

Adrenaline receptor 'frozen in action'

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Adrenaline, the hormone that prepares our body to fight or flight, acts on a hyperdynamic receptor. This molecule switches so fast between several positions, that it was impossible to image it. Until now. Scientists, including Jan Steyaert of VIB and the Vrije Universiteit Brussel in Belgium, and colleagues from Stanford University in the US, have "frozen the molecule in action" using Xaperones, tiny, stable antibodies developed by the Brussels scientists. The Xaperones bind like a key to a lock, holding the adrenaline receptor in one position -- the on position. After binding the adrenaline receptor to the Xaperone, the researchers could use X-ray crystallography techniques to determine its structure. The results are published in *Nature*.

The breakthrough is not only a scientific first, the newly developed technique also offers promising prospects for medicine. The adrenaline switch is the target of widely used drugs such as [asthma](#) inhibitors and [beta blockers](#). The latter are used worldwide as a medicine for [heart disease](#).

But the applications are not limited to asthma or heart disease. Over 30% of all drugs on sale in pharmacies today switch similar receptors on or off. Through the newly developed technique, these receptors can now be accurately described, which is a necessary first step to determine their action and develop new or better drugs.

Adrenaline is a hormone that is released under stress. It is a messenger molecule which causes the heart to beat faster, causes us to sweat suddenly and releases sugar as an immediately usable source of energy.

These reactions are the result of the fact that adrenaline binds with a specific switch (known as beta2-adrenergic receptor). This switch is embedded in the membrane surrounding our cells. When adrenaline binds to the receptor, the individual cell knows that the rest of the body is preparing for stress reactions such as fight or flight.

It is impossible to determine the structure of this kind of switches by using conventional methods. They move, oscillate and constantly change position, even when the signalling molecule such as adrenaline is absent. Together with researchers from Stanford University, Jan Steyaert and his colleagues have managed as it were to freeze the adrenaline switch in the "on" position. For this purpose, they used a Xaperone™ which attaches like a key in a lock to the switch and causes it to stop switching from one position to another. It is in this "frozen" on-position that the structure was determined using X-ray crystallography techniques.

Our body is equipped with hundreds of similar continually moving switches which determine how we react to our environment. The scientific term for these switches is GPCR (G-Protein-coupled [receptors](#)). The newly developed technique based on Xaperones™ can also be widely used in studying other GPCRs and proteins with therapeutic relevance.

Xaperones is a new application of the Nanobody technology developed at VIB-Vrije Universiteit Brussel. The development of therapeutic Nanobodies® forms the basis of the biopharmaceutics company Ablynx, a start-up of VIB and Vrije Universiteit Brussel.

The solution to fix proteins with Xaperones is comparable to the solution which the English scholar Eadweard Muybridge conceived of around 1900 to be able to study fast-moving objects. He was the first to prove, on the basis of a series of still photographs, that a galloping horse sometimes has all its legs off the ground.

http://en.wikipedia.org/wiki/Eadweard_Muybridge

More information: Structure of a nanobody-stabilized active state of the β 2 adrenoceptor, Nature, [doi:10.1038/nature09648](https://doi.org/10.1038/nature09648)

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