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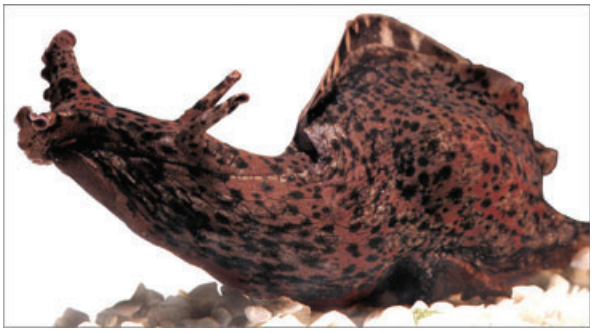
PICTURES & PROSE

Eric Kandel and *Aplysia californica*: their role in the elucidation of mechanisms of memory and the study of psychotherapy



Aplysia californica is a species of sea slug or gastropod mollusc. Through its seemingly simple neuroanatomy and its capacity for classical and operant conditioning, *A. californica* has served neuroscience well. The behavioural modification of the *Aplysia's* siphon-withdrawal reflex has been a particularly useful focus of research.

In the 1960s, James Schwartz and Eric Kandel embarked on a research program seeking to establish the biochemical and neuroanatomical basis of learning and memory. Their initial break-through came in the 1970s when they established that cAMP and later serotonin were synthesised in *Aplysia* ganglia during the process of short-term memory formation (1). Subsequent research showed that cAMP-dependent protein kinase (PKA) and its regulatory effects on potassium channels were relevant to learned behaviour and memory.

By the 1980s, Kandel and his co-workers had identified that protein synthesis was the basis of encoding long-term memory. The synthesis of C-reactive element binding (CREB) and its influence upon the formation of synaptic connections helped show that short-term memory was associated with functional changes in existing synapses, whereas long-term memory was associated with a change in the density of synaptic connections (2).

Thus, a simple reflex in an otherwise obscure sea mollusc helped elaborate a nexus between the brain and the external environment. This research earned Kandel the Nobel Prize in 2000.

Although the work of Kandel does not, in itself, resolve the mind–brain dilemma, it has been of enormous benefit to the field of psychotherapy. Kandel's work has arguably inspired numerous researchers to try to show the neural basis of the benefits of psychotherapy, e.g. Linden (3).

One of the first of these research programs was that of Baxter and co-workers, who showed similar metabolic changes in the head of the right caudate nucleus and orbitofrontal cortex in patients suffering from obsessive compulsive disorder, who had improved with either behaviour therapy or fluoxetine (4). Another example of such work was that of Brody and co-workers, who showed that severely depressed patients whose symptoms remitted after 12 weeks of treatment with either interpersonal psychotherapy or paroxetine showed similar alterations of neural metabolic abnormalities that were present in their original depressed state (5). Such research has also been applied to longer term psychotherapy with patients with personality disorder, showing normalisation of serotonin uptake following the completion of a course of psychotherapy (6).

Psychotherapy has weathered the decade of the brain in part because of studies such as those highlighted earlier, and the pioneering work of Kandel. Not only do efficacy studies show that psychotherapy is comparable to medication in a variety of non-psychotic disorders but the research inspired by the original *Aplysia* work also shows that the psychotherapies likely share the putative neural basis of such treatment responses.

Perhaps the true significance of this work lies in the notion of understanding the plasticity of the nervous system, and in particular the subcellular basis of learning. In essence, Kandel's work showed that the environment can exert a structural effect on the nervous system. Although subsequent research in humans has been limited to neuroimaging changes, the principle first elaborated in Kandel's *oeuvre* remains the core of this field.

Michael Robertson[1,2,3]
Garry Walter[1,4,5]

[1]Discipline of Psychiatry, University of Sydney, NSW 2006, Australia;
[2]Centre for Values, Ethics and the Law in Medicine, University of Sydney, NSW 2006, Australia;
[3]Sydney South West Area Health Service, Liverpool BC, NSW 1871, Australia;
[4]Child & Adolescent Mental Health Services, Northern Sydney Central Coast Health, Sydney, Australia; and

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[5]Department of Psychiatry, Dalhousie University, Halifax, Canada

Michael Robertson,
Centre for Values,
Ethics and the Law in Medicine,
University of Sydney,
NSW 2006, Australia.
Tel: +61 2 9036 3405;
Fax: +61 2 9515 6442;
E-mail: michael.robertson@sydney.edu.au

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