Diabetes-associated pain linked to disrupted insulin signalling

May 10 2018

The chronic pain experienced by a number of patients with diabetes has widely been assumed to originate from damage to blood vessels or to local tissue surrounding neurons caused by high blood-sugar levels. However, a new study reports that in fruit flies, this pain hypersensitivity results instead from disrupted insulin signalling in pain sensory neurons.

Chronic pain is a frequent complication of diabetes, with surveys reporting rates of 20% to over 60% of individuals with diabetes also having to deal with pain hypersensitivity, severe pain and/or numbness that makes self-management of their disease more difficult. The symptoms usually start with a tingling sensation at the distal extremities, spreading to cover all of the hands and lower legs as the severity of pain increases. Diabetes-associated pain is hard to treat because of the low effectiveness of drug choices for neuropathic pain, and because alternative treatment options such as massage, bathing or exercise result in different levels of pain relief between individuals. Most crucially, the treatments available merely relieve symptoms instead of providing a lasting cure.

New fly model shifts research focus

The underlying causes of diabetes-induced pain are still largely unknown. To date, most studies have used vertebrate models such as mice to focus on how diabetes might affect the tissue surrounding sensory neurons, with a possible impact on neuron function. However, a

wider investigation into whether other tissues could be linked to the development of disease-associated pain symptoms has yet to be undertaken by the field. The current prevalent theory is that diabetes-associated pain is a secondary effect of vascular changes or the toxicity of high sugar levels to neurons. Now, new research published in the open access journal *Disease Models & Mechanisms* instead implicates disrupted insulin signalling in pain sensory neurons, through use of a novel fly model. The leaders of the study team, Dr. Seol Hee Im and Dr. Michael Galko from the University of Texas MD Anderson Cancer Center, explain that, "Only very recently have researchers started to pay attention to the loss of insulin signalling in the pain sensory neurons. This is a gap that our work has helped to fill in—the *Drosophila* model has allowed tissue-specific manipulation of insulin signalling and measurement of the ensuing effects on pain sensitivity."

Fruit flies have been used for a number of years as a model organism for many aspects of diabetes research, including studies into the molecular mechanisms behind maintaining balanced glucose levels, and insulin production and sensitivity. Additionally, they have been used to model other diabetes-associated complications such as obesity-induced heart disease and metabolic syndromes. The diabetes-associated pain model described in this research paper is an extension of well-established fruit fly diabetes research models and assays for measuring pain in fly larvae. The crucial questions asked in this new research are whether the pain hypersensitivity experienced by individuals with diabetes is related to defects in insulin signalling in sensory neurons, and whether this pain can be modelled in fruit flies.

To answer these questions, the research team used three different fruit fly models; one with a genetic interruption of insulin signalling, and two established fly models of type 1 and type 2 diabetes. In the first model, the scientists knocked down a key insulin signalling protein in specific tissues and were surprised to discover that the Insulin receptor protein

functioned in pain sensory neurons instead of in metabolic tissues such as muscle and fat. In these neurons, faulty Insulin receptor function caused hyper-activation of the neurons and persistent pain hypersensitivity. Further, in both the genetic knockdown and type 2 diabetes model flies, the team were able to reverse pain hypersensitivity by increasing insulin signalling in sensory neurons.

Signalling the way forward

According to Drs Im and Galko, the key implication of this discovery to the field of diabetes research is that it is the simple loss of insulin signalling in pain sensory neurons that leads to the development of persistent pain hypersensitivity. This opens the doors for future research into ways to restore insulin signalling within the pain sensory neurons as a potential treatment for diabetic neuropathy patients.

Going forward, the team plans to combine tissue-specific genetic screens with the type 2 diabetes model to interrogate which genes are required to maintain persistent hypersensitivity in pain sensory neurons. Drs Im and Galko say, "Such screens can be either genetic or chemical in nature and could be performed in our models of genetic mutants or tissue-specific Insulin receptor knockouts as well. We can also expand our analysis to other sensory modalities such as cold or mechanical and chemical stimuli, as diabetes patients also experience these hypersensitivities." The research team hopes that their fruit fly model will eventually contribute to improved patient care and treatment. They visualise the first step to be the contribution of new hypotheses relating to the function of insulin signalling in pain sensory neurons to the fields of diabetic neuropathy and diabetic pain. This could then be extended into vertebrate models to see if the role of insulin signalling within pain sensory neurons is conserved across species.

"By linking the function of insulin signalling and persistent pain, our

study brings a new focus onto diminished insulin signalling in the pain sensory neurons in diabetic patients", explains Dr. Im. "These efforts could extend further to translational research and eventually we hope that our study will contribute toward the development of better treatment for diabetes-induced pain."

More information: Seol Hee Im et al, Drosophila Insulin receptor regulates the persistence of injury-induced nociceptive sensitization, *Disease Models & Mechanisms* (2018). DOI: 10.1242/dmm.034231

Provided by The Company of Biologists