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"There has been no interest in remedying addiction as a disease on the part of the pharmaceutical industry or health systems"

Fernando Rodríguez de Fonseca (IBIMA Institute - Regional University Hospital of Malaga) gave a seminar at the UAB Institut de Neurociències (INC) entitled "*Oleoylethanolamide as a modulator of drug abuse actions: applications in alcoholism therapeutics*". In this interview he talks about addiction as a disease, its important but undervalued social impact and possible treatments, as well as the lack of interest in remedying it on the part of the competent authorities.

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European Monitoring Centre for Drugs and Drug Dependence.

You run the Neuropsychopharmacology research group at the Institute of Biomedical Research in Malaga. What does this group do?
Our interest is basically the study of the biological basis of motivated behaviour. We understand motivation as anything that guides behaviour toward the purpose of recovering an individual's normality. There are many disorders, in the psychiatric sphere and also in the metabolic one, where there is a maladjustment and this motivated behaviour leads to a disease state. For example, excess fat intake or excessive alcohol consumption. The same can happens with an excessive defensive behaviour or a protective one, which can lead to symptoms of anxiety or depression.

We have always used a translational approach looking for animal models in which to mimic what occurs in humans and then trying to determine if what we found in the animal model is reproducible in humans, mainly with a view to developing new therapeutic strategies. In recent years we have changed our approach because the jump between species has produced many errors. Although this is very complicated, we are more likely to succeed if we start from the study of human disease and then model it in animals.

For example, we are studying patients with disorder of obesity, alcoholism and cocaine use. We seek mechanisms and biomarkers in these patients which then we tried to model in animals to try to have a working model in which to look for new therapeutic indications, either of existing drugs or of newly-created chemical molecules.

One of your lines of research is the study of the biological basis of diseases like drug abuse or obesity. Is there really such a biological basis?
I think drug addiction is, perhaps, the neuropsychiatric disease which has achieved the most perfect animal models. That is, fortunately for mankind, addiction is not just an unmodellable disease specific to our own species. We can find models in which animals self-administer and lose control over the use of substances that are used by humans. There is continuity between species. That has allowed the identification, from the 50s onwards, of a whole series of circuits and processes that are scalable from simple to more complex vertebrates, so we can say we know these biological bases, although therapeutic developments have not had the same degree of success because addiction is a disease that is only recognized in some countries, very few. For example, within Spain, Catalonia is an exception because the treatment units for addicts are in hospitals. In the other autonomies they are scattered around different social services departments, or health departments out of the loop of the national health system.

So, while we know a lot about these biological bases, there has been no interest in remedying them on the part of the pharmaceutical industry and health systems. The paradigmatic case is alcohol, the most toxic and lethal drug, but nevertheless legal. This indicates clearly what its social situation is. Alcoholism is a problem because of its links to cancer, mental illness and digestive disease, but there are few treatments for it. There are some, but few compared to other diseases such as diabetes, which has a similar impact but for which the therapeutic resources are infinite.

According to your research, do biological and cultural determinants have the same weight in drug use?

In our work, we first identify the mechanisms by which an individual goes the whole way from the first approach to a drug to losing control over its use. Obviously, there are cultural factors that condition drug use. For example, in the case of alcohol, in Spain we have been able to see how this pattern has changed as European globalization has also brought us the pattern of binge weekend consumption, a model that we did not have but which now is prevalent in the young and not so young, up to 30 years, much closer to that in other parts of Europe.

More than “cultural” conditions, I would rather try to call them “environmental” ones, because speaking of culture in animal models is complicated, and in human ones too. Many times we try to give a cognitive weight to culture, when culture often brings biological determinants. For example, diet or consumption patterns. There are societies in which wine and beer are food, and are treated as such. For example, in Spanish rural society, if you go to the section of ages between 60 and 80 years, alcohol, wine and beer were food. In fact, they were taken out to the fields as food, not for pleasure. Therefore, culture also has an environmental concept in which there are a number of important factors that have been modelling the brain.

There are a number of additional factors that can change over time. For example, the marginalisation that existed in the field of opiate use in the 70s and 80s has virtually disappeared. Drug use by young people is now much more accepted, with marginalisation only occurring at the end of the process, especially if there are associated infectious or psychiatric conditions that attach a stigma. Drug use now, culturally, has an environment that is completely different from the 70s or 80s party environment. That must clearly determine in a very different way how it impacts on the brain.

We have made animal models as to how drugs impact during adolescence, on the development process. Taking account of the social structure of your animal group and modifying it, making a separation of mother and offspring, or by isolation or overcrowding, you can see how these consumption patterns can change.

We have begun to do studies on consumers who come seeking treatment. We have now two major national studies on alcohol and cocaine, and we are starting to see cultural determinants. For example, a very striking thing is that all cocaine users have a level of education around two levels below the average ones of the healthy controls who we use. This may be because the impact of cocaine has removed them from the schooling process but it could also be thought that the educational and protective effect disappeared before and this facilitated the development of addiction. This is also seen for example in obesity. In a study that was done in the village of Pizarra, a longitudinal study conducted at my school, it was determined that obesity is directly related to the cultural level: the lower the cultural level, the higher the rates of obesity.

The social impact of these diseases is high.

Simply, if we remove the medical consequences of alcohol and tobacco from our hospitals, there would be between 20 and 30% fewer patients. Alcohol is completely underestimated as a factor in cancer: alcohol produces “as much cancer” as tobacco. Alcohol is carcinogenic because among other things, a metabolic product of alcohol, acetaldehyde, is a direct genetic modifier

that can cause structural changes in the genome. Breast cancer is linked to alcoholism, but people are completely unaware of this.

But on the other hand, in the case of people with low blood pressure, for example, their doctors have "prescribed" them a glass of wine a day.
Alcohol activates the adrenergic system, but they could do exercise, which also increases the adrenergic activity and helps you to increase the blood pressure.

There is a falsehood about alcohol being beneficial, recently a meta-analysis of all the articles that declared it was published, I think it was in *Lancet*. Somehow all these studies were biased: when one looked at the socio-educational levels of all persons with a moderate alcohol consumption, they belonged to the upper classes, who had much better access to health care. It is very difficult to find, in a spontaneous study, people with severe alcohol problems that belong to higher socio-educational levels. These people withdraw or are removed from their own social group, they are not found in studies. But if you go to a depressed neighbourhood, it is much for the problems to emerge than if you go to a rich neighbourhood like Pedralbes. No one will come out saying "look, this man, this neighbour, or my mother, uses drugs and alcohol". But you go to a peripheral neighbourhood and everyone knows who has these problems, and besides, they themselves come and tell you, because there is a very clear idea that marginalisation brings these problems, which does not agree with what epidemiology says. That is, the use of tobacco is identical in them and in Pedralbes, but in Pedralbes nobody will say what problems may arise from the consumption of tobacco. That stigmatisation is still very difficult.

The social impact is tremendous. And what is the big problem we have now? The social perception of drugs risk has fallen. I think that in the last CIS survey it was in place 26th or 36th place, I don't remember, but I mean it is not in the top 20 issues that matter to people. If one goes to 1985, it was the first or the second. It was the era of AIDS, the appearance of marginality and criminality associated with drugs. Criminality remains, but people do not care. Somehow, we have made the drug problem disappear. Meanwhile, the number of patients seeking care and admission for their cannabis dependence has multiplied by 5 in the last 4 years. And people do not know. We have grown from 600 to more than 3,000-4,000 requests for treatment. And why did this happen? Because people grow it at home, and cultivate varieties which have up to 7 times the psychoactive product than those bought on the black market. That has produced more severe dependencies and more complex psychiatric conditions. And that demands treatment, but does not appear in the newspapers.

Do you think that drug addiction is socially perceived as a disease?
Countries such as Germany have incorporated the concept of addictive disease since before World War II. In Spain, it is not incorporated into the public health system. They do not treat the addiction, they treat the medical consequences of addiction. There are no addictions units, except in Catalonia, whose pioneering role in this should be recognised. But it is still in a minority and the stigma remains.

There are more alcoholics than diabetics, but they are not in treatment because it does not matter. In Spain there have been eight attempts to restrict the use of alcohol by law. The last one, the law of alcohol and minors, was published by the ABC newspaper in draft status, I was

on the committee, and as soon as the alcohol lobby saw what the law involved they struck it down. No one has ever managed to get a law on alcohol in Spain. And in fact, our minors are the customers. When people say to me “to legalise drugs removes violence and drug trafficking,” OK, but who protects minors? Because everyone agrees on protecting minors. But the people buying cannabis and alcohol are under 25, making up 80% of the business. And the brain matures just at the age of 21-22. It is not about being of legal age or not, it is just common sense. If, from the age of 14 to 22 years, your brain is in the process of finalising its development and configuring its functional architecture, determining your personality and your skills, don’t put a spanner in the works.

As for treatment, are the healthcare professionals trained enough for it?
Here in Catalonia there are very good units. For example, I work with people from the Hospital del Mar, with Marta Torrens's group, and there are also extraordinarily well-trained people in the Public Health Agency of Barcelona, and the City Council, excellent professionals. But they remain exceptions.

First, it is not a specific area of knowledge. It can be found in some places as a master’s degree, that is, once you have finished a degree in, for example, psychology or neuroscience, maybe a particular university has a master’s degree in psychopharmacology of drugs of abuse, but they are a minority, and yet, the use of drugs is on a majority scale. It is noteworthy that on degree courses in psychology or medicine, drugs of abuse, which have a huge impact, are barely represented, but rare diseases are. And by that I don’t mean that rare diseases do not have to be treated, but the common ones, and addiction is a very common disease, at least should have the same consideration, respect and care as rare diseases. It doesn't make sense.

I spare none of the parties that have governed us from criticism. I remember the Minister Ana Salgado saying that obesity or addiction are lifestyles that one chooses. The anti-smoking law is introduced but payment for treatments is not covered. An anti-alcohol law is attempted and then blocked, but this one also skipped over the treatment issue anyway. And if one is obese, it is a lifestyle, and the industry does not develop anti-obesity drugs. Why? Because if you have a target population of 20-25%, and in some areas of Spain such as the Canary Islands and Andalusia, 30% are obese, what do you do with a drug that Social Security has to subsidise for 30% of the population? You would go bust. So, better not to call it a problem. It is a lifestyle, so we have personal protection measures.

We talk about obesity, but before reaching that point there is the overweight stage. That means the percentage reaches...
35-40%. In the United States I think all states have more than 30% of patients with obesity. All. And in some, up to 50 and 60%. It is a silent epidemic. It’s like that cartoon film from Pixar, *Wall-e*, where in the end we destroy the planet, we live in a spacecraft in which we live in zero gravity and we are all obese because we do not have the slightest interest in moving or doing anything, just enjoying ourselves. It is a bit of a catastrophic vision, but the truth is that in the United States it is there. In Spain, diabetes is the silent epidemic, now in 12% of the population, and obesity in 30%. And childhood obesity is tremendous. But it seems that there are other more pressing problems, or other pressure groups who do a better job.

Another line of research of the group is the development of new drugs for the treatment of disorders of motivated behaviour, especially drug addiction and obesity.
Within the circuits that regulate addictive processes, we have identified molecular targets, such as receptors or enzymes. That is, proteins, active molecules which are crucial for any of the processes that lead to loss of control over the use of a drug. Given the target, we can talk to people from medicinal chemistry so they can make models. For example, and this is what I will talk about in the seminar, we discovered a molecule produced in the intestine which regulates satiety. It is a fat, a derivative of oleic acid. Well, from that oleic acid derivative, oleoylethanolamide, working with the group of Rafael de la Torre and Jesús Jolar here in Barcelona, and the group of Pilar Goya in Madrid, we developed up to eight different series of compounds modelled from oleoylethanolamide which have similar actions and that may be potential drugs.

Our big problem is that all this work was under way just when the crisis appeared. Biotechnology in Spain, and pharmaceutical biotechnology in particular, has suffered tremendously and it has been practically impossible to develop them, but we have candidates for the treatment of addiction. We have 11 or 12 molecules that could have reached the clinic if there had been investment and interest.

But I think that a change is starting. In the US about 6 years ago it started with an office of clinical trials within the National Drug Institute to develop clinical trials on alcohol and drugs promoted by public entities. Spain is starting to try to move. However, while there is no social awareness of the disease, it will be extremely difficult to achieve.

You are also the coordinator of the Network of Addictive Disorders (RTA). What is it and what are its main objectives?
The Carlos III Health Institute, the principal Spanish public institution that promotes biomedical research took an idea based on the spirit generated by the 5th and 6th EU framework program, which was the creation of networks of excellence. Consideration was given to the idea of creating cooperative networks in which research professionals working in the same field were grouped and cooperated.

Then, in 2003, 22 research groups from 7 autonomous communities got together to form the Network of Addictive Disorders. We have worked together for 13 years. These groups have a fundamental mission: to convince society that addiction is a disease with very well-defined characteristics that can be assessed and incorporated into the National Health System and treated where possible, and promote research into prevention and knowledge of the pathological process that comprises addictive disease and the development of new therapeutics.

Two years ago, the new networks call forced us to focus on two integrated projects in which all members of the network were to cooperate on a common idea. One was on the medical consequences of alcoholism: to identify and know once and for all what is the real impact and to model and seek treatments for diseases that are a result of alcohol abuse. The other was something very specific: the psychiatric comorbidity of cocaine, because cocaine users have a very high incidence of associated psychiatric illness: mood disorders, anxiety disorders and psychosis. The aim was to investigate these medical consequences and then develop

therapeutic strategies.

If you want to add something else...

More than adding something I want to make a wakeup call to society to not forget that drugs of abuse are specific to our biological nature and also to animals, but the problem is that the only animal able to manufacture and sell them is the human being. But we have forgotten that when we lower our concern for them, their impact on society is tremendous. In addition, drug abuse always appears in the same social group: the group of adolescents and late adolescence, just before acquiring the autonomy of adulthood, and it can cause huge damage to those in which its impacts are absolutely predictable. Prevention is very important, we must never lower our guard and never cease to encourage research and support groups fighting to diminish the impact of this disease.

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