NEUROBIOLOGY OF BIPOLAR DISORDER - LESSONS FROM MIGRAINE DISORDERS

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SUMMARY

Treatment for Bipolar Affective Disorder is at present largely empirical, in the lack of a definitive understanding of the biological basis of the condition. Many theories have been proposed regarding the underlying neurobiology. These have included aetiologies relating to altered neurotrophic factor expression, mitochondrial endoplasmic reticulum dysfunction with related calcium changes, and loss of inhibitory interneurons. Here an attempt is made to integrate such current understanding, in part by considering the changes observed in migraine - a condition which has a number of similarities with bipolar disorder.

Key words: *migraine - bipolar disorder - depressive disorders*

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INTRODUCTION

Bipolar affective disorder has a surprisingly high prevalence, with reported worldwide aggregate lifetime prevalence of around 0.5% (Merikangas 2001), and is estimated to be the fourth greatest cause of loss of disability-adjusted-life-years amongst neuropsychiatric disorders (WHO 2002). The condition has a wide phenotype, ranging from the stereotypical state of 'mania' to much lesser elevation in mood with agitation ('hypomania'), intervened by usually more lengthy, often profound, depressive phases (WHO 2007).

'Migraine' is a term frequently used amongst the general population to describe long-lasting, disabling headaches, but is more formally defined in the International Headache Disorders Classification. It is considered to be the nineteenth greatest cause of disease-related disability worldwide (HIS 2005).

It shares a number of features in common with bipolar affective disorder; in particular it is often treated with the same agents as bipolar disorder, whilst studies have identified common genetic linkages between certain forms of migraine and bipolar disorder (Ortiz 2010). Also of note, chronic migraine has been noted to evolve into a treatment resistant state of 'transformed' migraine (Bigal 2006), similar to how some authors have observed progression of unipolar depression to bipolar depression (Fiedorowicz 2011).

In this article, by comparing some of these features of bipolar disorder and migraine, together with reviewing current theories on the aetiology of bipolar, we aim to expand the framework for further work in elucidating the neurobiology of bipolar disorder, opening routes for future research. Developing a model of the underlying biological changes will help advance treatment of this important, frequently underdiagnosed, mental health problem, and in turn reduce the associated mortality.

NEUROTROPHIC GROWTH FACTORS

Anti-epileptic drugs have been used in the control of both bipolar disorder and migraine. Although these agents have a wide range of mechanisms of action, several authors have looked at ways in which specific drugs could exert their effects in these conditions.

Sodium valproate is commonly associated with rapid effect to elevate brain GABA levels through inhibition of succinic semialdehyde dehydrogenase, and possibly increasing the activity of GABAergic neurons directly by other routes. Such mechanisms are appealing with regard to how they might prevent the erratic electrical activity in an epileptic seizure, but less satisfactory with regard to explaining the effect seen in other neuropsychiatric disorders, where the benefit of treatment can take longer to develop.

An additional mechanism of action may be through altering the expression of brain neurotrophic factors; valproate appears to activate the ERK signalling pathway, with increased expression of Bcl-2 and BDNF, indicating a neuroprotective/trophic effect (Hao 2004).

This may be significant with regards to bipolar disorder (and the affective disorders in general) where brain imaging frequently reveals loss of cortical grey matter. Serum BDNF levels have been found to be reduced in both unipolar and bipolar depressive patients, even when they are euthymic (Monteleone 2008), hinting towards underlying pathological change in the brain. Whilst treatment does not reliably appear to increase levels of neurotrophic factors, conceivably it may be sufficient to 'hold' them at current levels, limiting disease progression.

Regarding migraine, in addition to reduced CSF levels of BDNF, the closely related GDNF has also been found to be lower. It has been suggested that this leads to increased sensitisation of nociceptive pathways in the CNS, accounting for the chronic headache frequently associated with migraine (Sarchielli 2006). It is unclear whether treatment for migraine affects expression of these factors.

Thus in bipolar disorder, changes in neurotrophic factors might either lead to direct neuronal loss, or secondary altered connectivity between neurons, perhaps producing dysfunctional pathways of communication - and mood instability.

MITOCHONDRIAL ENDOPLASMIC RETICULUM AND CALCIUM

A range of metabolic abnormalities have been detected in the nervous system of patients with migraine or bipolar disease. For example, early studies found decreased glucose utilization in the brains of patients with either depression or bipolar disorder. Related to this, altered phosphocreatine metabolism was observed in both migraine and bipolar (Kato 1994).

Following this, authors have suggested that the underlying pathology in bipolar disorder involves altered mitochondrial endoplasmic reticulum function, a further manifestation of this being changes to intracellular calcium concentrations (Kato 2000). Specific mitochondrial DNA mutations have also been associated with some forms of migraine (Wang 2004).

Calcium is involved in a vast array of intracellular processes, including gene expression, filtering of electrical signals in neurons and in signalling cascades (Berridge 2000). Bcl-2 is believed to block calcium-induced apoptosis of cells and enable them to tolerate higher levels of intracellular calcium (Zhu 1999) - thus suggesting a means by which pharmacological therapies may have neuroprotective effects.

Altered calcium physiology could lead to bipolar and migraine disorders through multiple mechanisms, such as neuronal death leading or impaired signalling leading to ineffective neural circuits, and conversely increased neuronal excitability or altered plasticity leading to aberrant synapse formation.

GENETICS

A number of migraine types show a familial pattern of inheritance and thus research has addressed whether specific mutations underlie these. There is inconclusive evidence regarding genes involved in the common forms of migraine, but specific mutations have consistently been demonstrated in 'familial hemiplegic migraine' (Oedegaard 2010). Significantly, these include cell membrane calcium channels (Ophoff 1996), suggesting that calcium abnormalities outside of the mitochondria are also important.

The situation with bipolar disorder is similar, there being a multitude of genes and chromosomes sometimes seen with the condition, with relatively few definitive genetic changes identified. An exception are the various mitochondrial DNA mutations associated with affective disorders introduced above (Kato 2000, Wang 2004).

More recently, given the high co-morbidity of migraine with bipolar disorder, a search for mutations common to both disorders has ensued. Using approaches such as genome-linkage studies (Oedegaard 2010) as well as looking for more specific changes, such as the serotonin transporter promoter region (Marino 2010), given the frequent involvement of this neurotransmitter in affective and migraine disorders.

The mutations do not all affect the same pathways, but more generally involve cellular channels (Oedegaard 2010, Ophoff 1996), components of cell metabolism (Wang 2004), or neurotransmitter regulation (Marino 2010). Energy deficiency or improper signalling may thus be key mechanisms contributing towards development of migraine and bipolar disorder.

Possession of a few genetic changes likely increases the risk of disturbing the finely-tuned neuronal circuitry. This could account for the high degree of heritability observed in both - around 60% in bipolar and between 40-65% for migraine (Oedegaard 2010).

NEURONAL LOSS

Being relatively vulnerable cells, a feasible consequence of insufficient neurotrophic factor support, calcium or metabolic dysregulation is neuronal death. Structural changes in the brains of patients (particularly affecting the pre-frontal cortex) with unipolar depression have been well-described and are suggested to represent cell loss, and similar findings have been identified in bipolar patients (Drevets 1997).

It is unclear whether there are changes in grey-matter volume with chronic migraine (due to frequent co-morbidity with migraine, isolating it as a sole cause has been difficult) but changes in the functionality of neurons, particularly in the peri-aqueductal grey matter have been suggested (Welch 2001).

There may be additional processes contributing towards neuronal loss. In migraine, MRI techniques have demonstrated increased iron deposition in the peri-aqueductal grey matter, suggested to be a consequence of neuronal injury (Welch 2001). This could in turn accelerate further free radical mediated neuronal damage.

Considering the affective disorders, recent research suggests that successful responses to antidepressant therapy correlate with neural function (Lisiecka 2011); from this we might infer that untreated depression leads to progressive brain changes that may be prevented by treatment. This is likely to reflect increased ongoing neurotrophic factor support, but could in a similar way to the above indicate accumulation of cellular insults.

A further theory suggested to account of bipolar disorder, relating to neuronal loss, is death or loss of action of inhibitory interneurons (so-called "mood-stabilising" neurons) (Kato 2008). As decreased response to antidepressant treatment has been reported to correlate with increased frontal-cerebellar connectivity, perhaps a further set of neurons with roles for mood stabilisation exist in the cerebellum. In support of this, affective and other neuropsychiatric disorders often develop with cerebellar lesions and of note include mood instability, depression and obsessive-compulsive traits (Schmahmann 2007); the latter have been observed to be more common in patients with bipolar illness than the general population (Krüger 1995).

In migraine, much of the phenomenology such as aura has been attributed to a temporary loss of neuron and synaptic function (Hadjikhani 2001); in addition to this, structural changes, including somatosensory cortex thickening, have been observed (DaSilva 2007). Perhaps those patients with 'transformed' chronic migraine have developed more permanent loss of neuronal function through injury. In support of this idea, cortical spreading depression is believed to cause hypoxia and potential neuronal death, associated with altered dendrite morphology (Takano 2007).

Potentially, a similar loss of dendritic function in circuits controlling affective pathways could also contribute to bipolar disorder - an explanation for loss of function of mood-stabilising neurons. The hypoxia of cortical spreading depression was observed to occur in the absence of reduced blood flow and through increased metabolic demand (Takano 2007); it was previously mentioned that cortical glucose uptake in patients with affective disorders was decreased (Kato 1994), but possibly the other metabolic defects could lead to increased susceptibility to injury in a similar way - progressive changes with recurrent episodes of depression or mania.

In migraine, the functional loss of dendrites does not appear to necessary correlate with brain matter loss (for example the thickening of somatosensory cortex), thus offering an explanation for why although there is clearly altered function in affective disorders such as bipolar, findings regarding structural losses are often inconsistent.

SENSITISATION

Sensitisation, whereby individual episodes of migraine or affective disorders lead to changes increasing susceptibility to future events, has been proposed as another mechanism.

The end-effects of cellular stress in bipolar disorder may lead to altered neurotrophic factor expression, and impaired protective adaptation by neurons to such events. In turn this may lead to increased susceptibility to future episodes as well as resistance to treatments (whose effects may be mediated through these neurotrophic factors) (Post 2001) - hence the importance of early intervention.

In migraine, the idea of sensitization has moved beyond speculation, with evidence suggesting increased responses centrally in the brainstem trigeminal nucleus caudis, occurring following peripheral sensitization associated with inflammation resulting from the release of vasoactive peptides in migraine. Sensitization can have long-lasting effects and thus arresting such processes when migraine develops may help guide development of future therapy (Dodick 2006).

Although evidence at a molecular level for sensitisation in bipolar disorder is lacking, perhaps the observed progression to bipolar in some unipolar depressives (Fiedorowicz 2011) is a manifestation of this process, which could involve changes to the 'mood-stabilising neurons'.

CONCLUSIONS

With many different theories suggested as mechanism for bipolar disorder and migraine, there is a danger of not appreciating the 'bigger picture' of how multiple processes may contribute. It is likely that collectively they act to produce observed neuropathology.

Changes in neurotrophic factors, interacting with cellular metabolic defects, sometimes involving abnormalities of ion transport, could lead to progressive neuronal changes, in particular involving neuronal connectivity. These may be accelerated by processes of sensitisation - possibly as a result of the impaired neural networks altering downstream neurotrophic factor expression. A large element of the defects would seem to be attributable to genetic aspects. The end-result is abnormal function of affective circuits, which may sometimes be evidenced by gross structural changes, but perhaps more frequently by less evident synaptic changes.

Although we currently perceive migraine and bipolar disorder as two separate entities, there is clearly much overlap in the neuropathological mechanisms that may underlie the disorders. Here, current understanding of migraine has been used to help postulate pathways by which bipolar disorder may occur and so using our understanding of other aspects of migraine may help us further elucidate the basis of bipolar disorder.

REFERENCES

1. Berridge, M. J., Lipp, P., Bootman, M. D. *The Versatility and Universality of Calcium Signalling. Nature Reviews Molecular Cell Biology.* 2000 Oct; 1: 11-21.

2. Bigal, M. E., Lipton, R. B. *Modifiable Risk Factors for Migraine Progression. Headache.* 2006; 46: 1334-1343.

3. DaSilva, A. F. M., Granziera, C., Snyder, J., Hadjikhani, N. *Thickening in the somatosensory cortex of patients with migraine. Neurology.* 2007; 69(21):1990-1995.

4. Dodick, D., Silberstein, S. *Central Sensitization Theory of Migraine: Clinical Implications. Headache.* 2006; 46(s4): S182-S191.

5. Drevets, W. C., Price, J. L., Simpson Jr., J. R. et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature. 1997; 386: 824-827.

6. Fiedorowicz, J. G., Endicott, J., Leon, A. C. et al. Subthreshold Hypomanic Symptoms in Progression from Unipolar Major Depression to Bipolar Disorder. American Journal of Psychiatry. 2011; 168(1):40-48.

7. Hadjikhani, N., Sanchez del Rio, M., Wu, O. et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proceedings of the National Academy of Sciences of the United States of America. 2001 ; 98(8):4687-4692.

8. Hao, Y., Creson, T., Zhang, L. et al. Mood Stabilizer Valproate Promotes ERK Pathway-Dependent Cortical Neuronal Growth and Neurogenesis. The Journal of Neuroscience. 2004; 24(29):6590-6599.

9. IHS Classification ICHD-II. International Headache Society. Available online at http://ihs-classification.org /en/02_klassifikation/02_teil1/01.00.00_migraine.html (2005, accessed 11/07/11).

10. Kato, T., Takahashi, S., Shioiri, T. et al. Reduction of brain phosphocreatine in bipolar II disorder detected by phosphorus-31 magnetic resonance spectroscopy. Journal of Affective Disorders. 1994; 31: 125-133.

11. Kato, T., Kato, N. Mitochondrial dysfunction in bipolar disorder. Bipolar Disorders. 2000; 2: 180-190.

12. Kato, T. Molecular neurobiology of bipolar disorder: a disease of 'mood-stabilizing neurons'? Trends in Neurosciences. 2008; 31(10):495-503.

13. Krüger, S., Cooke, R. G., Hasey, G. M. et al. Comorbidity of obsessive compulsive disorder in bipolar disorder. Journal of Affective Disorders. 1995 ; 34(2):117-120.

14. Lisiecka, D., Meisenzahl, E., Scheuerecker, J. et al. Neural correlates of treatment outcome in major depression. International Journal of Neuropsychopharmacology. 2011; 14(4):521-534.

15. Marino, E., Fanny, B., Lorenzi, C. et al. Genetic bases of comorbidity between mood disorders and migraine: possible role of serotonin transporter gene. Neurological Sciences. 2010; 31: 387-391.

16. Merikangas, K. R., Jin, R., He, J-P., Kessler, R. C., et al. Prevalence and Correlates of Bipolar Spectrum in the World Mental Health Survey Initiative. Archives of General Psychiatry. 2011; 68(3):241-251.

17. Monteleone, P., Serritella, C., Martiadis, V., Maj. M. Decreased levels of serum brain-derived neurotrophic factor in both depressed and euthymic patients with unipolar depression and in euthymic patients with bipolar I and II disorders. Bipolar Disorders. 2008; 10(1):95-100.

18. Oedegaard, K. J., Greenwood, T. A., Lunde, A. et al. A genome-wide linkage study of bipolar disorder and co-morbid migraine: Replication of migraine linkage on chromosome 4q24, and suggestion of an overlapping susceptibility region for both disorders on chromosome 20p11. Journal of Affective Disorders. 2010; 122: 14-26.

19. Ophoff, R. A., Terwindt, G. M., Vergouwe, M. N. et al. Familial Hemiplegic Migraine and Episodic Ataxia Type-2 Are Caused by Mutations in the Ca2+ Channel Gene CACNL1A4. Cell. 1996; 87(3):543-552.

20. Ortiz, A., Cervantes, P., Zlotnik, G., et al. Cross-prevalence of migraine and bipolar disorder. Bipolar Disorders. 2010; 12: 397-403.

21. Post, R. M., Weiss, S. R. B., Leverich, G. S. et al. Sensitization and kindling-like phenomena in bipolar disorder: implications for psychopharmacology. Clinical Neuroscience Research. 2001; 1(1-2):69-81.

22. Sarchielli, P., Alberti, A., Candeliere, A. et al. Glial cell line-derived neurotrophic factor and somatostatin levels in cerebrospinal fluid of patients affected by chronic migraine and fibromyalgia. Cephalalgia. 2006; 26: 409-415.

23. Schmahmann, J. D., Weilburg, J. B., Sherman, J. C. The neuropsychiatry of the cerebellum - insights from the clinic. The Cerebellum. 2007; 6(3):254-267.

24. Takano, T., Guo-Feng, T., Peng, W. et al. Cortical spreading depression causes and coincides with tissue hypoxia. Nature Neuroscience. 2007; 10(6):754-762.

25. Wang, Q., Ito, M., Li, B. U. et al. Mitochondrial DNA control region sequence variation in migraine headache and cyclic vomiting syndrome. American Journal of Medical Genetics Part A. 2004; 131(1):50-58.

26. Welch, K. M. A., Nagesh, V., Aurora, S. K., Gelman, N. Periaqueductal Gray Matter Dysfunction in Migraine: Cause or the Burden of Illness? Headache. 2001; 41(7):629-637.

27. World Health Organisation. The World Health Report 2002: Reducing Risks, Promoting Health Life. Geneva, Switzerland: World Health Organization; 2002.

28. World Health Organisation. The ICD-10 Classification of Mental and Behavioural Disorders. Geneva, Switzerland: World Health Organisation; 2007.

29. Zhu, L., Ling, S., Xiao-Dan, Y. et al. Modulation of Mitochondrial Ca2+ Homeostasis by Bcl-2. The Journal of Biological Chemistry. 1999; 274(47):33267-33273.

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