IMMUNOLOGY

NO consumption by prostaglandin H synthase

Nitrogen-oxides (NO) properties of inhibiting platelets aggregation and inducing vasodilatation protect the body against inflammatory diseases. During inflammation, cytokines induces expression of inducible nitrogen oxide synthase (iNOS), which produces NO, as well as of prostaglandin H Synthase-2 (PGHS-2). Both enzymes are present in macrophages, where they have been shown to co-localize.

In their recent paper, Clark *et al.* [3] showed that, in macrophages and COS7 cells, PGHS-2 can catalytically consume NO and have, therefore, an effect opposite to iNOS. In macrophages that were treated with cytokine, in order to induce PHGS-2 and iNOS expression, NO consumption is increased in comparison with non-treated macrophages. In addition, activation of PHGS-2 with peroxides further increases NO consumption. These observations were confirmed by expressing PGHS-2 in COS7 cells, where iNOS is not present, showing also that NO consumption is also increased in these cell lines when PGHS-2 is overexpressed. Nevertheless, NO consumption remains higher in stimulated macrophages, where iNOS is present. Furthermore, the turnover rate of NO consumption by PGHS-2 is sufficient to deplete the endogenous NO. This suggest that, in macrophages, PGHS-2 use it as a substrate as soon as NO is produced by iNOS.

These findings not only attribute a new role for PGHS-2, but could also explain how PGHS-2 inhibition improves NO bioactivity during inflammation and cardiovascular diseases.

3 Clark, S.R. *et al.* (2005) Depletion of iNOS-derived nitric oxide by prostaglandin H synthase-2 in inflammation-activated J774.2 macrophages through lipohydroperoxidase turnover. *Biochem J.* 385, 815–821

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MICROBIOLOGY

Antimalarial activity of provitamin B5

An important vitamin required for the growth species, including the human malarial parasite *Plasmodium falciparum*, is pantothenic acid, also known as vitamin B5. This vitamin is a precursor to the important enzyme cofactor coenzyme A, and previous studies have shown that manipulating pantothenic acid levels in the host can affect the outcome of *Plasmodium* infections. Interestingly, pantothenic acid is not taken up by uninfected human erythrocytes; it enters parasitized erythrocytes via new permeability pathways induced in these cells by the parasite.

Pantothenol, or provitamin B5, the widely-used hair and skin care product supplement, has been previously shown to inhibit the growth of different bacteria. In a recent study by Saliba *et al.* [4], the authors reasoned that pantothenol could also have similar effects on *Plasmodium* organisms and could act by interfering with the pantothenic acid metabolic pathway. To test this hypothesis, the authors showed that pantothenol does indeed inhibit the growth of *P. falciparum in vitro* and that this is most likely due to competition between pantothenic acid and pantothenol for common sites in the parasite. Further experiments allowed the authors to show that pantothenol inhibited both the uptake and phosphorylation of pantothenic acid by the parasite.

NEUROSCIENCE

Discovering the painful genes

Nociceptive neurons are the first cells to receive painful input and are therefore of great interest for pain research. In order to understand which proteins play a key role in pain origin, knockout mice have been produced that completely lacked one or more genes. As most genes are expressed in several structures and not only in nociceptors, conclusions made from studies of these knockout mice are more general, and often the animals do not survive complete gene knockout. Therefore it is desirable to either knockout the gene of interest in the mature animal, or to do so only in specific cell systems.

A recent study seems to have solved this problem for the pain system. Stirling *et al.* describe an elegant way to knock out genes specifically in nociceptive neurons of mice [1]. They used the promotor of the voltage-gated sodium channel Nav1.8 to control tissue-specific expression of genes. This sodium channel is specifically expressed in nociceptive neurons and cannot be found in any other cell type. So its transcription is very selective for cells involved in pain perception. In their study, the authors inserted the DNA sequence for Cre recombinase directly upstream of the promotor for Nav1.8. Transcription of Nav1.8 in these heterozygous mice leads to expression of the sodium channel due to the nonmutated chromosome, and expression of the Cre recombinase protein due to its insertion into the mutated chromosome. Cre recombinase is able to cut out specifically marked genes from the genome, thereby knocking them out. It recognizes *loxP* sites in the DNA, sites that cannot be found in the normal mammalian genome. A gene artificially flanked with *loxP* sites, a so called *floxed* gene, will be eliminated from the chromosomes wherever Cre recombinase is expressed.

The mouse presented in the study had the Cre recombinase heterozygously inserted into the genome under the control of the promotor of Nav1.8, thereby rendering the mice into heterozygotic knockouts for this sodium channel. It has been shown previously [2] that heterozygous expression of this sodium channel is tolerated by the mice. In this supprot, Stirling *et al.* could not find any change in phenotype, pain behavior, or the voltage-gated sodium currents measured in cultured dorsal root ganglia cells from these mice.

The described alteration of the mouse genome provides a useful tool to discover more important genes and thereby painkiller drug targets involved in the pain pathway. This mouse, crossed with a mouse which has a *floxed* gene with possible impact on nociception, will provide animals that selectively lack the gene of interest in the nociceptive neurons. Thus, Stirling *et al.* have provided a useful tool for in-depth research targets involved in pain perception.

1 Stirling, L.C. *et al.* (2005). Nociceptor-specific gene deletion using heterozygous NaV1.8-Cre recombinase mice. *Pain* 113, 27–36
2 Akopian, A. *et al.* (1999). The tetrodotoxin-resistant sodium channel SNS has a specialized function in pain pathways. *Nat. Neurosci.* 2, 541–548

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To demonstrate an inhibitory effect of pantothenol in an *in vivo* experiment, the authors used the murine parasite *P. vinckei vinckei* in a mouse model of infection. The results showed that daily oral administration of pantothenol during four days immediately post-infection reduced parasitemia to levels 85% less than that of controls and prolonged the average survival time of the mice by ~five days. Given the ever-present need for new classes of antimalarial drugs, studies such as that reported in Saliba *et al*. show that the ability to inhibit the uptake and metabolism of key parasite nutrients (such as pantothenic acid) offer hope in the battle against malaria and other related diseases.

4 Saliba, K.J. *et al*. (2005) Provitamin B5 (pantothenol) inhibits growth of the intraerythrocytic malaria parasite. *Antimicrob. Agents Chemother*. 49, 632–637

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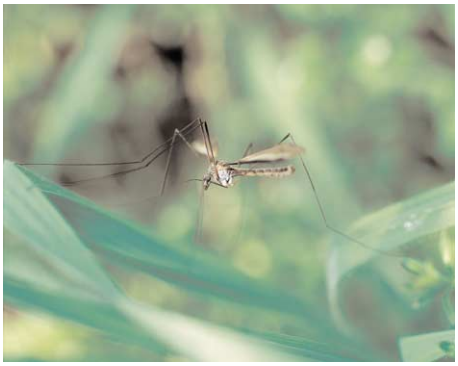
Ring-substituted 4-aminoquinolines and cross-resistance with chloroquine

Despite the recent widespread clinical deployment of artemisinin and its derivatives in antimalarial treatment, a desperate need remains for new antimalarial agents especially for use in combination therapy, which is now



recommended for all new antimalarial treatment regimens. Because of the past success of chloroquine, and evidence that the mechanism of drug resistance to chloroquine is independent of its mechanism of therapeutic action, the 4-aminoquinolines are still of great interest in spite of near universal chloroquine-resistance.

Considerable effort has thus focussed on elucidating structure activity relationships for both drug action and resistance in recent years. Changes to substituents, mainly at the 7-position on the quinoline ring as well as to the aminoalkyl side chain attached to the 4-amino group have suggested that the side chain is the main determinant of cross-resistance. On the other hand, the 4-amino-7-chloroquinoline nucleus together with the presence of a basic group in the side chain seems to confer the antimalarial activity of chloroquine. Nonetheless, a comprehensive study on the effect of quinoline ring substituents has not been available until now.

Madrid *et al*. [5] have now synthesized a library of 51 4-aminoquinolines with 32 different quinoline substitution patterns on the B (i.e. benzene) ring of the quinoline and with two different aminoalkyl side chains. The one side chain is identical to that of chloroquine, whereas the other is a shortened (aminopropyl) chain. Investigation of their *in vitro* antimalarial activities provides strong affirmation that the side chain is indeed the major recognition motif of the *Plasmodium falciparum* chloroquine resistance transporter (PfCRT). Intriguingly, however, the study does suggest a minor role for the quinoline ring as well, indicating that there could be value in searching for new quinoline nuclei for development of compounds with antimalarial activity. These findings are likely to be valuable in guiding the selection of new quinolines for investigation as potential antimalarials.

5 Madrid, P.B. *et al*. (2005) Synthesis of ring-substituted 4-aminoquinolines and evaluation of their antimalarial activities. *Bioorg. Med. Chem. Lett*. 15, 1015–1018

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