

PL01

Gordon Holmes and The Irish Spirit of Adventure; Lessons for Modern Thinkers

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On the Western Front of the First World War, Gordon Holmes transformed neurology. There, between 1915 and 1918, existed a coincidence of factors. These, combined with Holmes' voracious curiosity, adventurous nature and eclectic skillset produced a profound, lasting legacy.

His early life was spent in Castlebellingham, Ireland. Initial schooling may explain this adventurous spirit; The Dundalk Educational Institution produced three VC Awardees along with the most outstanding Irish fighter pilot of the First World War (McCrea and Patterson, 2014). He studied Medicine in Trinity College, Dublin, then spent two years at the Senckenberg Institute in Frankfurt, under Ludwig Edinger and Carl Wiegert (Fine *et al*, 2011). Thus, Holmes' training saw him grounded thoroughly in the German Neuroanatomy tradition which saw his stunning hand-drawn diagrams of Golz' famous "dog without a forebrain" published in the Journal of Physiology (Holmes, 1901). To this may be added his subsequent rigorous inculcation in clinical observation under Hughlings Jackson at Queen Square, London. In Holmes was a unique mix of artist, anatomist, physiologist and clinician, waiting for the right set of circumstances.

This mix of circumstances arrived in 1914 when Holmes was appointed as consultant neurologist to the British Armies in France. Harvey Cushing describes his tireless work thus; "*There are 900 acutely ill soldiers, convoys of 300 wounded might arrive in a day, and there were only 10 Doctors; in less than 9 months Holmes had amassed a lifes work*" (Lepore, 1994).

Here, a confluence of events led to some of the most important neurologic advances of the 20th Century. The Brodie helmet used on the Western front was designed to be cheaply produced from a single stamping of metal and provided good protection from airburst shells but not from rounds that burst closer to ground level, leaving the occipital cortex and cerebellum vulnerable (Shadrake and Pugh, 2014). The introduction of new rifles in the late 1800's imparted enough velocity to allow a projectile enter the skull and cause limited (and measurable) damage, but not so much velocity as to produce the lethal damage that modern weapons do.

Holmes' training in anatomy, physiology and clinical observation uniquely disposed him to the characterisation and mapping of visual field loss due to lesions of the occipital lobe. His extensive pre-war experience in measuring functional loss due to cerebellar tumours (Stewart and Holmes, 1904) was also invaluable when studying the large cerebellar lesions consequent to shrapnel and bullet wounds.

Holmes' maps of visual field localisation (Holmes, 1918) survived unaltered for 73 years (Horton and Hoyt, 1991). His description of the clinical signs of cerebellar damage (Holmes, 1917), provide neurologic tools in current use.

Ireland, The UK and Europe have cause to be proud of his legacy which has extended globally with warm tributes from notables such as Wilder Penfield (Penfield, 1967). His achievements resulted from his interdisciplinarity and refusal to think in narrow silos. The right person with the appropriate talents came forward to do their duty a time of unique challenge (and ironically) unique creativity.

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PL02

GABAergic signaling as a coordinating factor in brain development and disease: Focusing on postsynaptic ionic mechanisms

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The cornerstones of research on postsynaptic inhibition were laid by Charles Sherrington, who deduced its hyperpolarizing nature and, notably, emphasized “*Inhibition as a coordinative factor*” in the CNS (Nobel lecture, 1932). The prescient ideas of Sherrington have not only materialized in work on neuronal information processing in the mature CNS: it has become obvious that major milestones of brain development are associated with remarkable qualitative changes in the responses generated by postsynaptic GABA_A receptors. These, in turn, are attributable to coordinated alterations in the spatiotemporal expression patterns of plasmalemmal chloride transporters - such as the Na-K-2Cl cotransporter NKCC1 and the neuron-specific K-Cl cotransporter, KCC2 – and other ion-regulatory proteins, including carbonic anhydrases (CAs), whereof isoform CA7 is neuron-specific.

The default state of mammalian cells, including immature CNS neurons, is a high NKCC1-dependent intracellular Cl⁻ concentration ([Cl⁻]_i) which leads to a depolarizing action of GABA. Thus, the adult neurons with their low [Cl⁻]_i and hyperpolarizing GABA responses are an “aberrant” type of cells. As shown in our early work, upregulation of KCC2 expression accounts for the developmental hyperpolarizing shift in GABA action. This shift follows the distinct time courses of maturation in various neuronal populations and animal species, with striking differences in GABA actions during the perinatal period between altricial and precocial mammals. Current data indicate that in the full-term healthy human baby, GABA is hyperpolarizing in the cortex and, by implication, elsewhere in the brain.

A subsequent developmental shift or “switch” is caused by the abrupt emergence of the neuron-specific CA isoform 7 (CA7) at a developmental stage by which KCC2 has reached a near-maximum functionality. GABA_ARs have a significant permeability to HCO₃⁻, and because of its rather positive equilibrium (at around -10 mV), the HCO₃⁻ current component is depolarizing. In the cortex, intense activity of GABAergic interneurons results in fast collapse of the chloride gradient in principal neurons, giving rise to depolarizing and excitatory GABA actions. Indeed, selective interneuronal stimulation in the healthy brain can promote seizure activity, accentuated by an increase in extracellular [K⁺].

Soon after identifying the causal role of KCC2 in the ontogeny of hyperpolarizing postsynaptic GABA_AR responses, we found that kindling-induced seizures in adult mice led, within a few hours, to down-regulation of KCC2. This observation has since been replicated in virtually all models of cortico-hippocampal neuronal trauma (e.g. stroke, mechanical damage, and neuroinflammation). KCC2 down-regulation, paralleled by neuronal NKCC1 upregulation, may well be one aspect of neuronal dedifferentiation required for re-wiring of functional circuits in CNS disorders. Maintaining a low [Cl⁻]_i imposes a high burden on neuronal energy metabolism, especially during an energy crisis. Therefore, it is not immediately clear whether the depolarizing GABA responses have a

disease-promoting (maladaptive) or an adaptive/compensatory role. NKCC1-dependent depolarizing GABA signaling is likely to promote interictal activity - but not seizures - in the epileptic brain. The presence of NKCC1 in virtually all kinds of cells within and outside the brain has led to lots of confusion regarding the pharmacological actions of bumetanide and other NKCC1 blockers, especially in vivo.

In addition to their roles in modulating the efficacy of GABAergic inhibition, some ion-regulatory proteins act as morphogenic factors. For instance, the large C-terminus of KCC2 interacts with cytoskeletal elements influencing dendritic spinogenesis in cortical neurons, suggesting a role for KCC2 in coordinating the development of GABAergic and glutamatergic synapses. Such cytoskeletal effects are also likely to affect the neurological phenotype of disease mutations of KCC2, which is known to have a very high genic intolerance.

PL03

Endogenous physiological mechanisms as basis for treatment of obesity and type 2 diabetes

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Since their discovery there has been an interest in the translational aspects of the gut hormones, starting in 1906 with attempts to treat diabetes with gut extracts, continuing with search for inhibitors of acid secretion to treat duodenal ulcer disease as well as inhibitors of appetite and food intake to treat obesity. For diabetes therapy the interest focused around the incretins, and GIP (glucose-dependent insulinotropic polypeptide) was found to potently stimulate insulin secretion, but had no effect in T2DM. Further research resulted in discovery of another incretin, glucagon-like peptide-1, a product of the enteroendocrine L-cells. This peptide was soon demonstrated to also inhibit glucagon secretion, gastrointestinal secretion and motility, and to inhibit appetite and food intake. Importantly, it retained activity in T2D. Most recently, GLP-1 receptor agonists for weekly or even oral administration, given either alone or as the main component of compounds with additional receptor activities (GIP, glucagon) have demonstrated weight losses of up to 25 % within 1.5-2 years in obese individuals and normalization of average glucose levels in T2DM patients (> 50 % reaching < 5.7 % glycated hemoglobin). Therapy is also associated with a reduced risk of stroke, cognitive impairment, occurrence of dementia and occurrence of or aggravation of diabetic kidney disease. But most importantly, therapy of individuals at risk, both with and without T2DM, has been shown to reduce risk of major adverse cardiovascular events, including mortality, by 14-20 %. The underlying mechanisms have not been clearly elucidated but seem to include anti-atherosclerotic and anti-inflammatory actions. The new GLP-1RAs are now changing our approach to therapy of both T2DM and obesity.