EDITORIAL

Structure/function correlates of neuronal and network activity – an overview

Fiona E. N. LeBeau and Miles A. Whittington
Neuronal Dynamics Research Group, School of Biomedical Sciences, The Worsley Building, University of Leeds, Leeds LS2 9NQ, UK

Email: m.a.whittington@leeds.ac.uk

The Journal of Physiology supported a symposium to celebrate the past achievements and continuing influence of the work of the late Professor Eberhard H. Buhl, held at the University of Leeds in september 2004. The purpose of the symposium was to bring together former colleagues and collaborators of the late Professor Buhl to provide a forum for the discussion of the state of the art in his principal research field: the correlation between the anatomical structure and emergent function of neuronal networks.

The idea that networks of neurones may display patterns of activity that go beyond the sum of each component has been around for about a century since original anatomical studies suggested that the brain constitutes a 'functional syncytium'. The development of the 'Neuronal Doctrine' has interfered with this concept of brain function somewhat. However, increases in our understanding of the heterogeneity of neuronal subtypes, their intrinsic electrical properties and the immense diversity of interneuronal communication via synapses have led to the generation of a working hypothesis for network function which is critically dependent on the complex interplay between these phenomena. What has become increasingly apparent is that interactions within populations of GABAergic interneurones, and between these neurones and principal cells, can provide mechanisms which may underlie some classical EEG rhythms (theta, beta and gamma frequency activity in particular). The first demonstration of the ability of interneurone populations to generate emergent network activity of cognitive relevance came from the work of Roger Traub. In 1995 he used biologically realistic models of interconnected interneurones to provide an explanation for the experimental observation of population gamma frequency rhythms driven by interneurones alone and dependent on the properties of the synaptic connections between them (Whittington *et al.* 1995). At about the same time, Eberhard Buhl, working in Oxford, took this concept further, demonstrating that connections between interneurones and principal cells could powerfully control the output of these principal neurones, recruiting them into a theta frequency rhythm (Cobb *et al.* 1995). In addition, in a seminal paper published in 1998 (Fisahn *et al.* 1998), he showed that reciprocal synaptic connections between these two types of neurone were sufficient to generate a persistent gamma frequency population rhythm which has since been shown to demonstrate striking similarities with persistent gamma rhythms recorded in awake, behaving animals. From these promising beginnings work examining the consequences of the structure and function of interneurone subtypes has grown enormously.

The symposium concentrated on aspects of network topology, control and expression of synaptic and non-synaptic neuronal interactions, interactions between synaptic and intrinsic neuronal properties, target cell specificity and output patterns of interneurone subtypes and correlates with network activity in awake, behaving animals. This issue of *The Journal of Physiology* contains reviews from many of the invited speakers at the symposium and papers individually submitted for review by investigators working in this field of neuroscience.

The Symposium was opened by Professor Brian Robertson from Leeds University who provided a portrait of Eberhard Buhl as both a distinguished scientist and a wonderful human being. The scientific session began with Professor Peter Somogyi who presented data demonstrating interneurone subtype-specific firing patterns associated with different network behaviours in rats *in vivo* under urethane anaesthesia. A clear distinction was shown between the contribution of anatomically and immunocytochemically distinct interneurones and network rhythms associated with sleep and exploratory behaviour in behaving animals (Somogyi & Klausberger, 2005). John O'Keefe presented data illustrating the profile of such network activity, demonstrating the ability of principal neurones to code for various aspects of sensory information relating to an animals position and velocity on a running track (see Huxter *et al.* 2003). The important message delivered was that, unlike the large and relatively homogeneous principal cell population in the hippocampus, interneurone diversity had clear implications for emergent properties of networks.

Whatever interneurone subtype may be shown to be involved in network behaviour, it is the influence of the output from these cells that critically shapes population activity. Kai Kaila showed that this GABAergic synaptic activity is profoundly modified during brain development. The activity of two factors, the K^+–Cl^- cotransporter (KCC2) and neuronal carbonic anhydrase (CA VII) critically control the expression of GABAergic postsynaptic events as either depolarizing, during early development, or hyperpolarizing, in the mature brain (Rivera *et al.* 2005). A further, powerful demonstration of the degree of influence of interneuronal outputs on network function was provided in the form of DC EEG recordings from preterm babies. At times during development when output from interneurones was predominantly depolarizing EEG activity was seen to be completely different from that associated with hyperpolarizing interneurone-mediated events in adult brains. A further demonstration of the importance of hyperpolarizing inhibition in controlling network function was provided by Istvan Mody. Modulation of GABAergic activity by zinc was associated with changes in hippocampal function in the transition to epileptiform events. Mody provided evidence for a role for tonic GABAergic inhibition of postsynaptic cell targets, suggesting that principal cell function is under constant inhibitory control in addition to the phasic control of spike timing by the inhibitory system (Mody, 2005). The correlation between network activity and epileptiform activity was also addressed by Ivan Soltesz who used an insightful computer model to demonstrate the robustness of the network in the dentate gyrus to gradual neuronal cell loss. Evidence of small world topology was correlated with the observation that function only broke down after massive neuronal degeneration associated with hippocampal sclerosis *in vivo* (Foldy *et al.* 2005).

Further evidence for a pivotal role of interneurones in hippocampal network rhythmogenesis was provided by a number of speakers. Ole Paulsen used electrode microarrays and voltage-sensitive dyes to provide elegant demonstrations of the compartment specificity of interneuronal

 DOI: 10.1113/jphysiol.2004.078386

input to principal cells during population gamma rhythms. Interneuronal subtypes which specifically target the perisomatic compartments of principal cells (e.g. basket cells) were shown to be the source of this input (Mann *et al.* 2005). The nature of recruitment of these cells was examined in detail by André Fisahn. Using the kainate model of gamma rhythms *in vitro* he provided evidence for multiple factors controlling the output of this interneurone subtype. Both GluR5 and GluR6 were implicated in activation of interneurones, with GluR5 exerting its effect directly on interneurone axons (Fisahn, 2005). Katalyn Halasy presented data illustrating the rich diversity of modulatory influences on interneurones, in particular neuropeptides (see Racz & Halasy, 2002). The implications of the studies above have importance in understanding the conditions required to generate hippocampal gamma rhythms. Whilst phasic excitation of perisomatic compartments appears to play a major role, it is now also apparent that activation of extrasynaptic glutamate receptors can effectively bypass the orthodromic route of interneuronal activation and generate outputs by direct axonal excitation. In contrast, Gianmaria Maccaferri showed that other interneuronal subtypes in stratum oriens were shown to have properties favouring generation of theta frequency rhythms, with compartment-specific targeting of distal dendrites (Maccaferri, 2005). The role of cholinergic and metabotropic glutamate receptor activation in generation of theta and gamma rhythms was presented by Stuart Cobb (Cobb & Davies, 2005).

The above work on hippocampal structure/function was complemented by presentations illustrating the patterns of synaptic connectivity in entorhinal cortex and neocortex. Alex Thomson provided a thorough summary of the patterns of homo- and heterocellular synaptic connectivity between interneurones and principal cells. An overall pattern of the arrangement of connectivity was revealed indicating a predominant arrangement of principal cell–principal cell communication from superficial to deep cortical layers and principal–interneuron connectivity within layers and from deep to superficial layers (Watts & Thomson, 2005). Hannah Monyer used data from both hippocampus and neocortex to illustrate the fact that synaptic neuronal communication may only be part of the repertoire of cellular interactions making up neuronal networks. Evidence for direct electrical coupling between specific subtypes of interneurones and from interneurones to principal cells was shown and the role of connexin 36-containing and pannexin-containing gap junctions discussed (Blatow *et al.* 2005). Gabor Tamas focused on axo-axonic cells in neocortex, highlighting their pivotal role in controlling network behaviour (see Tamas & Szabadics, 2004). Roland Jones demonstrated that excitatory synaptic interactions in deep and superficial layers of entorhinal cortex had fundamentally different patterns of presynaptic modulation, with profound implications for background synaptic noise and sites of generation of network activity leading to epileptiform discharges (Jones & Woodhall, 2005).

Continuing the neocortical theme Vincenzo Crunelli presented a summary of some of his recent work indicating that intrinsic membrane properties of neurones can have a powerful influence on generation of network rhythms along the thalamocortical axis. In particular, the interaction between membrane potential and T-type calcium channels was shown to generate a 'window' current which was involved in the generation of classical thalamocortical rhythms (Crunelli *et al.* 2005). Roger Traub presented a précis of his single column thalamocortical computer model. With an emphasis on biological realism he demonstrated a number of network behaviours dependent on network properties highlighted by other speakers. Patterns of synaptic connectivity, intrinsic cell properties and gap-junctional communication were shown to combine to provide the rich temporal framework of activity typical of thalamocortical function *in vivo* (Traub *et al.* 2005).

We thank *The Journal of Physiology* for supporting this symposium and area of research with this issue of the journal. It brings together both the recent history of the field and the critical new findings influenced by the original work of Eberhard Buhl. The issue serves as a lasting testament to his contribution to the neuroscience community and also, more generally, demonstrates the power of network theories of neuronal activity as a framework for a greater understanding of brain function.

References

Blatow M, Caputi A & Monyer H (2005). *J Physiol* **562**, 99–105.

Cobb SR, Buhl EH, Halasy K, Paulsen O & Somogyi P (1995). *Nature* **378**, 75–78.

Cobb SR & Davies CH (2005). *J Physiol* **562**, 81–88.

Crunelli V, Toth TI, Cope DW, Blethyn KL & Hughes SW (2005). *J Physiol* **562**, 121–129.

Fisahn A (2005). *J Physiol* **562**, 65–72.

Fisahn A, Pike FG, Buhl EH & Paulsen O (1998). *Nature* **394**, 132–134.

Foldy C, Dyhrfjeld-Johnsen J & Soltesz I (2005). *J Physiol* **562**, 47–54.

Huxter J, Burgess N & O'Keefe J (2003). *Nature* **425**, 828–832.

Jones RSG & Woodhall GL (2005). *J Physiol* **562**, 107–120.

Maccaferri G (2005). *J Physiol* **562**, 73–80.

Mann EO, Radcliffe CA & Paulsen O (2005). *J Physiol* **562**, 55–63.

Mody I (2005). *J Physiol* **562**, 37–46.

Racz B & Halasy K (2002). *Brain Res* **931**, 50–55.

Rivera C, Voipio J & Kaila K (2005). *J Physiol* **562**, 27–36.

Somogyi P & Klausberger T (2005). *J Physiol* **562**, 9–26.

Tamas G & Szabadics J (2004). Cereb. *Cortex* **14**, 823–826.

Traub RD, Bibbig A, LeBeau FEN, Cunningham MO & Whittington MA (2005). *J Physiol* **562**, 3–8.

Watts J & Thomson AM (2005). *J Physiol* **562**, 89–97.

Whittington MA, Traub RD & Jefferys JG (1995). *Nature* **373**, 563–565.