have more energy and this is the study of Swan.
John Piero, one of research here.
Have a process stating that I was talking with him yesterday.
They have a lot of more results that I'm not going to explain to you, but what I'm going to what I'd like to share with you is this kind of a little bit unexpected because most most of time to talk city that we observe is by decreasing the levels of the 80P of the energy that the synthetic technologies, they increase this energy.
But it doesn't mean that it's a good thing because we are producing more energy, but this energy can have bad consequences, and in fact, we observed some of these bad consequences.
Uh, one of them is that we have an increase of tax.
OK, Caspase 3 activity.
Death by apoptosis and apoptosis need energy to to be effective, so perhaps this energy is used to himself.
Well, we have here another study, OK.
The mitochondria?
Another way for another kind of compounds, another kind of cells.
But anyway, the idea that I explained before is already explained it.
OK.
Last group last group that I would like to tell you.
So talk to you.
I talking so you about synthetic cathinones.
After that, the synthetic can be nice.
Now the last one is the synthetic formula means the synthetic millotii means is the third group.
They are sold as legal alternative to LSF and they can.
They can be ingested in tablets or fooling 1 ministration of paper set.
Put paper like a stamp.
OK, there are these kind of group.

We have more than 100 compounds.

What's the problem with you two?

And this compounds, usually they are divided in two families.

They are new if group we call fenil hetero.

This group we call hatil, we call there are two carbons, amines.

This is group I mean.

So Neil Ethylamine is different part, Neil, Ethyl amine.

OK.

But they can have some difference.

They can have some carbons that we put some.

Uh.

Substituents here and we call that to see family.

And we have Ambrosio family because they have this kind of group, we call that N bomb.

So the two families are these ones the two see and M bound to see because they have two carbons here.

OK.

But anyway.

Uh, you are going to see that this group are more potent and create more problems.

Fast absorption distribution for all the organs.

They also serve for phase one and phase two metabolites and they are eliminated mainly by you.

Where they they work, they work in this kind of receptors.

Silly tuning for receptors well.

They increase they permanent get interaction with FT.

They increase the level of compounds here that can act in this certain receptor.

Certain receptors are usually think that's compounds that are good for our mood.

OK.

When we are depressed, we try to use compounds.

I think quiz level of new transmitters that are more active to activate these receptors.

So increase level of certainty.

So the synthetic thing, nothing, I mean, increase our mood that are trying to to have the same effects.

OK, so they are stimulant and alcinoe genic substance because it depends part of the brain that they cannot achieve.

It's like the other compounds that I talk to you in.

In fact, I would like to emphasize this, if not only the compounds is the capacity of the compounds to enter the brain and to achieve the different part of our brain.

OK.

And it depends a lot of things, and because that we can have different kind of effects, we can have the good effects of related to this, but we can

have a lot of bad effects like aggressive and erratic behavior, anxiety, agitation, convulsion, seizure, the Lucia, nations, paranoia, dissolutions, because psychosis.

Sorry so this can happen because the compounds can achieve part of our brain that we're not supported to achieve, but for some reason it happened.

It's a toxicokinetic effect.

Well, they can also have problems in the other organs that are talking about kind of a squad from anarita gathering all them similar to the to the other component I talk to you before at the end we have multi organ failure and death.

OK Fam, Sam example of study that we did it.

With this kind of compounds, I have a PhD student ever that is finalizing her PhD and.

Well, we have some examples here.

Look to see to see compounds we have different ones.

This is N and this is B and we have the similar compounds with with the group the M bomb OK like I told you before, we have A to see and the N bomb family then bomb it's same compound but we put this growth and what she saw and this is unpublished results yet no it's fine.

It's already there.

OK, we saw that when we have the N bomb, we increase the toxicity.

So this is a parameter to see if the cells are there for now and you can see for the same concentrations the test increase it so so the N bomb seems to be more content and this toxicity is mediated by uh metabolism.

So this is an enzyme because when we inhibit we increase the toxicity.

Yeah, yeah, I have a another compounds and sometimes we have a detoxification.

Depends if we inhibit the movie or no, and this is an important issue because that I told you before the compounds have a different effect.

After the liver metabolism and we cannot expect that when you are taking the compounds and but is that they don't, it doesn't work in the similar way all times.

OK here this is studio certain cell phones from the brain.

And once again, you are going to see when one effect that mitochondria so they can, they can also be active in toxic effect that the mitochondria.

So all of them happen at cellular level in a similar way.

OK.

Uh, we have also an effect of oxidative stress.

Well, I I was talking before about mutation is important to protect ourselves and you can see that we have antiques of levels of rotation for all of them.

Are increasing toxicity of of the compounds and one one more and we can see that the presence of this group and bomb increase the toxicity of compounds.

Similar similar effects now at ETP level, so it's energetic level.

So we can see that all of them reduce the TPP labels and one more we can see that the dependence of NBOMe group increase the toxicity.

So in conclusion, what I'd like to show you he's he's toxic offnet properties and mechanism of toxicity and also to show you that in in fact we can have an expected results because compounds doesn't act.

Ohtar didn't have the same topical phonetic pathway always, and the way that they can act at the brain they it is.

It depends a lot of the capacity of the compound that shift.

The different part of the brands we made a lot of studies in different kind of self primary part of sites, neuronal cell, online intestinal cell line, 50 episodes, renal cells, neuroblastoma and we can have fun but very different studies, cytotoxicity, mitochondria, ATP, hective, oxygens productions with the time production or oxidation caspase activity that it related the pop.

Those is metabolic activities like this enzyme that I talked to you, the permeability that is important to the compound achieve or frame.

And with that, OK, I like to thank you for your attention.

And of course I'm able to answer your questions.

That was.

Any question?

I suppose it can also make by my first if you're the fire.

No questions.

Pirates interrupt sharing.

After that, I'm going to share with you the presentation and we can deal with this after also in our meeting that will be in Verona in April and we can discuss more detail some of these effects and perhaps I can represent you also some more results of our students and if you would be interested in some this kind of effects we can discuss in more detail.

OK, if you don't have any any questions, thank you.

To be with us and OK.

See you next seminar and have a good good day. Bye.



Sepideh Moeini - sepideh.moeini@studio.unibo.it 1:19:11

Thank you, professor. Bye.



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