Medicinal Chemistry
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Anti-Ulcer Agents

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Ok, so in the previous lecture we looked at the various aspects of cholinergic system, of course this is the principles involved here are also going to be involved in the other receptor ligand binding systems. So now we looked at how the molecule is actually you know has very little room for manoeuvre and one could develop new agents which can be agonist by systematically studying the binding capability and the agonist activity.

So now we will look at another important aspect of disease which is called as Ulcer ok, so we will briefly look at one of the important case studies in development of anti-ulcer agents and this gives us one of the important examples of rational drug design.

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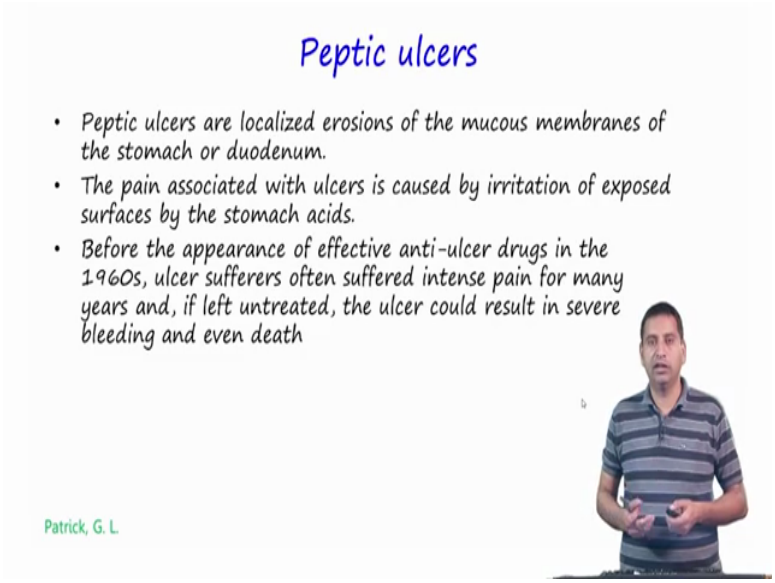

So just to give you a brief introduction to Peptic ulcers, so these occur when the there are erosions and the mucous membrane of the stomach or duodenum, so these are ulcers can be extremely painful especially when it is exposed to surfaces of the stomach acid. So before the appearance of effective anti-ulcers agents in the 1960s there used to be the people who suffered from ulcers had intense pain for many years ok, so what can also happen is because if you do not treat this it can lead to severe bleeding and eventually even death.

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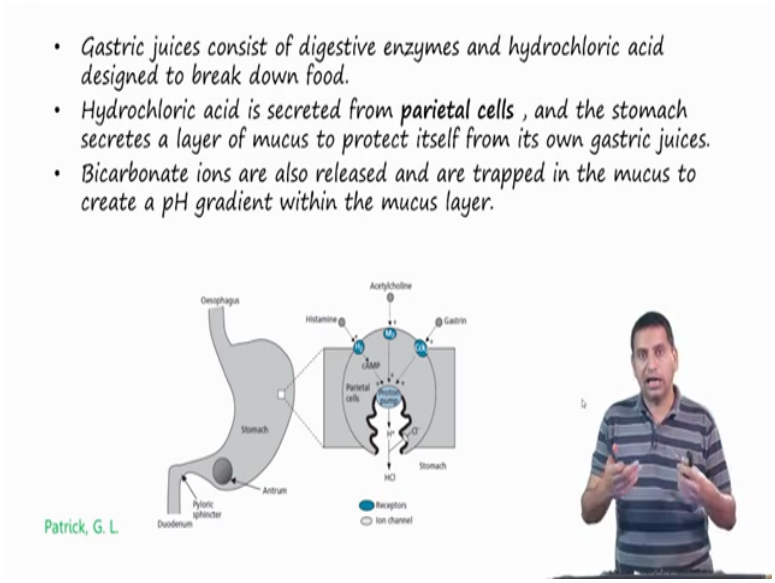

So just to recap what the system looks like, so here is the gastric system here the gastric juices are which contain digestive enzymes and hydrochloric acid these are break down food. So hydrochloric acid is actually secreted by parietal cells and the stomach secretes a layer of

mucus to protect itself from its own gastric juices. So Bicarbonate ions are also released and trapped in the mucus to create a pH gradient within the mucus layer, so this helps in protecting the stomach from the acid that it itself secretes.

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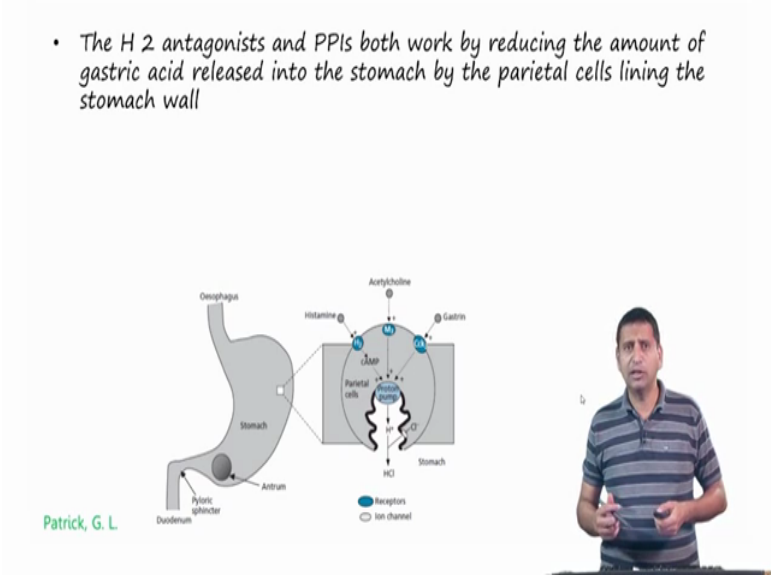

So here the H 2 antagonists and PPIs both work by reducing the amount of gastric acid, ok so one way in which we can treat this is to reduce the amount of secretion of acid by the parietal cells.

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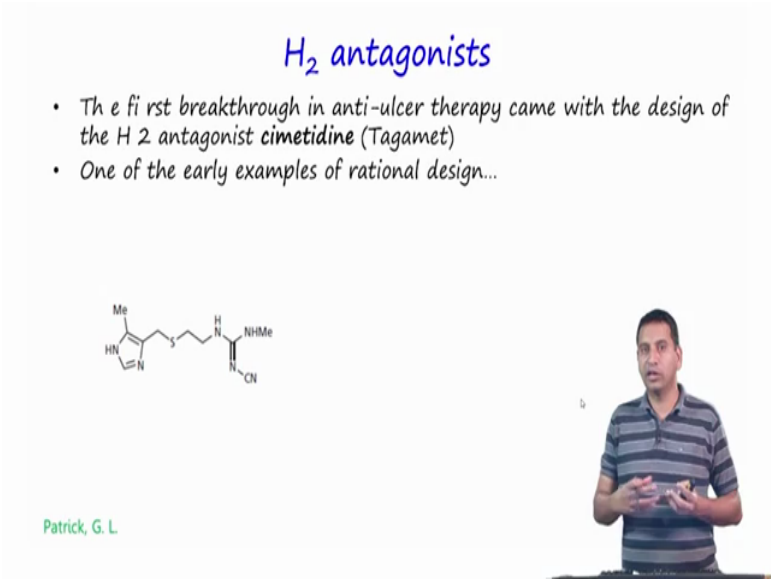

So now let us look at a case of the H 2 antagonists and it is important case study for us because it is considered as one of the first breakthroughs in anti-ulcer therapy which came by

the design of cimetidine. So here in today is lecture we will look at some of the aspects of this entire case study because the entire case study itself will take a lot of time and it also involves a the explanation of major concepts, so what i will do is i will walk you through some important aspects of it, ok.

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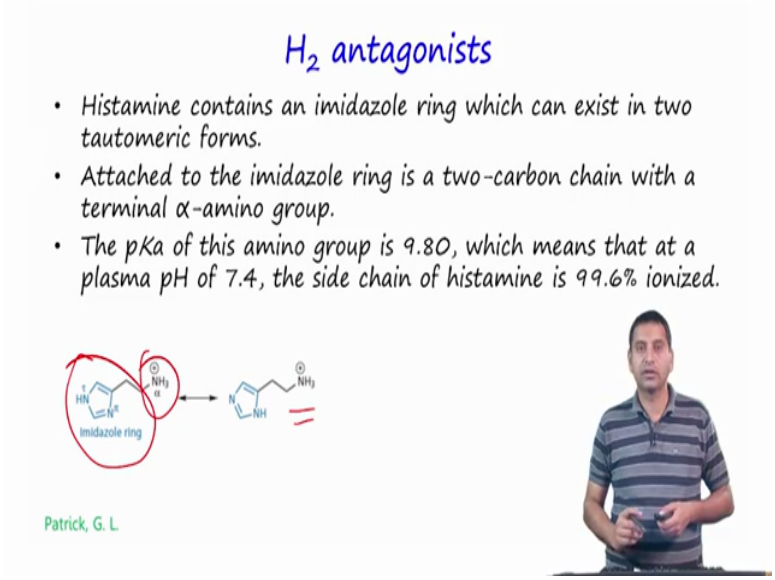

So just to give an introduction histamine is an important molecule and it contains an imidazole ring which can exist in two tautomeric forms, here is the imidazole ring of histamine. So the pKa of the amino group is about 9 point 8 ok which means that in the plasma pH of 7 point 4 the side chain of histamine is about 99 point 9 percent ionized, ok.

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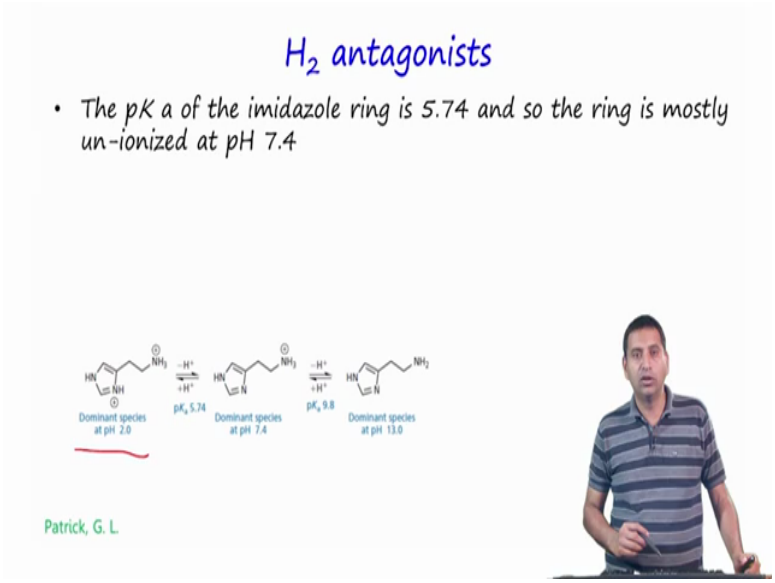

The pKa of the imidazole ring itself is 5 point 74, so the ring is mostly not ionized so except in the case of extremely low pH of two where it would be ionized.

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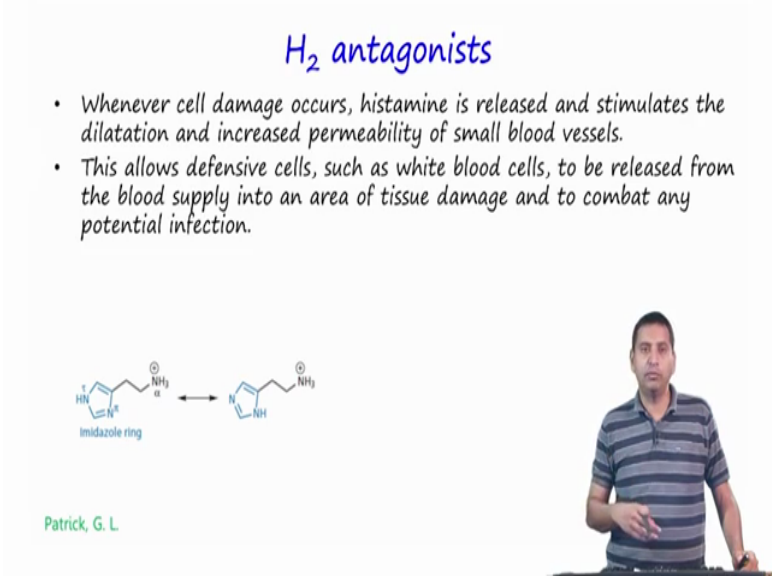

So whenever a cell damage occurs histamine is released in in the proximity and what this does is it stimulates the dilation and increases permeability of small blood vessels, so that allows the defensive cells such as WBCs to be released from the blood supply to repair the tissue damage and combat any potential infection.

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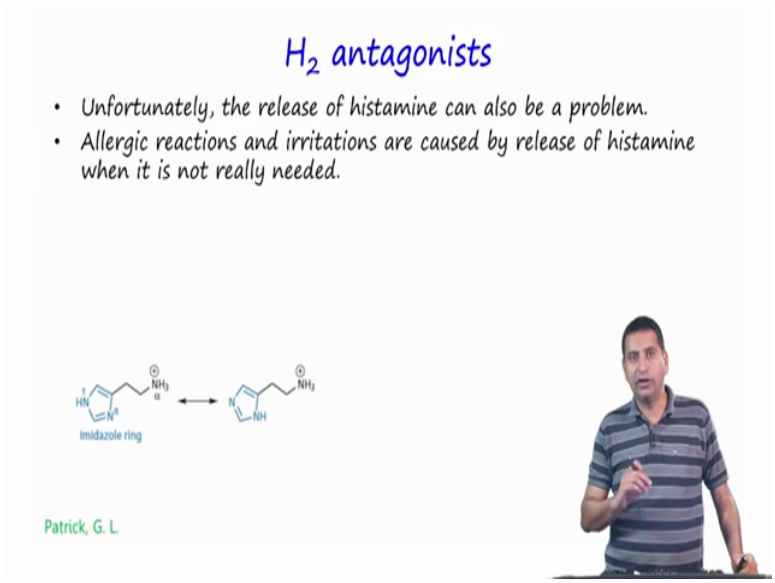

Unfortunately the release of histamine is also a problem because a number of allergic reactions and irritations are caused by the release of histamine when it is not really needed.

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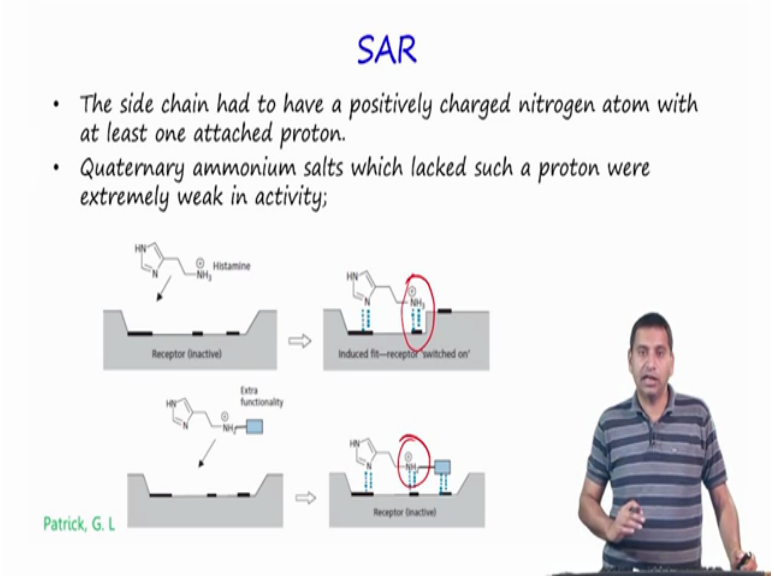

So the side chain of histamine is positively charged and it must bind to the receptor site in the following manner, so when you have the ammonium ion binding to one part of the receptor you have induced fit which then results in the signalling molecule, the quaternary ammonium salts which were which lacked the proton were extremely weak in activity.

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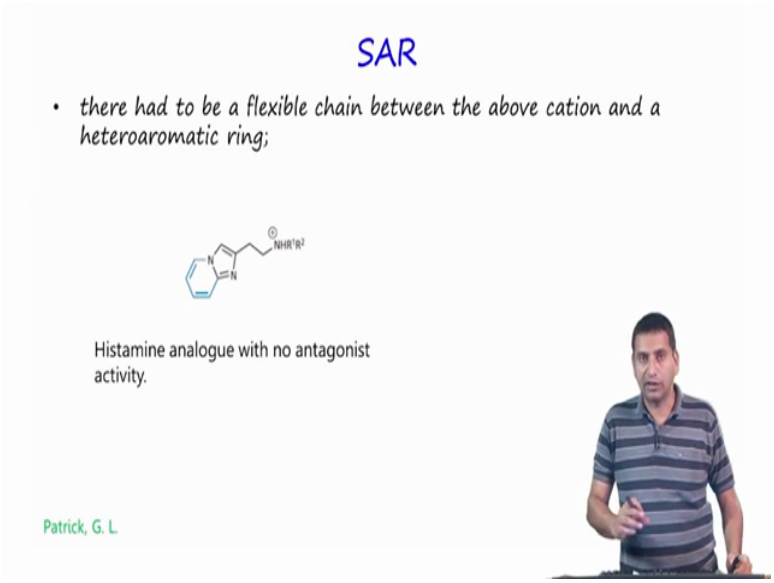

So the next part of the SAR involved the flexible chain between the above cation and the heteroaromatic ring. So when you had the chain to be less flexible then again it was not active.

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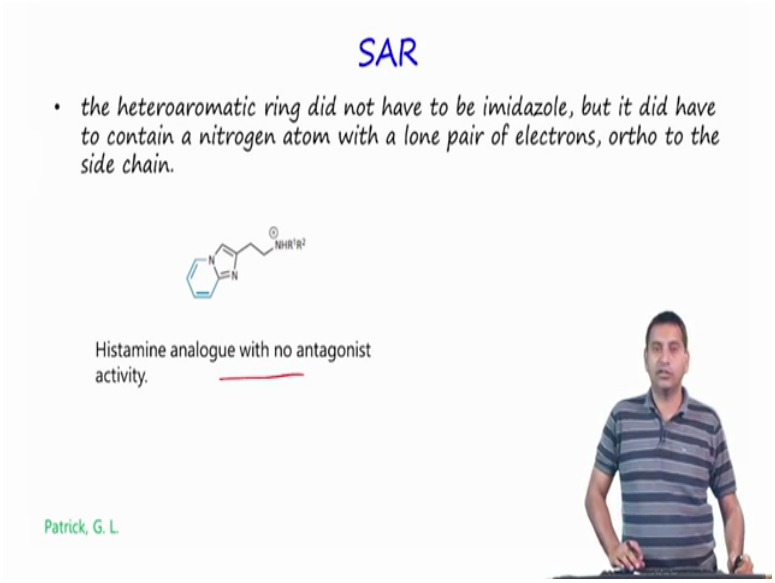

So the hetero aromatic ring does not have to be an imidazole but it had to be a side chain containing a nitrogen with the lone pair of electrons ortho to the side chain. So here is an example of a histamine analogue with no antagonist activity.

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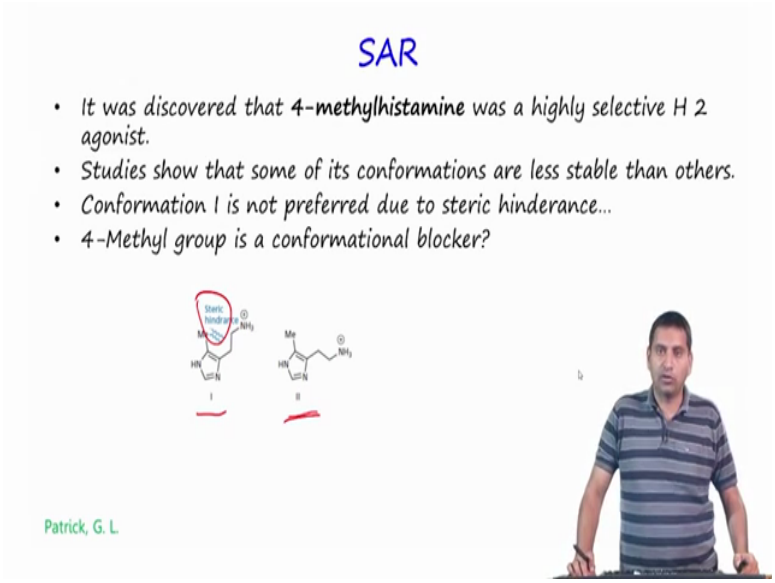

Then during this process it was discovered that 4 methylhistamine which was a highly selective H 2 agonist. So this shows that some of it is confirmations are less stable than others. So if we were to look at the various confirmations you would imagine that this could be one of the confirmations where there is significant steric hinderance between the methyl group and the side chain whereas here is a conformation to which does not have this kind of problem.

So the 4 methyl group was suggested to be a conformational blocker.

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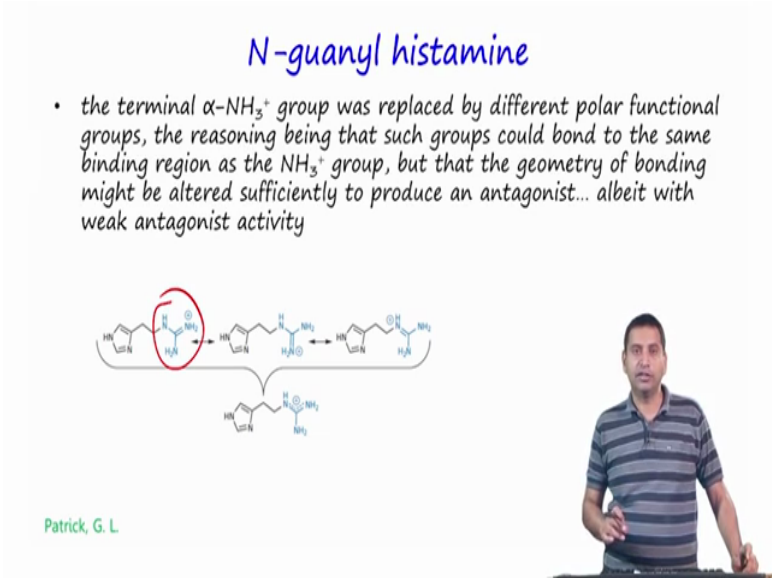

During the structure activity relationship study there was N guanyl histamine that was synthesized. So N guanyl histamine contains a functional group which is also present in arginine, so that is this N guanyl functional group and if you were to draw out the various protonated forms you would see this kind of a arrangement. So these actually are resonance forms and then the geometry of the of the guanyl group is actually planar.

So this molecule was found to have weak antagonist activity.

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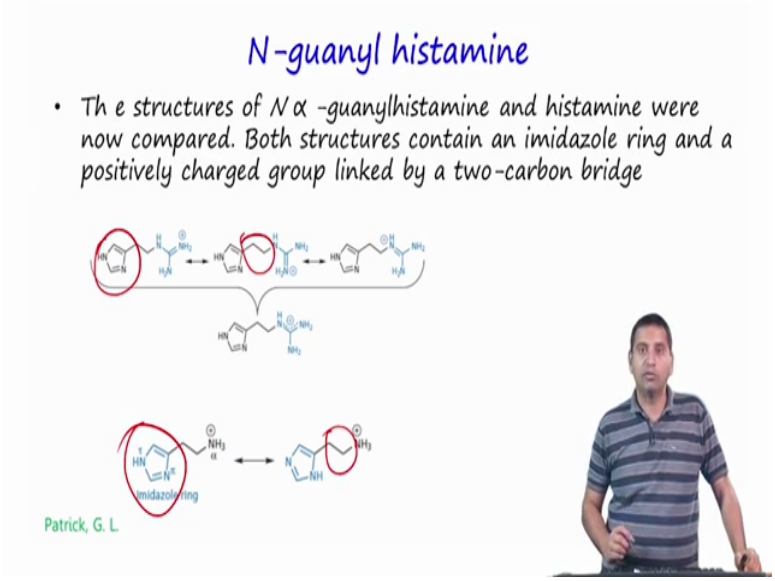

So the structure of N alpha guanylhistamine and histamine were now compared, so both these structures contain an imidazole ring, so this is a common part of the two structures and both structures also contain a two carbon bridge ok, so they also contain a two carbon bridge.

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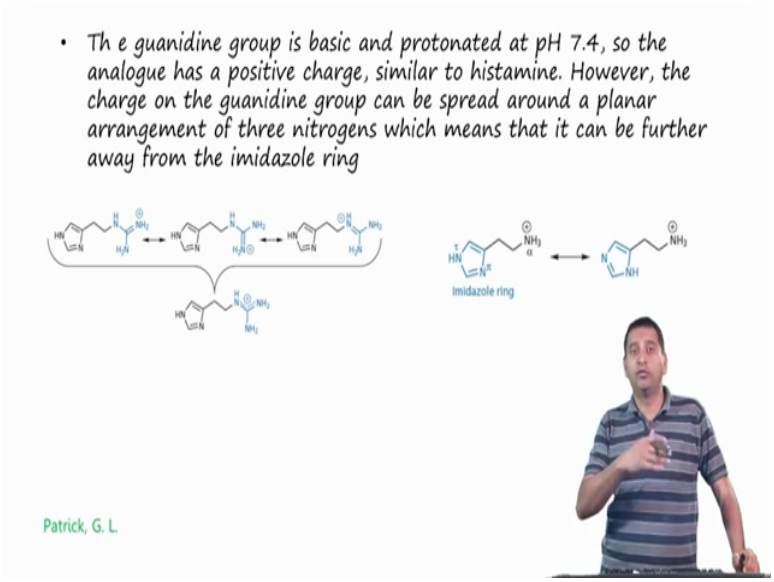

But one of the differences is that the protonation of the side chain, so the guanidine group is basic and protonated pH 7 point 4, so the analogue has a positive charge similar to histamine however the charge on the guanidine can be spread around a more planar arrangement of three nitrogens which means that it can be further away from the imidazole ring.

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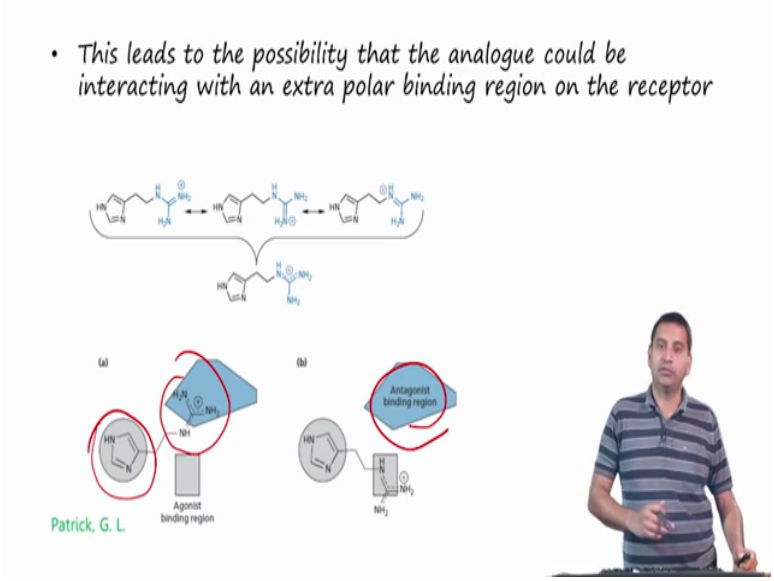

So this leads to the possibility that the analogue could be interacting with an extra polar binding group on the receptor, so what was hypothesized that if you have the receptor which binds to the imidazole ring in the case of the guanyl group you can have a situation where there is an antagonist binding region which can be accessed by this whereas this region is not accessible to histamine.

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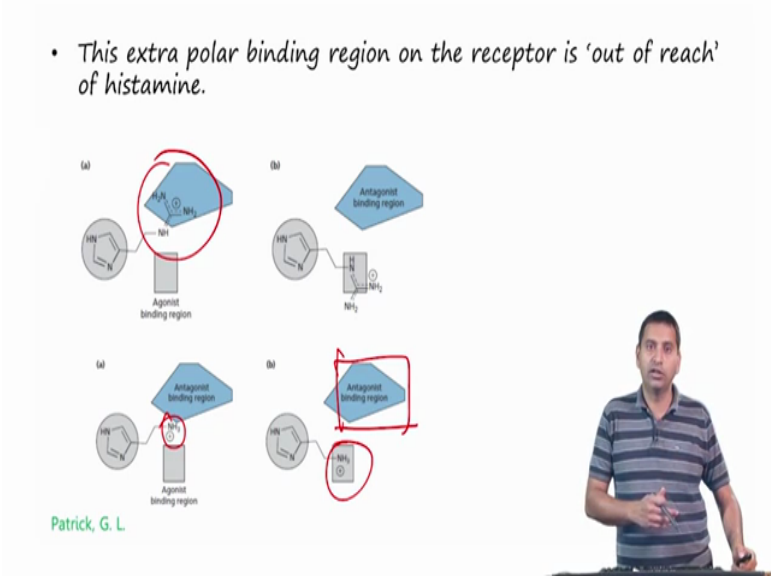

So if you compare these two structures as shown here histamine can bind to the agonist region but does not bind to the antagonist region whereas the guanyl group can actually bind to the antagonist region this suggests that the extra polar binding region is out of reach for histamine.

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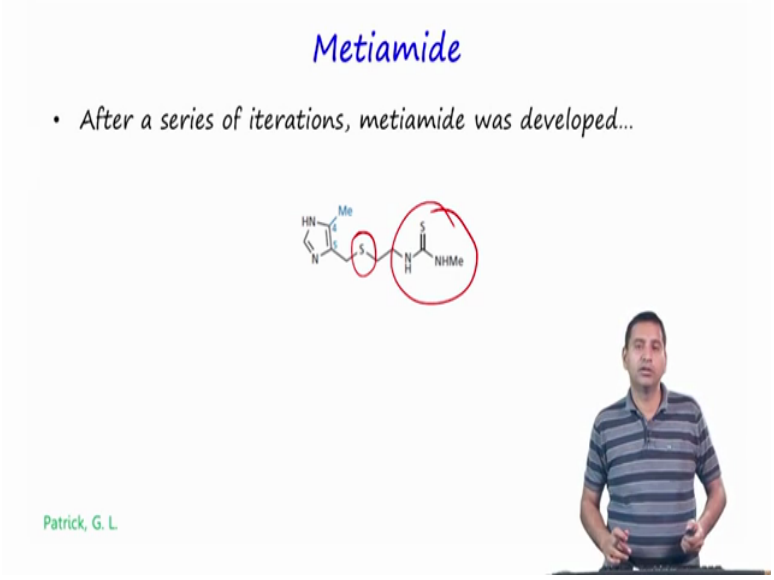

So again through a series of iterations this molecule known as Metiamide was developed, so here is the structure of Metiamide which has a similar guanidine group except that it has a thio guanidyl group and it has a sulphur in between which sort of allows for extra flexibility in this whole process.

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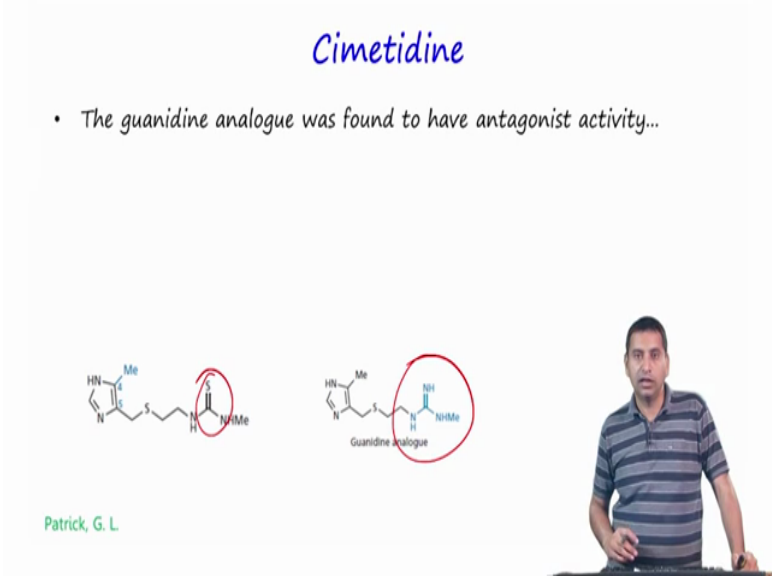

So this became the foundation for the development of Cimetidine. So it is proposed that this material might side effects which were associated with this thiourea group and thiourea group is not present it is not particularly common in human biochemistry. So what was suggested was that we could replace this with thiourea group with something that has a similar property. So the guanidine analogue which we have discussed earlier which is also found to have antagonist activity was then considered.

So now instead of this thiourea group we could then go with the guanidine analogue.

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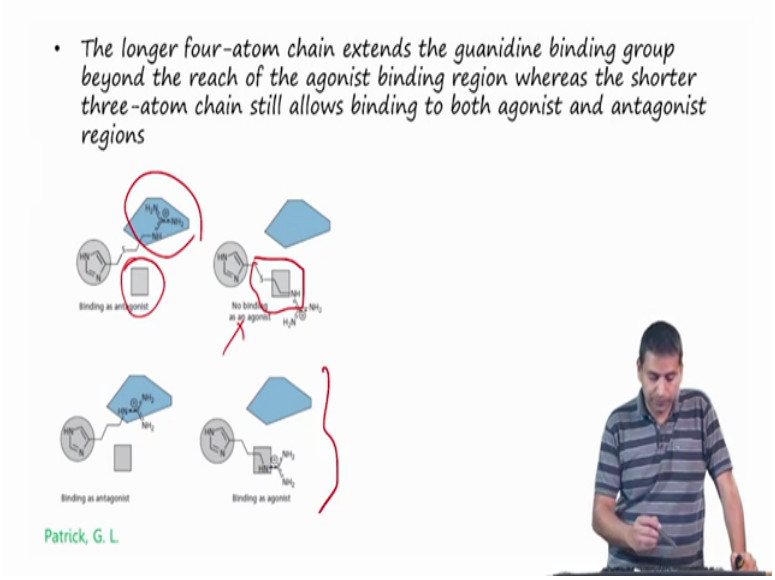

So a longer 4 atom chain also extends the guanidine binding region so here is how it binds as the as the antagonist that means it binds to the antagonist region binding region whereas since it has a longer chain it does not effectively bind as an agonist, so this molecule actually can act as a selectively as an antagonist because of the length of the carbon chain or the side chain that is present.

However the original molecule that we started with had both agonist and antagonist activity as shown here.

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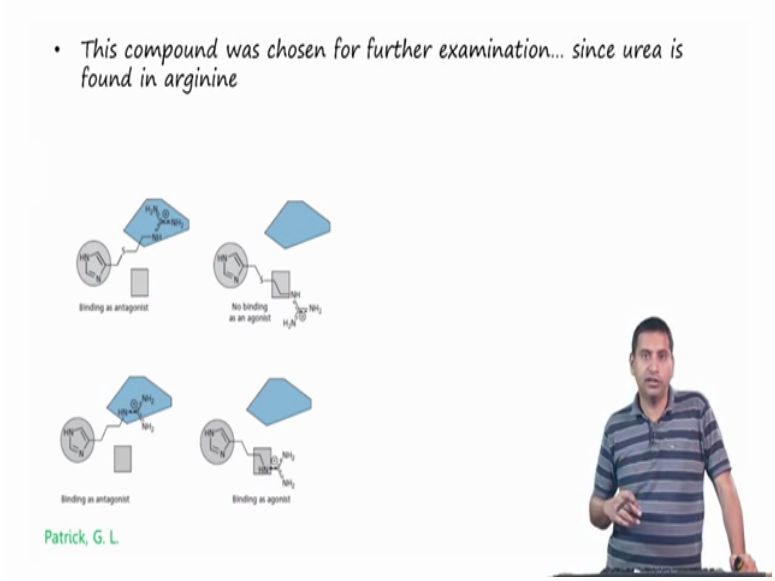

So this compound was chosen for further examination since urea as we discussed earlier is also present in arginine.

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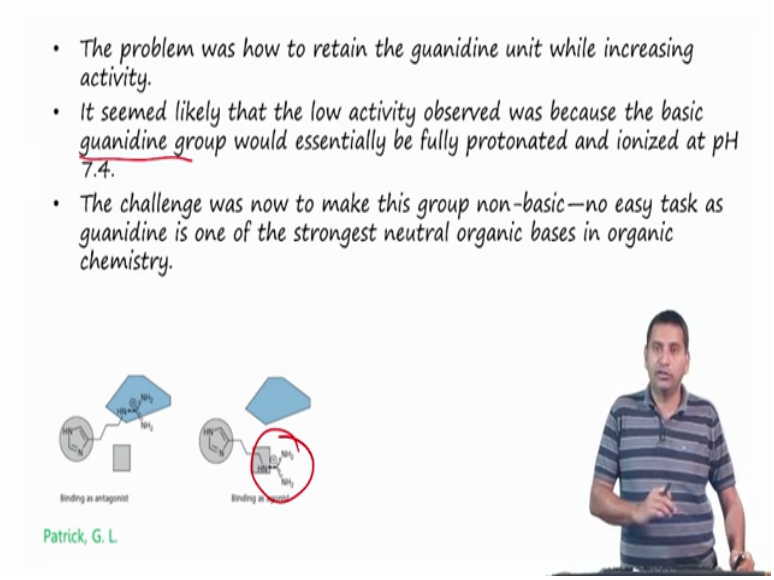

So the problem that the researchers face it was to figure out a way to retain the guanidine while we increase the activity, ok. So here it seemed that the low activity was because of the basic guanidine group as we have already discussed this is the basic guanidine group that we are interested in and this molecule would be essentially fully protonated and ionized at pH 7 point 4.

So the challenge that that now comes up was to make this molecule non-basic ok, this is a major problem because guanidine is one of the strongest neutral organic basis that we use in organic chemistry.

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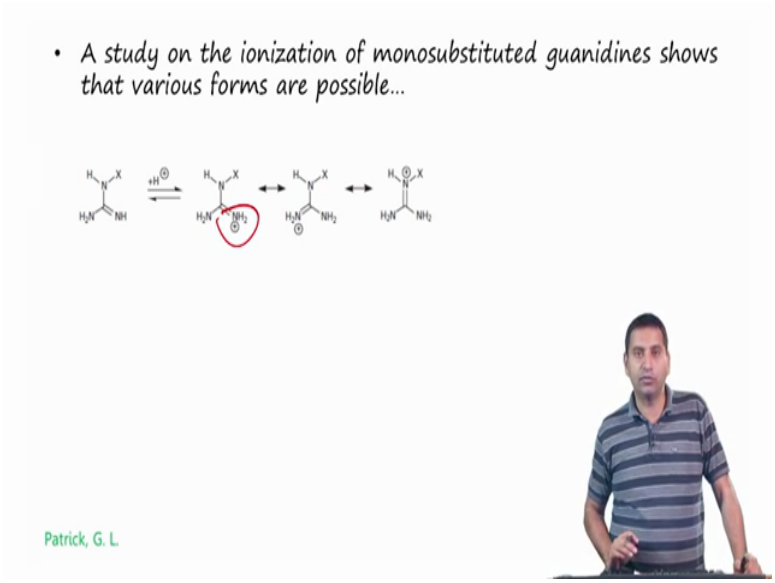

So if you look at the various guanidines that are shown here it can nicely get protonated and exist in these resonance forms.

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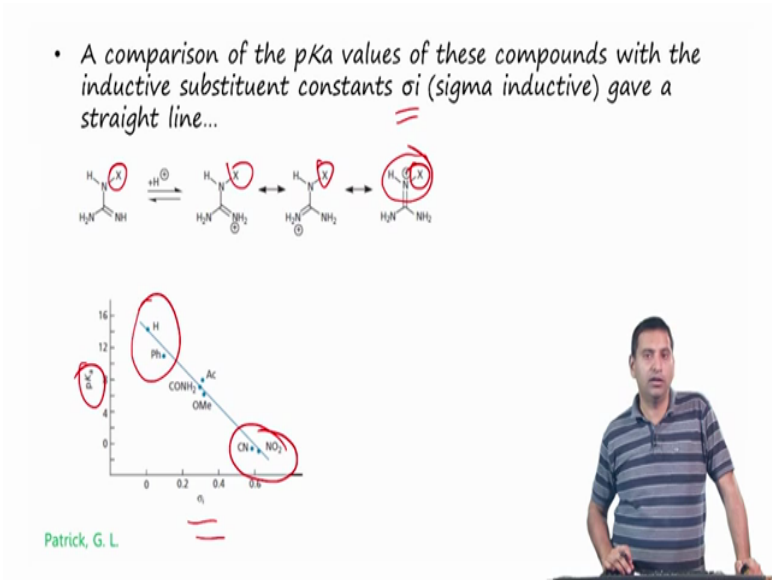

Now what was done was they varied this side chain or the substituent X with various functional groups and we have already looked at previously that there are inductive constants which can be determined which are known as sigma i and if we plot the pKa of this nitrogen versus sigma i we find that highly electron withdrawing groups such as I know actually reduce the pKa of the nitrogen whereas neutral groups such as hydrogen are going to increase the pKa of the nitrogen.

This is quite understandable because having an electron withdrawing group will destabilize this in this form.

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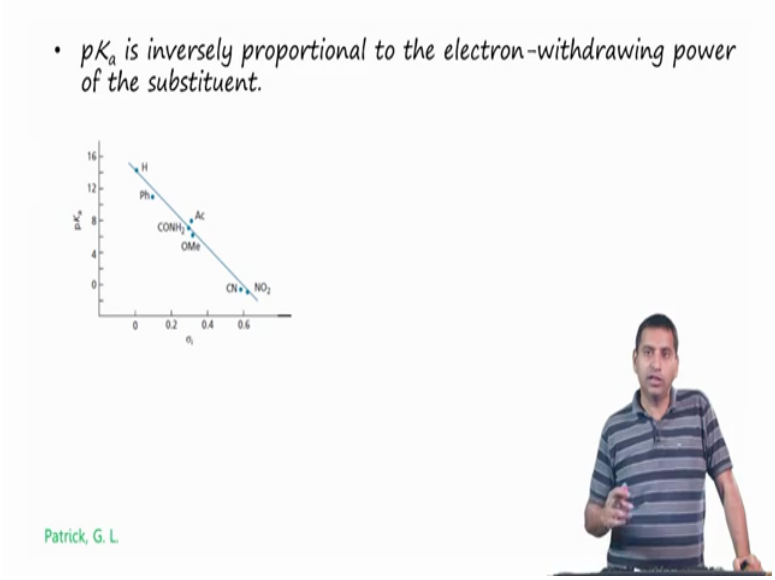

So therefore pKa is inversely proportional to the electron withdrawing power of the substituent.

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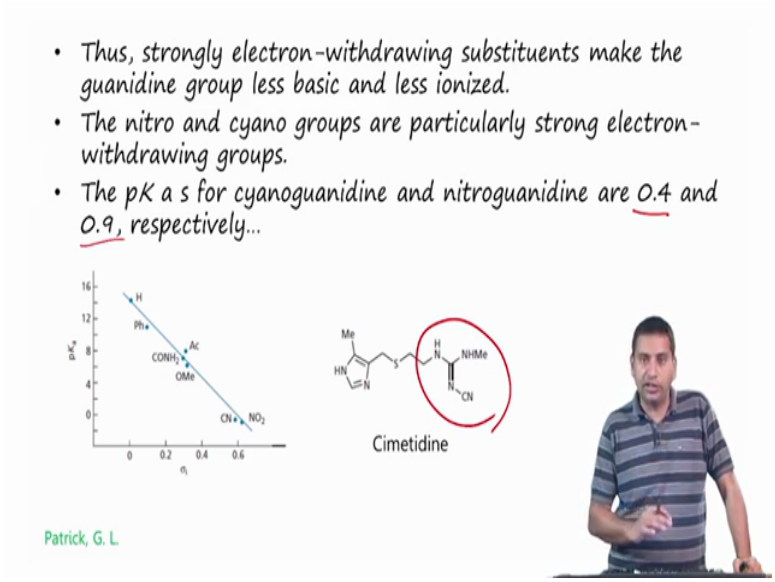

So having an electron withdrawing substituents makes the guanine less basic and less ionized. So the nitro and cyano groups are particularly electron withdrawing groups as we looked at previously and the pKa of these are point 4 and point 9, ok. So based on this, this molecule known as cimetidine was developed where in this guanidine group is actually neutral and

does not have a tendency to get ionized therefore this molecule was developed as a anti-ulcer agent.