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TARGETING THE INTERSTITIAL CELLS OF CAJAL IN THE DEVELPOMENT OF NOVEL PHARMACOTHERAPIES FOR DETRUSOR OVERACTIVITY.

Hypothesis / aims of study

The Interstitial Cells of Cajal (ICC) are pacemaker cells responsible for the generation of spontaneous activity in smooth muscle of the gastrointestinal tract. They are characterized by displaying receptors for c-kit antibodies, and ICC-like cells also displaying c-kit have been identified in the guinea-pig and human bladder (1,2), although their function is uncertain. A drug known to inhibit c-kit receptors is Glivec (imatinib mesylate, STI-571; Novartis Pharmaceuticals). It has known activity against tyrosine kinases, and has FDA approval for the treatment of Chronic Myeloid Leukaemia (CML) and gastrointestinal stromal tumours (GIST) (3). We have investigated the effects of Glivec on the whole guinea-pig bladder and both 'normal' and overactive human detrusor strips.

Study design, materials and methods

Whole organ bath set-up.

Whole bladders were retrieved from male Dunkin Hartley guinea-pigs (350-450g). The ureters were ligated and the urethra cannulated and connected to a signal transducer and syringe pump. The bladder was then suspended in a bath of carboxygenated Krebs' solution, kept at 37^{o}C, and filled with 2mls of normal saline (at 8mls/hr). After 60 minutes of equilibration, pressure changes in the bladder were recorded and the effects of Glivec on spontaneous activity and the responses to stimulation of the intrinsic nerves by electrical field stimulation (EFS) (20Hz, 5s train duration, 1ms pulses, 70V), and carbachol (CCh) 10^{-6}M were examined.

Human strip work

'Normal' human tissue was retrieved from 2 patients (one male and one female; mean age 54 years), taken at the time of cystectomy and from transplant donation. Detrusor was retrieved at myectomy in a 28-year-old female patient with urodynamically proven detrusor overactivity. Full ethical approval and consent were in place for all of the above. The tissue was stripped of mucosa, and smooth muscle strips (2mm x 2mm x 4mm) were dissected out and mounted vertically in a superfused organ bath apparatus (37^{o}C, pH 7.4). Changes in muscle tension were recorded after EFS (5-50Hz, 5s train duration, 0.05ms pulses, 50V), and after application of CCh 10^{-5}M in the presence of Glivec. The effect of Glivec on any strips developing spontaneous activity was also noted.

Results

Whole organ bath.

Glivec produced a dose-dependant decrease in the amplitude of spontaneous activity, which became significant from 10^{-6}M. Effects on frequency were variable. At concentrations of 10^{-5}M and $5x10^{-5}$M, Glivec significantly reduced detrusor responses to EFS to 84.35% ($p<0.0001$) and 76.54% (p 0.0007) of the control response respectively. Glivec $5x10^{-5}$M also significantly reduced the response to carbachol to 48.36% (p 0.029) of the control response, but lower concentrations had no effect.

Human detrusor strips

In 'normal' bladder, Glivec significantly inhibited EFS at 10^{-5} and $5x10^{-5}$M (maximally inhibited to 40% of the control at 50Hz), but only the highest concentration inhibited the response to carbachol (reduced to 41% of the control). However, in the overactive bladder, a dose-dependant inhibition of EFS was seen, which was significant from 10^{-6}M (response reduced to 59% of the control at 5Hz). Again the maximal inhibitory response was seen at $5x10^{-5}$M (maximally inhibited to 30% of the control at 50Hz). Glivec also produced a significant inhibition of the carbachol response from 10^{-6}M, although the overall effect was much less than for the nerve-evoked contraction (reduced to 90% of the control at 10^{-6}M; 87% at $5x10^{-6}$M; 72% at 10^{-5}M and 23% at $5x10^{-5}$M). Early results also indicate that Glivec 10^{-6}M and $5x10^{-6}$M appeared to reduce the frequency of spontaneous activity seen in overactive detrusor strips.

Interpretation of results

The effects of Glivec on spontaneous activity suggests that the ICCs may have a role in modulating activity in the bladder. Glivec significantly inhibited spontaneous activity at low concentrations (10^{-6}M) in the guinea-pig bladder, and in the overactive bladder strips. It is known that detrusor strips taken from patients with urodynamically proven bladder abnormalities (such as detrusor overactivity), have increased spontaneous activity that is likely to contribute to clinical symptoms, and it may be here that Glivec could play an important role.

At higher concentrations (10^{-5}M and $5x10^{-5}$M) it appears that Glivec is effective at inhibiting smooth muscle contraction evoked by EFS in both guinea-pig and 'normal' human detrusor, however effects on muscarinic evoked contraction are only seen at the highest concentrations (where effects may be non-specific). In contrast, the overactive bladder appeared to be extremely sensitive to the drug at low doses, and nerve stimulation appeared to be most susceptible to suppression by Glivec. Potentially, this could be developed to suppress abnormal contractions, and improve bladder capacity and the symptoms of frequency and urgency.

Concluding message

Glivec has proved to be a useful tool to explore the effects of blocking the ICC-like cells of the bladder, and to see if there is any clinical value to developing drugs to antagonize these specific targets. This early work does show some promising effects, especially on the overactive bladder. The suppression of evoked bladder contractions, and the potential ability to also suppress spontaneous activity in the overactive bladder, suggest that Glivec may be developed as a new treatment for the symptoms of detrusor overactivity.

References

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FUNDING: British Urological Foundation Scholarship and Oxfordshire Health Services Research Committee Research Grant