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# Serotonin$_{1A}$ receptor agonist acquires an antimalarial connection

Malaria is a major infectious disease. It affects over 100 million people worldwide in a year (Whitty *et al* 2002). In India alone, there are at least 2 million cases reported annually (Padmanaban 2003). The most severe form of the disease is caused by infection with the protozoan parasite *Plasmodium falciparum* leading to more than a million deaths a year (Whitty *et al* 2002). The morbidity and mortality are compounded by the spreading drug resistance to several existing malaria drugs. This has created an urgent need for novel drugs, which has become an important aspect of anti-malarial research (Biagini *et al* 2003). Since malaria is a highly complex, multifactorial disease, the spectrum of research activities for its prevention and management is vast. An interesting recent approach has been to target enzymes in the parasite necessary for biosynthesis of membrane components such as fatty acids (Bhat and Surolia 2001; Surolia and Surolia 2001) and sphingolipids (Lauer *et al* 1995).

Serotonin (5-hydroxytryptamine or 5-HT) receptors are members of a super-family of seven transmembrane domain receptors that couple to GTP-binding regulatory proteins (G-proteins). Serotonergic signalling appears to play a key role in the generation and modulation of various cognitive and behavioural functions. Among the types of serotonin receptors, the G-protein-coupled 5-HT$_{1A}$ receptor subtype has been the most extensively studied (Harikumar *et al* 2000). One of the main reasons for this is the availability of a selective agonist, 8-hydroxy-2-(di-*N*-propylamino)tetralin (8-OH-DPAT), that allows extensive biochemical, physiological, and pharmacological characterization of the receptor (Arvidsson *et al* 1981; Gozlan *et al* 1983).

A recent study by Locher *et al* (2003) reports that the selective serotonin$_{1A}$ receptor agonist 8-OH-DPAT inhibits growth of *P. falciparum in vitro* in a dose-dependent manner with a 50% inhibitory concentration ($IC_{50}$) in the micromolar range. The specificity of the effect was demonstrated by the fact that the growth of other pathogenic organisms such as *Leishmania infantum*, *Trypanosoma cruzi*, *Trypanosoma brucei brucei*, or *Trichostrongylus colubriformis* were not affected by 8-OH-DPAT. In addition, 8-OH-DPAT did not exhibit any cytotoxicity to the human lung fibroblast cell line MRC-5, used as a host to the parasite, implying that the action of 8-OH-DPAT on *P. falciparum* is specific. This is reinforced by the observation that the extent of growth inhibition of *P. falciparum* correlated well with the affinity of the specific agonist to the 5-HT$_{1A}$ receptor. Interestingly, specific antagonists of the serotonin$_{1A}$ receptor such as NAN-190 (hydrobromide 1-(2-methoxyphenyl)-4-(4-[2-phthalimido] butyl)piperizine) were found to be ineffective against the parasite and displayed $IC_{50}$ values which were ~ 100 times higher than the corresponding value for 8-OH-DPAT. Even this low inhibitory activity of the specific serotonin$_{1A}$ receptor antagonists did not show any correlation with the affinity of the antagonists for the receptor. This could be due to the insensitivity of G-protein subtypes, which are activated by the agonists, to the specific antagonists of the serotonin$_{1A}$ receptor (Harikumar and Chattopadhyay 1999). An encouraging aspect of the antimalarial activity of 8-OH-DPAT was that it was found to be synergestic when used in combination with other drugs such as chloroquine. Interestingly, 8-OH-DPAT did not reverse chloroquine resistance in *P. falciparum* isolates, but when the two drugs were combined, they were effective at nanomolar concentrations against chloroquine-resistant parasites. This is in contrast to the fact that when used alone, 8-OH-DPAT was effective at micromolar concentrations.

The mechanism underlying the antimalarial activity of 8-OH-DPAT is not clear. However, Locher *et al* (2003) have shown using a patch clamp assay that 8-OH-DPAT blocks a possible nutrient channel crucial for the development and growth of the parasite. It was earlier shown that 8-OH-DPAT

blocks voltage-sensitive $Na^+$ channels in rat synaptosomes and cortical membranes and this could be the basis for its action as a neuroprotectant (Melena *et al* 2000). Since there is no evidence for the presence of serotonin receptors either in the parasite or in the red blood cell, it is not clear at this point whether the mechanism of antimalarial activity of 8-OH-DPAT has any serotonergic component.

The inclusion of serotonin$_{1A}$ receptor agonists as potential antimalarial drugs opens up novel possibilities in the ever-challenging area of treatment and management of malaria. Since 8-OH-DPAT itself induces neurological and behavioural effects (Jackson and Kitchen 1989), it may not be possible to directly use this compound as an antimalarial agent. However, new lead compounds derived from 8-OH-DPAT by combinatorial synthesis – compounds which are suitably modified to prevent potential neurological side effects – could prove to be useful in combating malaria.

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