Relaxin: a potential new treatment for vasoconstrictive disorders

The hormone, relaxin, could be used to treat disorders resulting from vascular insufficiency, such as non-healing ulcers in peripheral arterial disease, and some cardiovascular and renal conditions. Relaxin is a peptide hormone that is produced during pregnancy and is structurally related to insulin and insulin-like growth factor 1.

Mechanism of action of relaxin

During pregnancy, relaxin is secreted by the corpus luteum and the placenta. By inhibiting collagen synthesis and promoting collagen breakdown through increased synthesis of collagenase, this hormone facilitates enlargement of the uterus, abdomen and breasts and loosens the pelvic ligaments. It is also thought to mediate blood vessel dilation, both in pregnancy and during the menstrual cycle[1]. The vasodilatory effects can be replicated in male animals[2].

This pro-angiogenic action of relaxin is caused by induction of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) expression[1,3]. Relaxin also stimulates the formation of new blood vessels *in vivo* in mice fitted with Matrigel plugs[3]. Another physiological change that occurs during pregnancy is vasodilation, which is particularly marked in the renal circulation[4]. Relaxin is thought to be involved in this response, via the induction of nitric oxide. Recent work by Conrad and colleagues shows that relaxin attenuates the renal vasoconstrictive effects of angiotensin II in rats[4], and mediates renal vasodilation through the endothelin B receptor.

These properties make relaxin a potential treatment for a range of disorders that are caused by inadequate blood flow. Formerly extracted from pigs, the hormone is now available in recombinant human form (rhRlx; Fig. 1). Studies in patients with scleroderma (systemic sclerosis), where rhRlx is in Phase II/III clinical trials for its anti-fibrotic action, have shown that it is safe and well tolerated[5].

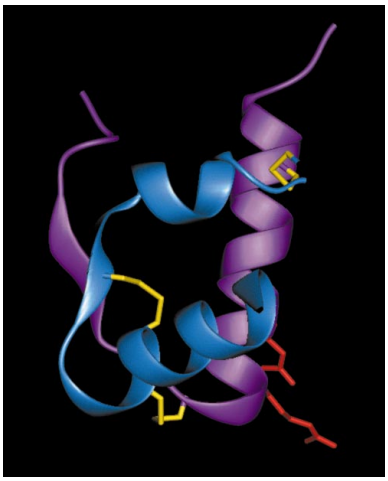

Figure 1. *Recombinant human relaxin. (Reproduced by permission from Connetics Corporation.)*

Relaxin in wound healing

In work presented to the *Wound Healing Society's 2000* meeting (4–6 June 2000) in Toronto, Canada, researchers at Connetics Corporation (Palo Alto, CA, USA) reported that relaxin stimulates ischaemic wound healing in rats (Arnold, G. *et al.* Systemic administration of recombinant human relaxin stimulates ischaemic wound healing in rats.). Rats were fitted with Hunt-Schilling wound chambers at either the shoulder (which has a good blood supply) or in the hip region (which is more ischaemic). RhRlx or vehicle was infused subcutaneously using implanted pumps and, after 18 days, fluid and cells collected from the wounds were analyzed for vascular endothelial growth factor (VEGF) mRNA and basic fibroblast growth factor (bFGF; another angiogenic agent).

Expression of both factors was increased at both wound sites in the relaxin-treated rats compared with controls (Fig. 2). In the more ischaemic hip wounds, relaxin also produced a significant increase in granulation tissue and in the number of capillaries formed. In another group of rats,

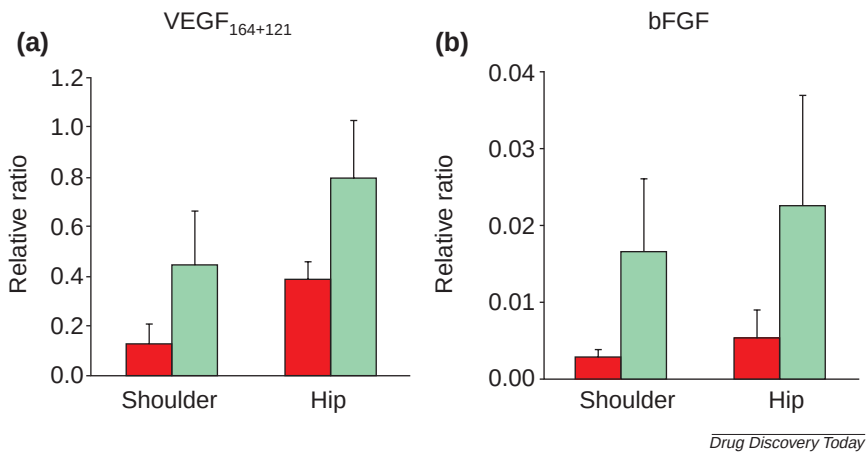

Figure 2. *Systemic administration of rhRlx increases expression of (a) VEGF and (b) bFGF in experimental wound chambers in rats, compared with controls. The acetate response is shown in red and the relaxin response is shown in green. (Reproduced by permission from Connetics Corporation.)*

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standardized ischaemic H-shaped double-flap wounds were created on the back. After 14 days, relaxin-treated rats had a significantly smaller area of surface necrosis at the wound than controls. Relaxin is thought to have stimulated healing of the ischaemic wounds by increasing blood flow through vasodilation and angiogenesis. However, it had no effect on healing times for well-vascularized wounds.

Potential future clinical uses

Connetics believes that the vasodilatory and pro-angiogenic properties of relaxin could be used to treat conditions caused by constricted blood vessels, including peripheral arterial, cardiovascular and renal disease. There are currently few treatment options for the advanced stages of these diseases. In peripheral arterial disease, surgery is often necessary, resulting in approximately 179,000 revascularization surgeries and 68,000 amputations in the US each year. 'We are very optimistic about relaxin for peripheral vascular indications,' said Krisztina Zsebo, Executive Vice President of Research and Product Development at Connetics.

Enrollment will begin shortly for a Phase II clinical trial of 120–140 peripheral arterial disease patients who have recently undergone surgical revascularization of a lower extremity and who have at least one unhealed ischaemic or operative wound in that region. They will be treated for 16 weeks with continuous subcutaneous infusion of rhRlx at 10, 25 or 100 $\mu g\ kg^{-1}\ day^{-1}$, or placebo. The study will evaluate the time to complete wound healing, as well as a range of related parameters. As peripheral arterial disease is often accompanied by renal disease, the study will also evaluate the effect of rhRlx on renal function.

As well as working on a range of cardiovascular and renovascular indications, Connetics is also pursuing clinical development of relaxin for the treatment of infertility, and conducting ongoing trials in scleroderma.

REFERENCES

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Jo Whelan

Startling new impetus for schizophrenia research

An abnormal reaction to prepulse inhibition (PPI) of the startle reflex (see Box 1 and Fig. 1) is common in schizophrenics. Tonmoy Sharma and colleagues (Institute of Psychiatry, London, UK) have now shown that the severity of this abnormal response can accurately distinguish between early-onset and adult-onset disease[1]. This new information could lead to a significant reduction in time necessary for the development of new antipsychotics.

'These two identifiable subtypes of schizophrenia are well known but until now, there has been no marker: patients have been categorized by medical history and, if a late diagnosis was made, the picture becomes very cloudy,' explains Sharma.

A complex disorder

Schizophrenia is a group of disorders, first recognised in the 1940s. Since then, progress in developing therapeutic strategies and in understanding the molecular basis of the disorder has been relatively slow compared with, for example, cognitive disorders such as

Box 1. Prepulse inhibition

Prepulse inhibition of the startle reflex is the reduction in a strong startle response in people subjected to a lesser stimulus before the main stimulus. In this study, the main stimulus was 40 ms of white noise at 115 dB – a click loud enough to elicit a blink response. The pre-pulse was 20 ms of white noise at 85 dB – not enough to elicit a blink response. The pre-pulse was presented 30, 60 and 120 ms before the main pulse response, or not at all. In normal subjects, the main stimulus alone elicits the blink response.

The pre-pulse inhibits their response to the main stimulus, making them less likely to blink. The inhibitory mechanisms activated by the prepulse are thought to reduce the impact of the pulse to prevent the brain from 'overload' of information. Reduced prepulse inhibition has been repeatedly demonstrated in schizophrenics, which fits the proposed deficiencies of information processing that are thought to underlie the disease.

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