BIOGRAPHICAL SKETCH

NAME: SHARKEY, Keith A.

POSITION TITLE: Professor, Hotchkiss Brain Institute, Department of Physiology and Pharmacology, University of Calgary.

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include doctoral, postdoctoral, and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND COUNTRY	DEGREE *(if applicable)*	COMPLETION DATE (MM/YYYY)	FIELD OF STUDY
University of London, London, UK	B.Sc. (Hons)	06/1981	Nutrition
University of Liverpool, Liverpool, UK	Ph.D.	03/1985	GI Physiology
University of Bristol	Postdoctoral	12/1987	Neurogastroenterology
University of Calgary, Calgary, AB, Canada	Postdoctoral	03/1990	Neurogastroenterology

A. Research Focus

I have focused for most of my independent career on understanding the neural control of the gastrointestinal (GI) tract in health and disease. My research has spanned studies of both the brain-gut axis and the enteric nervous system. For example, my laboratory identified and characterized the effects of intestinal inflammation on neuronal, and enteroendocrine physiology in the GI tract, providing a mechanistic understanding of how altered neural signaling in the gut gives rise to functional alterations in inflammatory bowel disease. In addition to this work, my lab also has a longstanding interest in the endocannabinoid system. Before their roles had been widely appreciated, we proposed that endocannabinoids regulate secretory and motor functions in the GI tract. We discovered that cannabinoid CB_2 receptors were found in the brainstem (Science 2005) and were also localized on enteric nerves.

We have studied the impact of inflammatory bowel disease on the brain and in a series of studies have demonstrated central neural mechanisms of dysfunction (e.g, PNAS 2008), that lead to behavioural abnormalities associated with inflammatory bowel disease. We have discovered key roles of the gut microbiota in the regulation of both central and peripheral neural control of the GI tract (e.g., Microbiome 2021, Brain Behav. Immun. 2022). With my collaborators Drs. G. Pfeffer and M.D. Nguyen we have recently discovered an important role of the gut microbiota in the development of amyotrophic lateral sclerosis.

B. Positions and Honours

Positions:

1990-1995 Assistant Professor, Dept. Physiology & Biophysics, University of Calgary, Calgary, AB
1995-1999 Associate Professor, Dept. Physiology & Biophysics, University of Calgary, Calgary, AB
2010-2017 Deputy Director, Hotchkiss Brain Institute, University of Calgary, Calgary, AB
2017-2018 Director, Hotchkiss Brain Institute, University of Calgary, Calgary, AB
1999-present Professor, Dept. Physiology & Pharmacology, University of Calgary, Calgary, AB

Selected honours and representative professional activities:

2024 *Fellow* of the Royal Society of Canada
2024 Outstanding Reviewer Award, Canadian Institutes of Health Research
2021 Distinguished Research Award, Gastrointestinal & Liver Physiology Section, American Physiological Society (presented at Experimental Biology, 2022)
2021 Cumming School of Medicine's van de Sande Distinguished Achievement Award for Mentorship.
2015 *Fellow* of the Canadian Academy of Health Sciences
2014 *Fellow* of the *Canadian Association of Gastroenterology*
2013 Killam Annual Professor Award, *University of Calgary*
2009 Research Leadership Award, *Crohn's and Colitis Foundation of Canada (CCFC)*
2006-2021 Crohn's and Colitis Canada Chair in IBD Research, *Cumming School of Medicine, University of Calgary*
2002 Janssen Master's Award in Gastroenterology, *American Gastroenterological Association*

2013-2017 Reviewing Editor, *The Journal of Physiology*
2013-present Member, *Expert Advisory Board, Nature Reviews Gastroenterology and Hepatology*
2006-2011 Basic Science Editor, *Neurogastroenterology and Motility*

C. Contributions to Science

H index **90** (>29,500 total citations, 77 papers cited ≥100 times; Google Scholar).

287 Peer-reviewed publications, including significant discoveries published in:

Science 2005; Nature 2022; Nature Medicine 2001, 2012; Gastroenterology 19 papers including, 2012, 2015, 2016; Nature Communications 2020; Microbiome 2021; PNAS 2008, 2019.

Google Scholar: https://scholar.google.ca/citations?user=5kFjd7oAAAAJ&hl=en

1. **Role of the gut microbiota in regulating the central and peripheral neural control of the gastrointestinal (GI) tract.** Increasing evidence supports a role of the gut microbiota in regulating neural control mechanisms in the gut, but also in the brain and spinal cord. My lab and our collaborators have shown that the gut microbiota contributes to sensitization of visceral primary afferent nerves leading to chronic pain in animals that have recovered from colitis (Cell Mol Gastroenterol Hepatol 2020). We discovered a role for fungal components of the gut microbiome in regulating intestinal physiology and the development of colitis (Nat Commun 2020, >170 citations). We recently showed that the aryl hydrocarbon receptor mediates depression-like behaviours that are regulated by the crosstalk between the intestinal microbiota and the host (Brain, Behav Immun 2021). We identified a key role of the gut microbiota in regulating the structure and function of the GI tract in a sex-independent manner. Moreover, we demonstrated that enteric bacteria are essential for the maintenance of the integrity of the enteric nervous system, by regulating neuronal survival and promoting neurogenesis (Microbiome 2021, >150 citations). Together these studies advance the concepts of microbiota directly and indirectly regulating neural control mechanisms. These findings have contributed to the concept of the brain-gut axis, which has profoundly influenced the field neuroscience. The brain and spinal cord are no longer considered in isolation – being bidirectionally linked to the gut. This thinking has changed the way we view neurodegenerative and neuropsychiatric disorders and has opened up new avenues to understand their pathogenesis and to treat them.

van Tilburg Bernardes, E., Pettersen, V.K., Gutierrez, M.W., Laforest-Lapointe, I., Jendzjowsky, N.G., Cavin, J.B., Vicentini, F.A., Keenan, C.M., Ramay, H.R., Samara, J., MacNaughton, W.K., Wilson, R.J.A., Kelly, M.M., McCoy, K.D., **Sharkey, K.A.** and Arrieta, M.C. (2020). Intestinal fungi are causally implicated in microbiome assembly and immune development in mice. *Nature Communications*, **11**, 2577.

Esquerre, N., Basso, L., Defaye, M., Vicentini, F.A., Cluny, N., Bihan, D., Hirota, S.A., Schick, A., Jijon, H.B., Lewis, I.A., Geuking, M.B., **Sharkey, K.A.**, Altier, C. and Nasser, Y. (2020). Colitis-induced

microbial perturbation promotes postinflammatory visceral hypersensitivity. *Cellular and Molecular Gastroenterology and Hepatology*, 10, 225-244.

Vicentini, F.A., Mathews, A.J., Pittman, Q.J., Swain, M.G., **Sharkey, K.A.*** and Hirota, S.A.* (2021). Behavioural adaptations after antibiotic treatment in male mice are reversed by activation of the aryl hydrocarbon receptor. *Brain, Behaviour and Immunity*, **98**, 317-329. [*Co-senior authors].

Vicentini, F.A., Keenan, C.M., Wallace, L.E., Woods, C., Cavin, J.-B., Flockton, A., Macklin, W.B., Belkind-Gerson, J.*, Hirota, S.A.* and **Sharkey, K.A.*** (2021). Intestinal microbiota shapes gut physiology and regulates enteric neurons and glia. *Microbiome*, 9, 210. [*Co-senior authors].

2. **Central mechanisms of behavioural dysfunction in intestinal inflammation**. How the brain is impacted by peripheral inflammatory diseases was not well understood. We have elucidated mechanisms of altered brain function in experimental colitis. We discovered that activated microglia release inflammatory cytokines that alter the expression of ion channels in central neurons (PNAS 2008, >470 citations; J Neurosci 2015, >220 citations). We found that central cytokines upregulate the expression of the degradative enzyme for the endocannabinoid anandamide, which leads to alterations in corticolimbic circuits that mediate anxiety. We showed that TNF in the brain drives post-inflammation depression-like behavior and persistent pain. We have recently found that specific gut bacteria from animals with colitis can transfer anxiety-like behaviour in the absence of intestinal inflammation (Brain, Behav Immun 2022). Also, in colitis, α4β7 integrins direct the recruitment of neutrophils to the cerebral vasculature, leading to elevated interleukin-1β that mediates anxiety-like behaviour (J Neuroinflammation 2022). Together these findings help explain the behavioural commorbities of peripheral inflammation and describe novel mechanisms of gut-brain communication.

Riazi, K., Galic, M.A., Kuzmiski, B., Ho, W., **Sharkey, K.A.** and Pittman, Q.J. (2008). Microglial activation and TNFα production mediate altered CNS excitability following peripheral inflammation. *Proceedings of the National Academy of Sciences USA*, **105**, 17151-17156.

Riazi, K., Galic, M.A., Kentner, A.C., Reid, A.Y., **Sharkey, K.A.** and Pittman, Q.J. (2015). Microglia dependent alteration of glutamatergic synaptic transmission and plasticity in the hippocampus during peripheral inflammation. *Journal of Neuroscience*, **35**, 4942-4952.

Vicentini, F.A., Szamosi, J.C., Rossi, L., Griffin, L., Nieves, K., Bihan, D., Lewis, I.A., Pittman, Q.J., Swain, M.G., Surette, M.G., Hirota, S.A.* and **Sharkey, K.A.*** (2022). Colitis-associated microbiota drives changes in behaviour in male mice in the absence of inflammation. *Brain, Behaviour, and Immunity*, 102, 266-278. [*Co-senior authors].

Cluny, N.L., Nyuyki, K.D., Almishri, W., Griffin, L., Lee, B.H., Hirota, S.A., Pittman, Q.J.*, Swain, M.G.* and **Sharkey, K.A.***. (2022). Recruitment of α4β7 monocytes and neutrophils to the brain in experimental colitis are associated with elevated cytokines and anxiety-like behaviour. *Journal of Neuroinflammation*, 19, 73. [*Co-senior authors].

3. **Role of neural mechanisms in inflammation-induced gut dysfunction**. Intestinal inflammation leads to significant GI symptoms. Since gut function is controlled by the enteric nervous system, we embarked on studies to examine the neural mechanisms of inflammation-associated gut dysfunction. We have identified and characterized the effects of intestinal inflammation on neuronal, synaptic and enteroendocrine physiology in the GI tract. These findings are the first systematic and mechanistic account of altered neural signaling in the gut in intestinal inflammation and inflammatory bowel disease (IBD). We have established the neural mechanisms underlying disordered motility in animal models of IBD and identified specific molecular targets for the treatment of motility disturbances. (Gastroenterology 2004, >930 citations; Nature Med 2012, >430 citations).

Neurons of the enteric nervous system are surrounded by a unique type of peripheral glial cell - enteric glia. My laboratory has defined many of the features of enteric glia in the normal and inflamed gut. We were the first to show that enteric glia respond to inflammation and inflammatory mediators, undergoing a process called reactive gliosis. We discovered that enteric glia express inducible nitric oxide synthase under normal physiological conditions and that nitric oxide from enteric glia plays a significant inhibitory role in the regulation of intestinal secretion in the normal and inflamed colon. We showed that enteric glia are important participants in enteric neurotransmission, particularly involving them as a novel target for sympathetic nerve terminals in the GI tract (Gastroenterology 2009, 190 citations; J Neurosci 2010, 100 citations). These studies explain how stressful events can manifest themselves in the gut and alter its function through actions at the level of the enteric nervous system. Importantly my laboratory have shown that enteric glia are active players in neural signaling (as they are in the brain) and play an essential role in maintaining homeostasis, especially in disease states such as intestinal inflammation, where they contribute to the regulation of motility and secretion. Together, these studies reveal new targets and mechanisms for the treatment of GI disorders.

Coates, M.D., Mahoney, C.R., Linden, D. R., Sampson, J.E., Chen, J., Blaszyk, H., Crowell, M.D., **Sharkey, K.A.**, Gershon, M.D., Mawe, G.M., Moses, P.L. (2004). Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. *Gastroenterology*, 126, 1657-1664.

Gulbransen, B.D. and **Sharkey, K.A.** (2009). Purinergic neuron-to-glia signaling in the enteric nervous system. *Gastroenterology*, 136, 1349-1358.

Gulbransen, B.D., Bains, J.S and Sharkey, K.A. (2010). Enteric glia are targets of the sympathetic innervation of the myenteric plexus in the guinea pig distal colon. *Journal of Neuroscience*, 30, 6801-6809.

Gulbransen, B.D., Bashashati, M., Hirota, S.A., Roberts, J.A., Beck, P.L., MacDonald, J.A., Muruve, D.A., McKay, D.M., Mawe, G.M., Thompson, R.J. and **Sharkey, K.A.** (2012). Activation of neuronal P2X7 receptor-pannexin-1 mediates death of enteric neurons during colitis. *Nature Medicine*, 18, 600-605.

4. **Function of cannabinoid receptors in motor and secretory function neural control in the GI tract**. The endocannabinoid system, the molecular target of the action of cannabis, is an important regulatory system in the brain and body. Before their roles had been widely appreciated, we proposed that endocannabinoids regulate secretory and motor functions in the GI tract via the two receptors of this system, CB_1 and CB_2. We discovered and functionally characterized CB_2 receptors in neurons in the brainstem that control vomiting (Science 2005; >1800 citations) and built on these insights to identify a functional role of CB_2 receptors in the regulation of intestinal motility and the control of intestinal inflammation (IBD 2009, >210 citations). With the use of novel compounds that can modify endocannabinoid signaling, we have provided evidence for functional roles of the components of the endocannabinoid system in regulating motility, secretion and neurotransmission in the GI tract. Enteric neuronal CB receptors can modify intestinal motility in inflammation, therefore providing a unique mechanism for the maintenance of intestinal homeostasis that may have therapeutic potential in other GI disorders, including irritable bowel syndrome (Cell Mol Gastroenterol Hepatol 2022).

Van Sickle, M.D., Duncan, M., Kingsley, P.J., Mouihate, A., Urbani, P., Mackie, K., Stella, N., Makriyannis, A., Piomelli, D., Davison, J.S., Marnett, L.J., Di Marzo, V., Pittman, Q.J., Patel, K.D. and **Sharkey, K.A.** (2005). Identification and functional characterization of cannabinoid (CB)2 receptors in the brainstem. *Science*, 310, 329-332.

Storr, M.A., Keenan, C.M., Zhang, H., Patel, K.D., Makriyannis, A. and **Sharkey, K.A.** (2009). Activation of the cannabinoid 2 receptor (CB2) protects against experimental colitis. *Inflammatory Bowel Diseases*, 15, 1678-1685.

Cuddihey, H., MacNaughton, W.K. and **Sharkey, K.A.** (2022). The role of the endocannabinoid system in the regulation of intestinal homeostasis. Cellular and Molecular Gastroenterology and Hepatology, 14, 947-963.