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Magnopulse® Studies Overview

Overview

The following outline is provided to enable assessment of the applicability of obtaining enhanced Intellectual Property protection based upon recent discoveries of specific and focussed clinical application of magnetic therapy together with novel observations relating to the modes of action within the human subject.

Background

The epidemiology and pathology of peripheral vascular disease

In pathological terms atherosclerosis remains the most common and hence the most clinically important cardiovascular disease. It is a generalised disease affecting the coronary, cerebral and peripheral circulations and is ubiquitous in Western populations. Cardiovascular disease may present clinically as myocardial ischaemia, stroke, and peripheral vascular diseases. Mortality is principally a consequence of ischaemic heart disease.

Peripheral vascular disease [PVD] is a result of stenotic occlusion of large peripheral arteries consequent upon changes in the vascular wall, which reduces blood flow to the limb. The most common of the serious peripheral vascular diseases are the occlusive arterial diseases [PAOD].

In the Western world mortality is generally a consequence of coronary artery and cerebrovascular disease, whereas PAOD is largely a morbid condition causing chronic disability and pain with a consequent reduction in the quality of life. However, as the same risk factors exist for both coronary heart disease [CHD] and PVD, they frequently coexist. Moreover, it has been recognised that mortality of patients with concomitant PVD and CHD is substantially greater than that in patients with PVD free from coronary ischaemic manifestations.

Atherosclerosis

Atherosclerosis is a dynamic process that involves interactions between the vascular wall and the blood and also the activation of a number of biological systems. The essential components of the disease pathogenesis are repeated damage to vascular endothelial cells, coagulation, the deposition, migration and esterification of lipids within the vascular wall and the proliferation of vascular smooth muscle cells. Atheroma lead to alterations in arterial elasticity, luminal narrowing, vasospasm and a reduction or cessation of the blood supply to tissues and critical organs.

The mechanisms by which disequilibrium occurs are not fully understood. However, the exposure of the sub-endothelial connective tissue (principally collagen) to the blood at the sites of vascular endothelial injury initiates thrombotic platelet aggregation and leads to the activation of the intrinsic coagulation system. Current theories regarding the pathogenesis of atherosclerosis are based upon our understanding of the interactions between the vascular wall and the blood.

Restless Leg Syndrome

The term Restless Leg Syndrome was coined by Professor Karl-Axel Ekbom in 1944 and is therefore also known as "Ekbom's disease". Restless legs syndrome (RLS) is a neurological disorder with unpleasant sensations in the legs and an uncontrollable urge to

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move when at rest to try to relieve these feelings. RLS sensations are often described by people as burning, creeping, tugging, or like insects crawling inside the legs, and a wide variety of descriptions is included in diagnostic criteria. Often called paresthesias (abnormal sensations) or dysesthesias (unpleasant abnormal sensations), the sensations range in severity from uncomfortable to irritating to painful.

Lying down and trying to relax activates the symptoms or makes them worse. Most people with RLS have difficulty falling asleep and staying asleep. People are exhausted with daytime fatigue and sleepiness. Many people with RLS report that job, personal relations, and activities of daily living are strongly affected as a result of this exhaustion, because they are unable to concentrate, or have impaired memory.

RLS probably affects 5-10% of people, but may be under diagnosed and, in some cases, misdiagnosed. Some people with RLS will not seek medical attention, believing that they will not be taken seriously, that their symptoms are too mild, or that their condition is not treatable. Some physicians wrongly attribute the symptoms to nervousness, insomnia, stress, arthritis, muscle cramps, or aging.

In most cases, the cause of RLS is unknown (referred to as idiopathic).

Methods

Six subjects with a clinical diagnosis of Restless leg syndrome were assessed prior to magnetic therapy and a comprehensive haematology coagulation profile obtained at baseline and following one month of unilateral therapy. The device was applied to the most affected leg.

The LegCare[®] wrap contains four powerful neodymium magnets (2000 gauss). Each magnet has patented and unique directional plates that allow the negative (south-facing) enhanced magnetic field to be absorbed deeper into the tissues; it is thought that this gives more effective and longer lasting effect. The wraps are fitted below the knee and above the calf muscle (not under compression) and are held in place by “hook and loop” fastening tape. The leg wraps are double lined for comfort, and are adjustable and washable.

Results

All subjects reported an improvement of Restless leg symptoms. This is in keeping with a recent survey completed by Dr N. Eccles.

Quote: “We previously reported findings from a survey of 459 subjects who suffered from Restless Leg Syndrome. The median duration of symptoms in subjects surveyed was 10 years.

It was found that after analysing the symptoms reported before and after the use of the LegCare[®] device, that there was a statistically significant reduction $p < 0.001$ for all symptoms) in all the symptoms associated with RLS (pain, tingling, loss of sleep) with overall symptoms being reduced by 50% ($p < 0.001$). This was statistically significantly better than the amount of relief that these subjects had obtained with drugs (20%, $p < 0.001$) and other non-drug treatments (10%, $p < 0.001$). 66.1% of subjects had greater than 30% improvement and 45% had greater than 50% improvement in symptoms.

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Moreover, a statistically significant improvement in quality of life was also reported. The same group of subjects were asked to report back by questionnaire after 5 months use of the device.”

von Willebrand’s factor antigen

von Willebrand’s factor [vWF] is a shear-induced plasma glycoprotein, which is normally synthesised by platelets, endothelial cells and megakaryocytes. vWF promotes thrombus formation by mediating adhesion of platelets to the site of injury on the vessel wall and to each other. The plasma concentration and activity of vWF are influenced by several factors, including blood group, inflammation, and proteolysis which reflect the degree of platelet activation; and hence may be used as a marker of vascular injury (Ruggeri, 1997; Bongers et al, 2006).

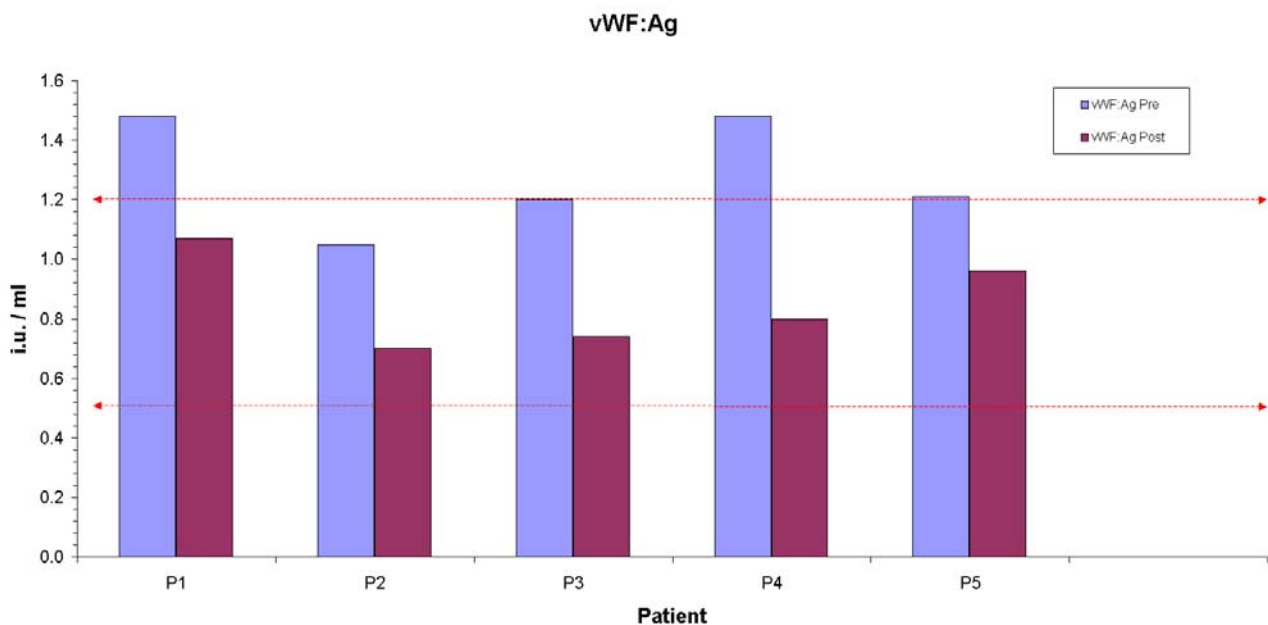
High vWF antigen levels are a risk factor for cardiovascular disease.

Ruggeri ZM. (1997)
von Willebrand factor.
J Clin Invest 99(4):559-64.

Bongers et al. (2006)
High von Willebrand Factor Levels Increase the Risk of First Ischemic Stroke
Influence of ADAMTS13, Inflammation, and Genetic Variability
Stroke ;37;2672-2677.

Figure X

Demonstrates a significant reduction in the vWF antigen following one month of unilateral magnetic therapy in patients with Restless Leg syndrome. The horizontal red dashed lines represent the upper and lower normal ranges. Of the five Subjects reported below, all demonstrated a significant decrease in vWF:Ag following therapy. Importantly, four had abnormally elevated vWF at baseline which decreased to normal following therapy.



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Platelet Aggregation

Long recognized as having a role in inflammation, platelets and platelet–leukocyte aggregates are now known to contribute to ongoing injury at atheromatous sites, and in plaque disruption. Platelet P-selectin (CD62P) interacts with its natural ligand on neutrophils and monocytes, and P-selectin, to allow formation of platelet monocyte aggregates, thus providing an anchoring source for inflammatory cells on activated platelets.

These bioactive platelet–monocyte aggregates have been shown to be important in cardiovascular disease in humans as they are involved in ongoing vascular inflammation and thrombosis.

The measurement of indicators of platelet activation during routine haematological investigations offer advantages in the clinical evaluation and management of patients at risk from thrombotic and other diseases. The assays were performed in accordance to the protocols designed and reported in Macey et al 2003.

Macey M, McCarthy D, Azam U, Milne T, Golledge P, Newland A. (2003)

Ethylenediaminetetraacetic acid plus citrate-theophylline-adenosine-dipyridamole (EDTA-CTAD): a novel anticoagulant for the flow cytometric assessment of platelet and neutrophil activation ex vivo in whole blood.

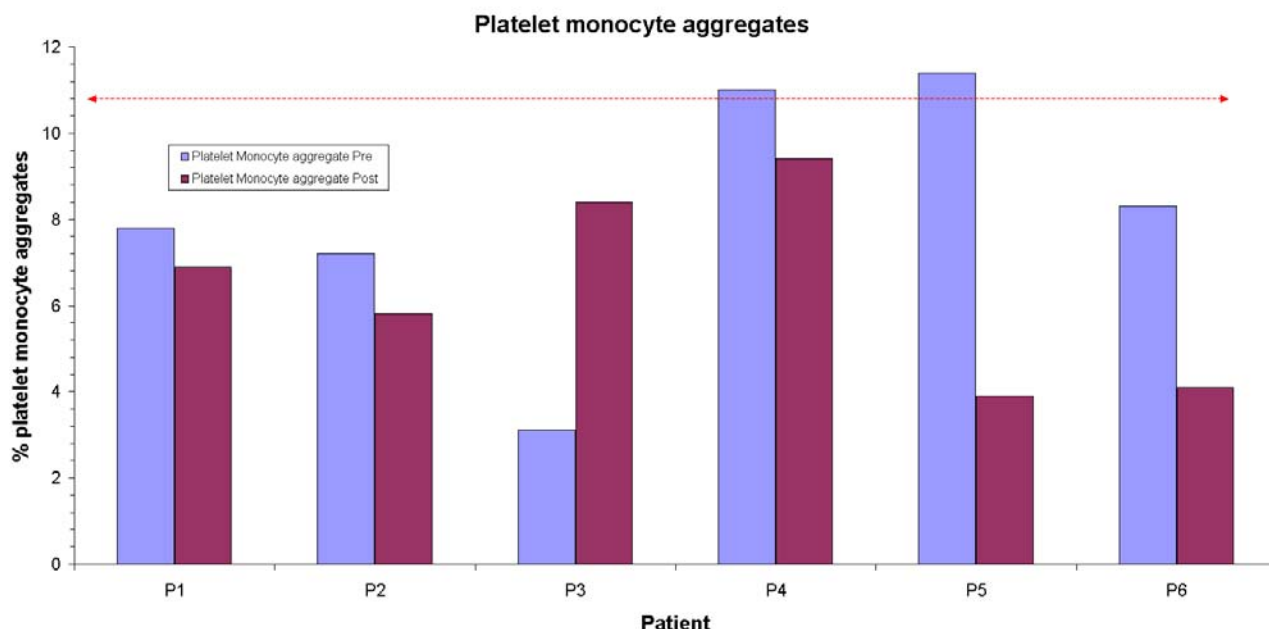
Cytometry B Clin Cytom. ;51(1):30-40

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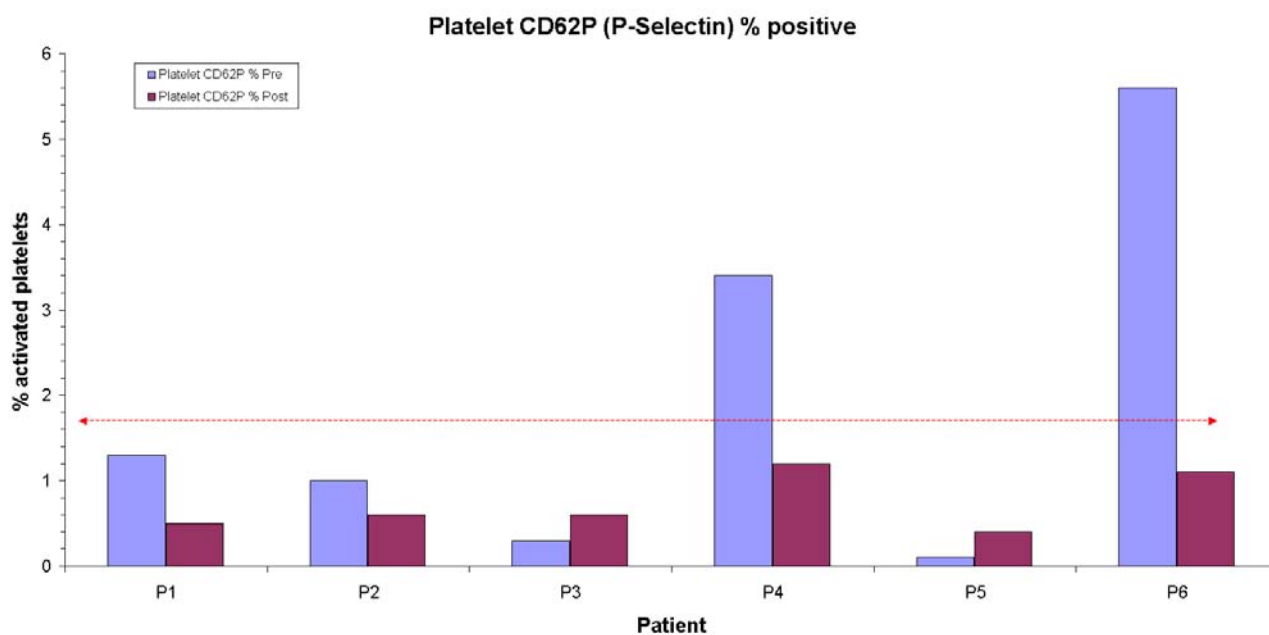
Figure Y

Demonstrates alterations in the levels of [a] Platelet monocyte Aggregates and [b] Platelet P-Selection levels in patients with Restless Leg syndrome. The horizontal red dashed line represents the upper normal ranges.

In graph [a] Platelet monocyte Aggregates, five of the Subjects demonstrated a fall in aggregates. Importantly two had abnormally elevated monocyte aggregates at baseline which decreased to normal following therapy.



In graph [a] [b] Platelet P-Selection, four of the Subjects demonstrated a fall in aggregates; two had abnormally elevated monocyte aggregates at baseline, which decreased to normal following therapy.



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Interpretation

The application of magnetic therapy in the Magnopulse[®] South-pole configuration, when applied to the lower limb elicited clinical improvement in the symptoms of Restless leg syndrome indicating local biological effects.

The therapy furthermore had a systemic effect on blood coagulation markers, in particular vWF:Ag and Platelet Aggregation.

Modulation of these biological processes have application in the treatment and prevention of Restless Leg syndrome.

Modulation of these biological processes have application in the treatment and prevention of cardiovascular diseases including myocardial ischaemia, stroke, and peripheral vascular diseases.

Centrally related to these new claims of application, we propose that the mechanisms of action are not a magnetic effect on the erythrocyte (red blood cell) due to its iron content as is alluded to in many of the patent documents and literature relating to magnetic therapy.

The data presented above indicates a novel and to date unrecognised mode of action of this specific magnetic therapy via the vascular endothelium, which explains both the local and systemic effects of the therapy.

The vascular endothelium lies as a monolayer of cells on the luminal surface of all normal blood vessels. On the abluminal surface of the endothelial cells there is a basement membrane composed of fine connective strands binding the cells to the sub-endothelium. The latter is composed of connective tissue and contains collagen fibres, which if exposed to the blood by endothelial disruption immediately initiate clotting, and later endothelial repair. The greater part of the vascular wall, the media, is composed of a variable amount of vascular smooth muscle cells and elastic tissue.

The vascular endothelium is integral to the normal function of blood vessels. Under normal conditions the luminal endothelial membrane provides an anti-inflammatory barrier and a non-thrombogenic surface to circulating platelets. This refractiveness to platelet adhesion appears to be a result of membrane polarity and a repulsion of negatively charged cell membranes. The vascular endothelium also regulates permeability to water and solutes via actin and myosin interactions within the endothelial cells. However, selected plasma protein molecules are able to permeate the vascular wall and gain access to the interstitial spaces and cell junctions. Additionally, there exists a vast heterogeneity of the morphology and function of vascular endothelium at different sites e.g. the kidney, liver, blood/brain barrier.

Only recently has it become recognised that intact vascular endothelial cells are also responsible for the elaboration and secretion of a number of vasoactive factors. These compounds have both autocoidal and paracoidal activities and play a pivotal role in the control of blood flow by participating in the local regulation of tone in the vascular smooth muscle. Endothelial-derived vasoactive factors not only control vascular tone, but also vascular smooth muscle cell proliferation and the maintenance of the non-thrombogenic characteristics of the endothelial surface to circulating blood platelets.

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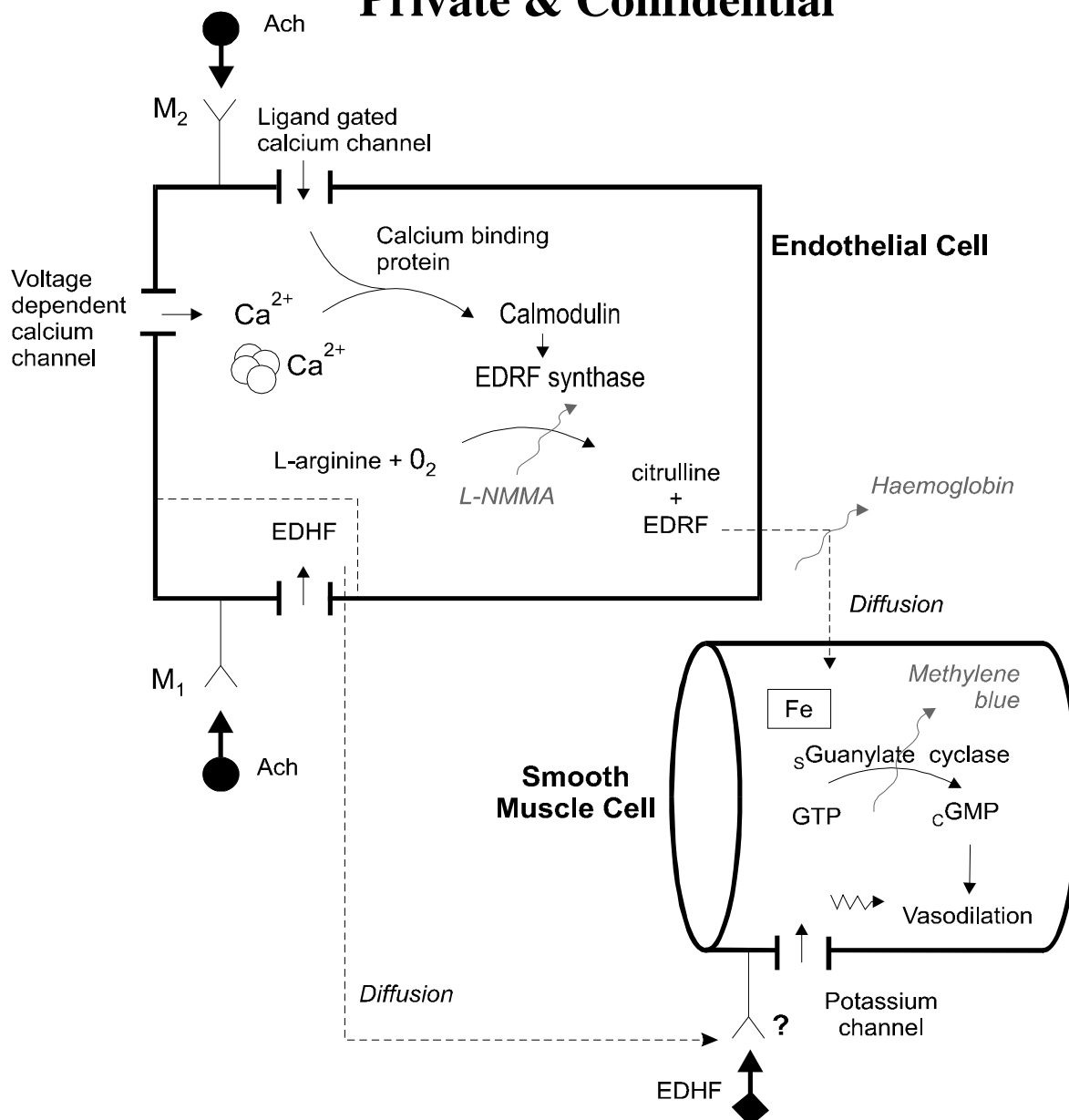
We propose that the biological effects of this specific magnetic therapy are elicited via the modulation of the endothelial cell functions, and specifically mammalian cellular receptors and ion channels such as calcium, potassium and sodium gates.

These 'gates' are responsible for cellular communication and influence a wide variety of biological processes that involve rapid changes in cells, such as cardiac, skeletal, and smooth muscle contraction, endothelial transport of nutrients and ions, T-cell activation and pancreatic beta-cell insulin release

Such mechanisms of action may be further reasonably extended to the principal cellular components of the blood such as immune cells (white blood cells), platelets and erythrocytes (red blood cells).

These cellular receptors and gates exist both intracellularly and on the within the cell wall where they are intimately involved in the balance between anti-aggregatory and pro-aggregatory factors. An example of which is provided below for illustration purposes.

Furthermore, modulation of these essential components of the classical inflammatory response would indicate to the person 'skilled in the art' that such therapy would have beneficial application to disease processes which have a substantive inflammatory component; such as rheumatological diseases, inflammatory bowel disease, atherosclerosis and psoriasis.



Schematic representation of the production and release of endothelium-derived relaxing factor in response to acetylcholine stimulation.

A messenger molecule such as acetylcholine [Ach] binds to the type-2 muscarinic [M₂] receptor on the endothelial cell, activating inward calcium currents and utilising intracellular calcium stores. Calcium binds to calmodulin and activates endothelial cell endothelium-derived relaxing factor [EDRF] synthase, which converts L-arginine in the presence of oxygen into citrulline and EDRF. EDRF diffuses out of the endothelial cell into an adjacent smooth muscle cell, there activating guanylate cyclase by binding to the iron in its haem group. The resulting reduction of 3'-5'-guanosine triphosphate [cGTP] to cyclic 3'-5'-guanosine monophosphate [cGMP] and the increase of calcium uptake by the smooth endoplasmic reticulum results in vasodilation. Endothelium-derived hyperpolarising factor [EDHF] production occurs following Ach binding to the type-1 muscarinic [M₁] receptor via a yet unknown pathway. EDHF diffuses out of the endothelial cell into the adjacent smooth muscle cell where it causes hyperpolarisation of the cell membrane and enhances the uptake of EDRF. Basal production of EDRF may also occur via the utilisation of intracellular calcium stores. The L-arginine cascade may be inhibited at a number of levels by N^G-monomethyl L-arginine [L-NMMA], haemoglobin and methylene blue.