Professor Eugenia Carvalho discusses drug-induced metabolic dysfunction, which she describes as an understudied and underfunded area of research

Prescription drugs – not without consequences

Life as we know it has been extended greatly thanks to modern medicine. However, many of us encounter high levels of stress often just to be able to cope with the rush of everyday life, and stress affects one's health significantly. In addition, more prescription drugs are given today than ever before, and they are used to cure all kinds of illnesses, some more severe than others. In certain societies, drugs are even being prescribed to young children and adolescents when they have attention deficits and/or hyperactivity, particularly at school when, in many cases, what they really suffer from is lack of sleep. The general population is being over medicated.

More people every day are taking anti-depressive medication, immunosuppressive agents (IAs) – particularly for post-organ transplantation and immune disorders – and antipsychotic drugs (ASD) to treat severe depression and anxiety, particularly in the elderly, but also to treat mental illnesses, including Schizophrenia, to name just a few that are commonly being prescribed today.

Many of these drugs, if not all, have side effects that can be severe if not deadly. Most can cause metabolic dysfunction that can lead to insulin resistance, hypertension, cardiovascular disease and type 2 diabetes (DM). Studies unraveling the *in vivo* metabolic effects of these drugs on peripheral tissues and cells are scarce. In addition, the mechanisms of action of these drugs at the levels of cells and tissues *in vivo* are, for the most part, not well known. Moreover, funding to study drug-induced metabolic dysfunction is almost nonexistent.

The *in vivo* effects of IAs

My laboratory, in collaboration with other colleagues in Europe, has been evaluating, for over a decade now, the *in vivo* effects of IAs, namely cyclosporine, tacrolimus and sirolimus, on glucose and lipid metabolism in peripheral tissues, without almost no funding. We have observed that these drugs have different mechanisms of action in the various insulin sensitive tissues, when studied *ex vivo* or *in vivo*. While cyclosporine and tacrolimus appear to regulate the entry of glucose into cells through a non-insulin dependant mechanism involving, at least in part, vesicle trafficking, sirolimus, on the other hand, acts through the disruption of insulin action. Cyclosporine, in particular, is an old medication that, in spite of the severe side effects, it is still one of the most used IAs in the clinic today. New efforts in research are needed and thus more funding for this important area of research, as more people are receiving transplants each day and need IAs for survival.

Research consortium

More recently, and as part of a European research consortium, TREATMENT, a Marie Curie Innovative Training Network, we have started to evaluate the *in vivo* mechanisms of action of two second generation antipsychotic drugs, Olanzapine and Aripiprazole, on peripheral tissues. Most studies to date on ASDs have focused on evaluating their effects on parts of the central nervous system that are responsible for metabolic control, such as the hypothalamus. On the other hand, there are very few studies evaluating their effects in cells and on peripheral tissues. This consortium funds 15 PhD students to carry out their work during the course of a three year period. However, very little funding has been granted for the actual bench work to be performed.

I feel that drug-induced metabolic dysfunction is an important research topic to focus on, given the amount of people taking prescription drugs today. This field is still understudied, and it is greatly underfunded.

There are very few studies evaluating the effects of ASDs in cells and on peripheral tissues

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