german research
Magazine of the Deutsche Forschungsgemeinschaft

3/2014

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WILEY-VCH

DFG

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The Value of Aversion

The human immune system is capable of learning. To investigate how it communicates with the brain during learning processes, researchers employ the paradigm of classical conditioning. Their aim is to achieve a better understanding of immune responses and to establish learning protocols as supportive therapy for the treatment of diseases.

In 1886, American surgeon John Mackenzie reported a striking observation in the American Journal of Medical Science: when a woman who was allergic to roses was exposed to an artificial rose, she suffered an asthma attack. She was experiencing a severe reaction of her immune system caused by the previous association of the allergen (roses) and the subsequent allergic immune response, an example of classical conditioning.

Learning and memory are not only established concepts in behavioural science and neuroscience, but also important terms in immunology, where they describe the recognition of antigens by the body's immune cells. Immune

responses can be however also influenced by classical learning processes. These learned immune responses are based firstly on the exchange of information between the brain and the peripheral immune system, which communicate continuously through biochemical and neuroanatomical paths, and secondly on the phenomenon of the classical conditioning of physiological responses, first described by Ivan Petrovich Pavlov over 100 years ago, and still found today in every school biology textbook.

The classical conditioning of immunological responses is best illustrated by the phenomenon of "conditioned taste aversion" in an animal model. Rats or mice are offered a new taste, usually a sweet-tasting saccharine solution, in drinking water as a conditioned stimulus (CS). This taste stimulus is directly combined once or, ideally, several times with the injection of a drug that suppresses immune functions and acts as an unconditioned stimulus (US). When the taste stimulus (CS) is offered again without the injection, the animals avoid the saccharine solution. This is described as a "conditioned taste aversion".

Conditioned responses can also be observed as immunosuppressive effects that correspond, in a weaker form, to the immunopharmacological effects of the drug used as the US. Based on experimental findings in animals, researchers have identified the communication paths between the brain and immune system that are activated in the classical conditioning of immunosuppressive effects. They are able to explain what may at first appear to be an astonishing phenomenon: the fact that a taste stimulus can influence immunological processes.

Further experiments with animals have demonstrated that these learned immune responses are not merely interesting laboratory phenomena of no real importance to the organism, but clinically significant response patterns. For example, the progress of a chronic inflammatory autoimmune disease like arthritis can be mitigated by learned immunosuppression and the rejection process of transplanted organs can be delayed.

The classical conditioning of immunosuppressive responses as observed in animal models has also been transferred to humans. Interestingly, the conditioning protocols employed for human subjects are similar to the learning protocols used for laboratory animals. Volunteers take the immunosuppressive drug Cyclosporin A as the US, which is often used in clinical situations where it is necessary to suppress a patient's immune response. As a conditioned stimulus (CS), the volunteers are given a green-coloured strawberry milk with a lavender flavour. In the learning phase, the drug is offered several times together with the taste stimulus. After an interval of one week,

Left: In the learning phase volunteers are given the immunosuppressive drug (unconditioned stimulus) together with ... an unfamiliar-tasting green drink that serves as the conditioned stimulus. Below: In the lab, researchers investigate whether and how the conditioning process suppresses the activity of T lymphocytes in comparison with the effect of the drug.

Illustrations: Martin Kaiser/Universitätsklinikum Essen

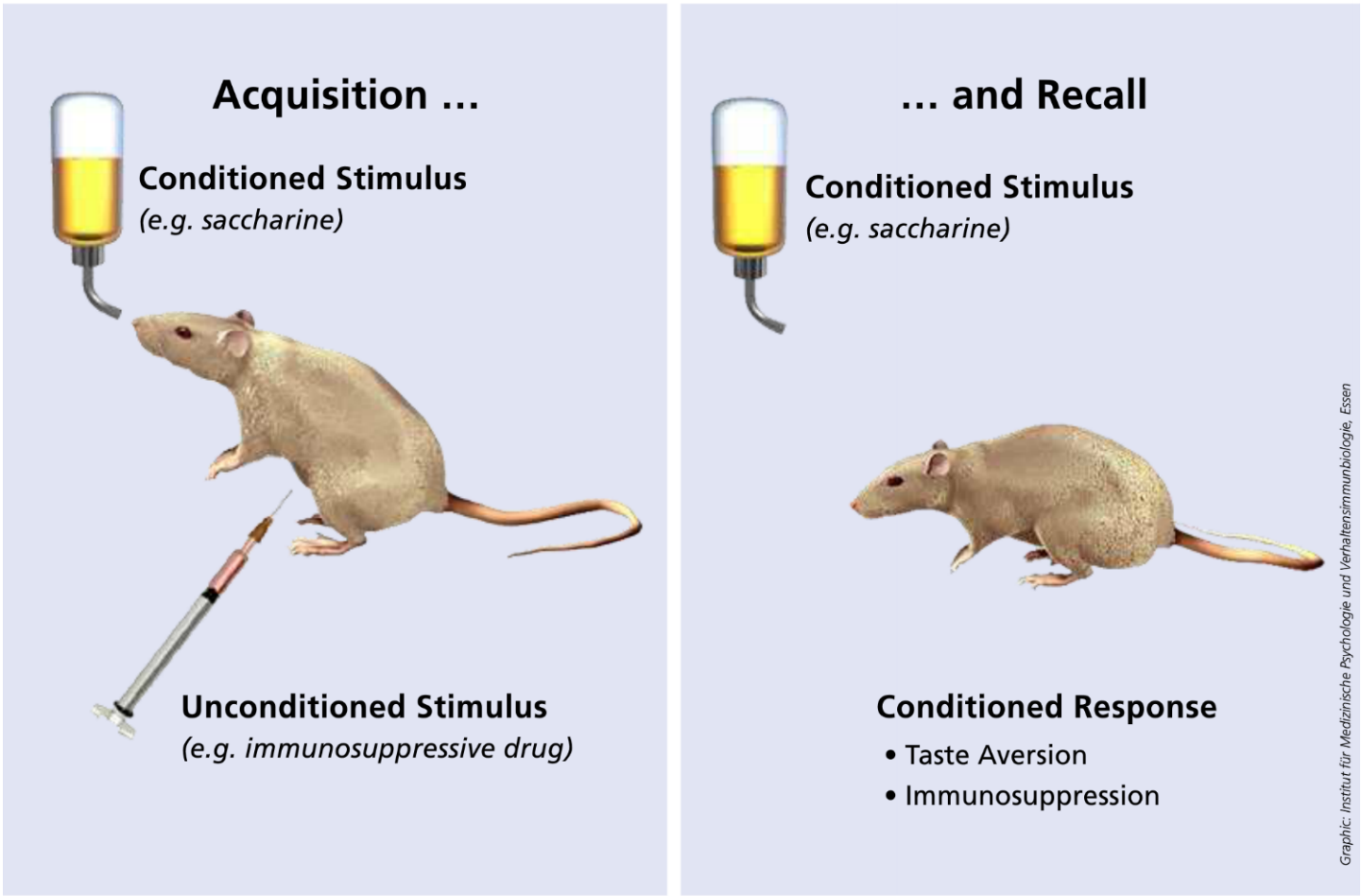
the volunteers are given the same drink, this time with a placebo (a pill with no effect).

Meanwhile a control group goes through the same conditioning protocol, but receives only a placebo during the learning phase instead of the drug. At the end of the learning phase, blood samples are taken. Immunological analysis shows the typical inhibition of T cell proliferation and reduced production of cytokines, the chemical messengers responsible for the activation of T lymphocytes, caused by Cyclosporin A. A similar, although less marked, suppression of the immune response can be produced as a learned immunosuppression by the consumption of the drink (the conditioned stimulus).

These learned effects on the body's defence system produced by conditioning are a fascinating example of "bidirectional" communication between behaviour, the brain and the peripheral immune system. The model makes it possible to carry out a detailed analysis of this communication network. However, the phenomenon of learned immune response also has clinical implications. In addition to increasing basic scientific knowledge, it is also hoped that this research will make it possible to refine conditioning protocols to serve as supportive intervention strategies for patients under pharmacological treatment. This would allow drug dosage and undesirable side-effects to be reduced while maximising therapeutic effectiveness for the patient's benefit.

However, a few fundamental questions remain to be answered before these protocols can be employed in routine clinical practice. For example, if the learned immune response is limited to a single event, it still remains a useful model for investigating interactions between the brain and immune system. But in clinical situations in which continuous immunosuppression is required over

Simplified model of conditioned taste aversion in the acquisition and recall phases, tested on rats in the laboratory.



In a human experiment, volunteers are given a green coloured drink with a lavender flavour.

a long (perhaps very long) period, the model would have no value. Recent experiments with human volunteers show, however, that a learned immune response can be triggered again after a long break by consuming the drink (CS).

As with other learning processes, the conditioned immunosuppressive effects subside after a certain time. Research is therefore currently underway to investigate whether the extinction of the learned immune response can be delayed or even prevented altogether.

As with other medical treatments, volunteers react to conditioning with differing sensitivity. Studies have identified psychological and neuroendocrine factors (so-called predictor variables) which are associated with learned immunosuppression and therefore have predictive value. However, the reliability and quality of these predictor variables needs to be further refined and tested in routine clinical practice.

Even if it is premature to anticipate a clinical application, conditioning protocols can still serve as a useful model because they allow us to investigate whether learned effects on the immune response also occur with other substance classes; it may even be possible to transfer these to other physiological systems such as the hormonal or cardiovascular systems. The research, which has been interdisciplinary from the outset, has led to a better understanding of human biology through the analysis of the mechanisms steering the communication between brain, behaviour and the immune system. In the long term it could also help us to develop new and promising approaches to the treatment of disease.

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Impressum

german research is published by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation);
Publisher: WILEY-VCH Verlag GmbH & Co. KGaA, P.O. Box 101161, D-69541 Weinheim;
For the annual subscription rate please refer to the Wiley Online Library:
http://olabout.wiley.com/WileyCDA/Section/id-404508.html
Address of editorial staff: DFG, Press and Public Relations Office, Kennedyallee 40, 53175 Bonn;
postmaster@dfg.de; www.dfg.de

Editor-in-chief: Marco Finetti (responsible for content)
Publishing Executive Editor: Dr. Rembert Unterstell
Copy Editors: Stephanie Henseler, Angela Kügler-Seifert
Translation: SciTech Communications GmbH, Heidelberg; oneword GmbH, Böblingen
Printed by: Bonner Universitäts-Buchdruckerei (BUB);
Printed on Inapa Oxygen silk, coated, 100% recycled, FSC certified paper with a semi-matt surface.

ISSN 0172-1518