# The Intersection of Drug Metabolism and Diabetes

*Dr. David Moore*

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Dr. Moore's presentation focused on nuclear hormone receptors, which are proteins that help certain chemicals, such as vitamin D or the sex hormones estrogen and testosterone, exert some of their effects. Typically, when one of these chemicals enters a cell it binds to its receptor, and the hormone-receptor complex then interacts with both specific DNA sites and other proteins to turn some genes in the nucleus "on" and others "off." Most of the 48 nuclear hormone receptors encoded by the human genome actually bind—not to true hormones—but to other chemicals coming from outside the body. Through support from NIDDK, the National Heart, Lung, and Blood Institute and the National Institute of Environmental Health Sciences, the Nuclear Receptor Signaling Atlas project is cataloging the diverse and extremely important physiological effects of these proteins. An important subset of these receptors plays a vital role in triggering the process by which the body eliminates certain drugs or toxins, a process called drug metabolism.

Dr. Moore first discussed recent research from his laboratory that has shed light on the way that type 1 diabetes influences drug metabolism via CAR, a member of the nuclear hormone receptor family origi nally cloned in his laboratory. Dr. Moore then presented work showing that drug metabolism mediated by CAR may be helpful in achieving healthier blood glucose levels in patients with type 2 diabetes. Thus, not only can diabetes influence drug metabolism, but also drug metabolism can affect diabetes.

**Diabetes Impacts Drug Metabolism**

The experiments Dr. Moore highlighted were inspired by observations from other researchers that type 1 diabetes accelerates metabolism of certain drugs, both in humans and in rodent models. Dr. Moore's lab looked at drug metabolism genes that are turned on by CAR. The researchers found that these genes were turned on in a mouse model of type 1 diabetes. Controlling the diabetes reversed the effect: when insulin was given to the mice, the CAR-induced genes turned off.

In fact, type 1 diabetes not only leads to activation of drug metabolic genes, but also has a profound effect on the metabolism of certain drugs. Mice with induced type 1 diabetes rapidly clear their systems of a compound that induces temporary paralysis, while normal mice cannot. These experiments also underline the central importance of the CAR nuclear receptor in affecting drug metabolism: mice without CAR take much longer to clear the drug, whether or not they have diabetes.

How does CAR promote speedier drug metabolism in animals or people with diabetes? The answer may have to do with an unusual property of CAR compared to other nuclear hormone receptors. In addition to its response to binding to a hormone or other activating molecule from outside the cell, CAR can move into the

nucleus and turn on its target genes when it is activated by an enzyme within the cell called AMP kinase. Not surprisingly, AMP kinase is activated by certain drugs. In addition, the Moore lab found it to be modestly activated in the livers of mice with uncontrolled type 1 diabetes. Further research will be required to extend these suggestive results and determine the actual mechanism underlying the impact of type 1 diabetes on drug metabolism.

**Drug Metabolism Impacts Diabetes**

Early in the course of type 2 diabetes, the pancreas reacts to elevated blood glucose by producing more insulin to try to compensate. However, because the disease is characterized by insulin resistance, the result is that both blood sugar and insulin are elevated in these patients if they do not have proper treatment. Gradually, during the course of the disease, years of elevated blood glucose take their toll on insulin-producing cells, diminishing their ability to produce the vital hormone. Thus, without proper treatment, glucose control often goes from bad to worse.

Surprisingly, researchers have found that phenobarbital, a medication formerly used to treat epilepsy, also has the effect of reducing blood glucose levels in people with type 2 diabetes. The effect is only observed in patients whose disease is in its early stages and whose ability to produce insulin is not yet seriously diminished or lost. Phenobarbital has no impact on blood glucose or insulin levels either in those whose type 2 diabetes has progressed to the point where insulin production falls, or in people who do not have the disease.

Phenobarbital is an effective treatment for epilepsy, but it is no longer widely used because it has two serious side effects: it is a potent sedative, and it is such a powerful activator of drug metabolism (via CAR) that it can adversely affect the way a patient's other medications are handled by the body. The effect on blood glucose can also be thought of as a side effect, albeit a potentially beneficial one in some patients due to its theoretical benefit for some people with type 2 diabetes. However, because of its serious side effects and the availability of safer medications that improve insulin sensitivity, phenobarbital is not a recommended treatment for the disease.

Nevertheless, understanding the way phenobarbital exerts its effects might point the way to other avenues of diabetes treatment. The lower blood glucose levels observed in type 2 diabetes patients taking phenobarbital might result from an overall improvement in insulin sensitivity among the body's cells that allows them to absorb more glucose, or they might come from a more subtle metabolic effect.

To distinguish between these possibilities, the Moore lab examined a strain of mice that are obese because they lack a key hormonal mediator of appetite control. Invariably, the uncontrolled appetite of these mice leads them to become obese and to develop type 2 diabetes at a very young age. As in humans, a drug treatment that stimulates CAR helped normalize the otherwise sharply elevated blood glucose levels typically observed in these animals. When the obese mouse strain was modified by deleting the gene for CAR, the drug treatment had no effect on blood glucose, indicating that CAR is necessary for the effect.

If CAR has a general effect on insulin sensitivity, CAR stimulation would be expected to improve the ability of all tissues in the animal to absorb glucose. However, when the Moore group looked more carefully at how specific tissues in these mice respond to a sudden surge of injected glucose, they discovered this was not the case. CAR stimulation did not improve glucose clearance in peripheral tissues. Rather, the effect was confined to the liver.

One possible explanation for the importance of the liver in mediating CAR's glucose-modulating effects relates to the liver's vital metabolic role in keeping blood glucose sufficiently high to facilitate brain function during periods of fasting. The liver does this

by liberating glucose from energy stores. One of the important messages insulin sends to the body is to tell the liver that it should stop producing glucose when blood levels of the molecule begin to rise after a meal, and to signal to the body that it should instead switch to replenishing energy stores. Because of the insulin resistance observed in type 2 diabetes, however, the liver continues to produce glucose even when its concentration in the blood is already too high. Interestingly, CAR seems to reduce the activities of several proteins with a key function in liver glucose production, while stimulating proteins that direct blood glucose into energy stores.

**Conclusion**

Dr. Moore's presentation made the surprising case for two distinct intersections between the physiology of drug metabolism and that of diabetes. First, he recounted research that has shown the profound effect that type 1 diabetes can have on the metabolism of certain drugs by stimulating the CAR nuclear receptor. These data may ultimately bear not only on the way type 1 diabetes is treated, but also on the way people with the disease are treated for other conditions. Second, he showed that drug treatments that trigger CAR signaling can impact blood glucose levels in a mouse model of type 2 diabetes, probably by modulating glucose metabolism in the liver. These observations suggest that inhibiting glucose production and/or stimulating glucose storage by the liver is a potentially valuable approach to treating type 2 diabetes, perhaps in conjunction with other therapies.