



The CCIC Podcast

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This month: Prof. Keith Sharkey
Interview by Dr. Mark A. Ware

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Introduction

Hello and welcome to the CCIC Podcast. The CCIC Podcast is a series of in depth interviews with leading experts and opinion leaders in the world of medical cannabis and cannabinoids.

The CCIC Podcast is brought to you by CannTrust™, a Canadian licensed medical cannabis producer.

In this edition of the podcast we are delighted to welcome Prof. Keith Sharkey from the University of Calgary, talking about cannabinoids and intestinal inflammation:

“We recently published work on inflammation demonstrating very clearly that you needed a central cannabinoid affect to modulate intestinal inflammation. Therefore I think it is a combination of peripheral and central effects, even though we are actually studying a peripheral function or a peripheral set of disorders.”

and the need for cannabis research in GI disorders that require further study:

“I think the patients are craving the opportunity to really understand whether cannabis may help them. And in some case there is enormous evidence to support this. But as a recommendation more broadly to a population, one has to be far more careful, and therefore trials are needed”

Professor Keith Sharkey is Professor of Physiology and Pharmacology and Deputy Director of the Hotchkiss Brain Institute in the Cumming School of Medicine at the University of Calgary. He also holds the Crohn’s and Colitis Canada Chair in inflammatory bowel disease research.

We spoke on April 1⁷^h, 2015.

Dr. Ware: Thank you very much for joining me Keith. Let me ask you, what first brought you in to the cannabinoid research area?

Prof Sharkey: I recently joined the faculty at the university of Calgary in around 1990, and we were studying the neural mechanisms of emesis (vomiting). And at that time, there wasn’t that much known about the mechanisms, but it was well known that cannabis was anti-emetic. The CIHR in the mid ‘90s got more interested in medical marijuana in

collaboration with Health Canada, and they had the opportunity to apply for funds and basically I took advantage of that, was successful, and have been in the cannabinoid field since that time.

Dr. Ware: Since that time, you have been involved with studying the endogenous cannabinoid system in G.I disorders. What have been the major breakthroughs or findings that have taken place in that time?

Prof Sharkey: Well, I think the first major finding was the endocannabinoid system. When I started, that was just becoming something that people accepted as a real entity. It was only a few years after the discovery of endocannabinoids that I started to come in to the field and in the GI system, they were known about but really there was very little known. And so when we were studying the mechanisms of emesis, we described the endocannabinoid system in the brain stem that was involved in the control of emesis. So that was a very exciting finding, and subsequently moved down from the brain stem into the enteric system of the GI tract, and because of my interest in intestinal inflammation, studied the endocannabinoid system in the GI tract in relation to both motility and inflammation, and so all that was brand new in that time, so there were some remarkable new findings. I think in addition to those findings, really a lot more research on the role of administered cannabinoids, particularly any of the phytocannabinoids, on GI functions (basically regulation of inflammation and regulation of motility) have been the two best and most understood ones in relation to GI disorders. I think we are increasingly beginning to recognize the role of the endocannabinoid system and cannabinoids in general in mucosal functions, including the barrier function of the gut which you know is a defensive function linked to not only things like inflammation, but I would say increasingly recognized for more systemic roles particularly that of the metabolism and energy balance.

Dr. Ware: Sounds to me like you have moved from centrally modulating affects, to the periphery. Do you think that the use of cannabinoids for therapeutic purposes has more of a peripheral target or are there a combination of central affects, or both?

Prof Sharkey: I think that one of the things that is starting to surprise me about the findings that we are making. A year or two ago I would have said it's all in the periphery. If you could have peripherally restricted cannabinoids life would be great! I don't think that our data is supporting that. We recently published work on inflammation demonstrating very clearly that you needed a central cannabinoid affect to modulate intestinal inflammation. Therefore I think it is a combination of peripheral and central effects, even though we are actually studying a peripheral function or a peripheral set of disorders. Obviously the ubiquitous nature of the cannabinoid receptors, the inducible nature of the CB2 receptor, and the way that the cannabinoid system interacts with

other systems is something challenging, but also very exciting in terms of what the cannabinoid system is doing. It does make it tricky for harnessing it I think, and we will get to that with other questions, but we are still studying the central effects. Actually I am strictly working on nausea right now, which is a very important and potentially exciting area in the cannabinoid system. But I would caution really just peripheral actions as being those that will affect the periphery because I think the periphery is affected by both central and peripheral actions of cannabinoids.

Dr. Ware: That said, what do you see the potential for harnessing the endocannabinoid system and the management of inflammatory bowel disease, either with phytocannabinoids or, as you said, modulators of the cannabinoid system?

Prof Sharkey: Now that is a very interesting area. As you know, the anti-inflammatory actions of cannabinoids suggest that it should be an effective anti-inflammatory, and indeed it is. There are a number of studies that point to either exogenous cannabinoids or harnessing the endogenous cannabinoid system that will support the idea of reduced intestinal inflammation and that seems to be good. Some points of concern however, is that recently there have been some analysis done suggesting that there is a higher risk of surgery in patents that smoke cannabis for Crohn's disease but again this was not a properly controlled trial or anything of that nature. So I think the potential is there, but there may be other issues, so one has to be mindful of the fact that the cannabinoid system, because of its ubiquitous nature may have side affects or off target affects that are specifically receptor mediated but that are not perhaps desirable for the treatment of a given condition. But the role of the phytocannabinoids have been really under-explored, and even the few studies that have explored either cannabis, or the endocannabinoid system are all fairly positive, so I think there is a role, and I think there is a lot of potential, but we really lack data at this point.

Dr. Ware: You are aware that patients have reported using cannabis in various forms for managing their Crohn's or ulcerative colitis, and yet as you point out, the research is lacking. What do you see as the barriers or obstacles that prevent us from moving forward with this approach?

Prof Sharkey: Yes that is a big challenge in our field and in our wanting to understand the system for the benefit of the patients. The challenges are quite numerable, the first is the smoking, and certainly smoking tobacco can have profoundly different affects on Crohn's disease verse ulcerative colitis. So nicotine or tobacco smoking is severely contraindicated for Crohn's disease, and as well has proven to be harmful in numerous studies. So I'm not certain whether smoked cannabis is harmful, but certainly smoking tobacco is really bad for Crohn's disease. But the paradox is that clinical studies support the fact that in ulcerative colitis, smoking appears to be protective and potentially beneficial. So that's one issue, how will you deliver the cannabinoid in a way that may not itself be a problem for inflammatory bowel disease. So in UC, it's okay to have smoked cannabis in a

trial, but in Crohn's it may not be okay, because smoking, for whatever reason, (and we don't really understand) is clearly detrimental. Whether smoked cannabis versus smoked tobacco, is really unclear. So that's a big problem, the different forms of the disease, and their response to smoking, if you didn't smoke the compound, and took the compound as a vaporizer or something of that nature. Another big challenge of course is the standardization of the product. Doing any type of clinical trial really requires a multi-center approach I would say for a number of reasons, and therefore you need a standardized product, and I would say that remains in the current world something of a problem. As you know, cannabis is now made widely available in many respects, in Canada and other countries, and there is a market. There is also this development of what I believe some people call "skunk cannabis" which is the higher potency cannabis plant with enormous quantities of THC, and very low quantities of cannabidiol, and who knows about the other cannabinoids because they are not really well studied, so I think we need to better understand whether perhaps the original studies and the early anecdotal work on the benefits of THC in IBD, whether that related to a low potency strain without CBD, versus some of these crazy high potency strains which I think are detrimental. So I think we need to understand those things, and then as I indicated, there is a sense of harm incurring in certain circumstances, therefore physicians are of course reluctant to do clinical trials if they don't sense a positive benefit to the agents they are using, despite physicians being highly objective in many cases, well we know that's not completely the truth, and so there is a stigma amongst physicians to use cannabis and cannabinoids and that's another obstacle to moving it forward. I think the patients are craving the opportunity to really understand whether cannabis may help them. And in some cases there is enormous evidence to support this. But as a recommendation more broadly to a population, one has to be far more careful, and therefore trials are needed. There are certainly hints of benefits, but there are large obstacles unfortunately.

Dr. Ware: Cannabinoid induced hyperemesis is showing up in a lot of emergency rooms, and when I go around the country talking to physicians it is appearing anecdotally to be a problem, especially that young people have been coming in with this syndrome. Is this something that has been a focus for your work and do you have any thoughts about nausea getting worse with using cannabis?

Prof Sharkey: Yeah it's one of those paradox things. This was discovered many years ago, I think mostly from Australia. It's showing up now everywhere, I think it's linked to the excessive use of higher potency cannabis amongst young people. Why it should have occurred, I do not know to be honest. We are not studying it because we don't really have a mechanism to study it. There are no similarities that are seen in animal models, there is some evidence from one researcher that cannabinoids may induce emesis, but in most of the models we see exactly the opposite, and it doesn't seem that anything we do with cannabinoids in our animal models cause them to have this hyperemesis like condition, so very tricky

for us to study. As I said, I don't really understand what is going on mechanistically, the only thing I wonder and purely speculate, is for those who take relatively high quantities, which clearly seem to be the group that are affected whether there is a down regulation of the endocannabinoid system that is occurring in some fashion. And we know, that the endocannabinoid system is tonically active to prevent emesis. So if you downregulate it in some way, there is a possibility that might explain why one sees this, but it's such a small group of people, so it's very hard to explain it, because you would expect, if that was the case, more widely. So I don't have an explanation, it's a tricky one, and unfortunately there is no model that has allowed us to study it that I've seen, or at least in our own laboratory, we have never seen anything like it. So it's a real paradox.

Dr. Ware: And there are reports that say they have to take a hot shower or bath to treat it. I struggled with the attempt to understand whether its peripheral vascular dilatation, or some TRPV1 effect, or the heat, it's so consistently reported that it's almost pathognomonic of the condition, perhaps that is a window to what is going on?

Prof Sharkey: Yes we have thought about that, and you may be on to something with the heat sensitive channels. Of course we know the TRP channels and the cannabinoid system interact in the brain stem to regulate vomiting and we have published that with Vincenzo DiMarzo a few years ago and we have published how they interact, so maybe it's a TRP channel thing, that's the best guess I ever had, but you are right, hot showers or hot baths do seem to work but really I have no idea of to understand how the mechanism. It would be really fascinating to study, but hard to do.

Dr. Ware: What do you see your lab doing in the next ten or so years, is there anything really critical that you think has to get done in the next stage of your career?

Prof Sharkey: Well yes absolutely. I'm planning to stay in this field, and study things as far as we can in terms of the cannabinoid system. Hopefully the CIHR and our other funding agencies will continue to believe in our research. I think, as I hinted at earlier, barrier functions of the cannabinoid system or the regulation of intestinal barrier function is a really important area being suggested from the literature but very little work has been done to understand how and where the endocannabinoid system is regulating barrier function. Does the endocannabinoid system in the gut in any way interact with the intestinal microbiota that we are increasingly seeing as critical in GI health as well as in general health. We had a hint of something in preliminary data that is now submitted for a grant and also we are working on our first manuscript to suggest that cannabis can indeed alter the intestinal microbiota and this is exciting new work, and I think if this continues, then I think we will see some new very exciting areas where we can really start to harness the endocannabinoid system for more general health benefits. Particularly around mucosal functions of the gut so that's an area that I'd love to get into, and I really think it is open at this stage from the literature, but very little. We saw

a recent study suggesting cannabinoid receptors were present on enteroenteric cells, which are hormone producing cells that line the intestine all the way from the stomach downwards, and this would be a new area to look at cannabinoid humoral regulation, those gut hormones do a lot of things far beyond affects and digestion, and again, very little is known. So I think there are many new areas to fully understand the endocannabinoid system, in even motility where we are scratching the surface, for example working on the metabolic enzymes. They are involved in cannabinoid degradation or metabolism. We are just starting to understand the potential for interactions with the cyclooxygenase system, in collaboration with Larry Monet's (?) group for example started studying GI functions of substrate Inhibitors suggesting that COX may be very importantly involved in the regulation of cannabinoid levels, and as you would immediately imagine particularly in inflammatory states, all new areas and so there's a lot of exciting things, a lot of potential for drug development, as well as the use of both endogenous and exogenous cannabinoids. And that doesn't even touch on the role of phytocannabinoids, which we are becoming increasingly aware of, are really important. I have done a bit of work on cannabidiol but that's about it. There are plenty of phytocannabinoids with likely active properties, and I think it's a very exciting field. I wish there were more people involved in it to be honest and more funding that would support this type of research, because there is a lot of excitement and a lot of potential.

Dr. Ware: Before we close, do you have any reflections on the medical cannabis story, as it is perceived in the media, it is a very popular topic for the public interest. Anything on that story from your perspective that's been striking you in the last few years?

Prof Sharkey: The public has a huge appetite for knowledge in this area. They are generally aware of cannabis and cannabinoids, but are not very well educated to this yet. I regularly get emails and phone calls from people craving knowledge about the system, about the potential, both harm and good. I think there is an enormous interest to understand it, and understand the repercussions, for both health and disease. We recently had a forum here, in relation to mental health, but I was involved with, as deputy director of the Hotchkiss Brain Institute, and the room was packed in a way that we typically don't see, and it was packed with people from every faculty virtually. It wasn't a public forum it was a research forum around youth mental health, and we had all the neuroscientists, all the mental health people, the psychiatry people, (that's no surprise!) but people from education, social work, nursing, and a whole bunch of other areas that wanted to know what was going on. Because cannabis affects their academic research, and it impacts the practical application of those, particularly in the context of social work in the school system and everywhere. I think the lack of real understanding the controversies around cannabis, and the rather bizarre stance of the government where in one way they're promoting it, and other ways they are hiding it or not promoting it. It's a very tricky area in Canada because of our legislation and the way it works, and I think the public is sum what confused, but very interested. I was amazed at how much

interest there was in my research, as well as just the general field, and I find that that it something I wouldn't have predicted when we first got into it.

Dr. Ware: Professor Keith Sharkey thank you very much for taking the time this morning to speak with me, congratulations on the success of your work, and good luck in the future. Thanks again for your time speaking with us on the podcast, and I wish you all the best in the coming years.

That was Professor Keith Sharkey, speaking to us via Skype from Calgary, Alberta

Thank you for joining us.

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