The lifetime effects of stress

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(PhysOrg.com) -- Professor Stafford Lightman and his team in the Laboratories for Integrative Neuroscience and Endocrinology are interested in how stress impacts upon human health throughout the lifespan - just how does it affect your body and the way it responds to disease?

Stress-related disease is a rapidly increasing feature of our society, but the mechanisms through which stress causes disease are poorly understood. It is an area of research that fascinates Stafford Lightman, who has been working on finding answers to some of these questions for many years. Recently he has been able to demonstrate that events that happen to you around the time of your birth, or even before you are born, can have epigenetic effects on your later life. What that means is that while such events do not actually affect the genes themselves they can affect the way your genes function. So if you had a very stressful childhood, this can have long-lasting influences throughout the whole of your life.

Lightman has looked at these effects in rodents and has seen that if rats are stressed early on in their lives, this can change the way they produce their stress hormones throughout the rest of their lives. For example, if a mother rat neglects her pups, when those pups become adults and are examined to see how they respond to stress they have a much stronger response than pups that had caring mothers. In adult rats the levels of the stress hormone corticosterone in those stressed as pups goes much higher during a stressful event and lasts much longer than in rats that were well looked after as pups.

In humans the situation is much the same. If adult stress is superimposed on a stressful childhood, that combination not only means that are you more susceptible to stress in later life, but also that when you encounter a stressful situation your stress hormones - called cortisol in humans - dramatically increase. If these hormone levels are raised chronically for a long period of time, they can cause problems with the whole range of biochemical processes that occur within us and we become more susceptible to diseases such as depression, diabetes and hypertension, and also to memory loss. High levels of cortisol cause shrinkage of the hippocampus which can lead to poor memory function.

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Having established that stress hormones can have such effects, Lightman naturally asked the question - how does it happen? What he found was extremely interesting. It seems that cortisol is secreted in a circadian rhythm, which means that it has a peak level early in the morning and then decreases throughout the rest of the day. In humans, this peak occurs just before we wake up; cortisol is thus labelled as an 'anticipatory hormone' because it goes up in anticipation of what our body will need during the day. Since cortisol and corticosterone act on the liver to release glucose, this morning peak ensures that we have enough sugar in our blood to provide sufficient energy for us to function properly during the day. One fascinating outcome from Lightman's studies is the fact that the circadian rhythm of cortisol and corticosterone is made up of multiple pulses that occur roughly every hour, so in fact hormone levels are going up and down all the time, especially in the morning in humans when cortisol levels are really high and the pulses are very big.

The relevance of these pulses is that they allow the body's tissues to respond not just to the level of the hormones, but also to the frequency with which the hormone pulses occur. In fact, it is the basis of a digital signalling system. In arthritis, for example, the frequency of these pulses is doubled, allowing our natural hormones to moderate the disease process. Also, in patients with obstructive sleep apnea - an unpleasant condition in which people stop breathing for periods of a few seconds several times every night whilst they are asleep - the size of each individual cortisol pulse is markedly increased. This may well be one of the reasons why these patients develop high blood pressure, heart disease, diabetes and other stress-related disorders. Indeed, it is clear that in different physiological or pathological conditions not only do levels of hormones change but the frequency and pattern of their pulses change as well.

The next step for Lightman and his team was to look at the molecular biology of these pulses to try to understand what was going on at the cellular level. What they revealed is that every single pulse of corticosterone in rats is associated with a pulse of corticosterone receptors charging into the nucleus of the cell, binding on to DNA and making messenger RNA. Almost all cells in the body have these receptors which can be thought of as the 'lock' in a cell that is activated by the hormonal 'key' of corticosterone. The messenger RNA that is made in response to these pulses is the signal for the production of new proteins by the cell and thus is vital for normal cellular function.

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The other important discovery was that different tissues in the body experience these pulses in different ways. The liver, for example, is

extremely sensitive to pulses and so immediately responds to every individual pulse. Some parts of the brain, however, need two or three pulses before a response is generated. This is useful, as in a stressful situation you need your blood sugar levels to rise very quickly, while the brain may need more time for preparation before it wakes up. This research area is still in its infancy and its implications are not yet fully understood. However, what Lightman's group does know is that these fluctuations or oscillations of hormones, which are going on all the time, allow us to have a system that reacts extremely fast in stressful situations. When confronted with a lion, for example, you want to have a really massive hormone response so that your brain focuses on how to escape and your blood sugar goes up so you have the energy to run away very fast.

But what does all this mean in today's society where we are not often confronted by lions? "Now that we understand how these stress mechanisms work," says Lightman, "we can begin to work out why some people appear to be at greater risk than others of getting diseases that are associated with stress. Furthermore, we will be much better positioned to design therapeutic ways of dealing with it. In the longer term we hope to be able to identify people who have had a particularly stressful childhood, for example, and provide them with advice that will protect them from developing the diseases to which they will be susceptible." In the future, Lightman hopes to better understand what is called the epigenome - the way that past experiences have modified our cells, making us more vulnerable to certain diseases. "We will be able to look at people who, perhaps because of their childhood experiences, have had a change in their epigenome, which means that their genes respond more readily to stress, thereby putting them at more risk of getting certain diseases. Whether or not it's a good or a bad thing, of course, one can argue about, but I think it will happen in the not-too-distant future. So personalised medicine won't only be related to the genes you have - your genome - it will also be related to your epigenome." Despite these

fascinating results, there is still a great deal of work to be done investigating whether or not stress is a risk factor for all kinds of diseases. While we know, for instance, that there is a good correlation between being depressed and having a heart attack, we don't know what mediates that. "Is it because the individual has a cortisol abnormality?" asks Lightman. "We know that people who are depressed have abnormal cortisol secretion. Is that the link?" Clearly the answer to these questions with regard to specific individuals would be extremely valuable.

To help further this work, Lightman and his team were thrilled to discover recently they had won a grant of £1.7 million from the Wellcome Trust. They will use these funds to look at how different patterns of stress hormones can affect genes in the brain and the liver, as well as how these patterns affect memory and the development of diseases such as diabetes. Undoubtedly they will have more answers in a few years' time.

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