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Losing sleep over delirium

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Delirium is an acute cognitive disorder that presents with alterations in levels of consciousness accompanied by a change in cognition or perceptual disturbance that develops over a short period (hours to days) and fluctuates over time (1). For almost 2 decades, it has been recognized that the occurrence of delirium has significant impact on outcomes in critically ill patients (2,3). The importance of early detection and management of delirium has been stressed in Societal guideline statements (4) and in knowledge implementation resources (see www.iculiberation.org). However, effective treatments to reduce duration and associated mortality have been limited (5–7). This is likely, in part, due to a lack of detailed understanding of the mechanisms that subtend this important neurobehavioural syndrome.

Although there are several etiological accounts of delirium in adult patients including neuroinflammatory, neuronal aging, oxidative stress, neurotransmitter deficiency, neuroendocrine, diurnal dysregulation, and network disconnectivity hypotheses (for a detailed review see [8]), it is likely that most of these pathways overlap, rather than occurring in isolation. Therefore it is extremely unlikely that one model system will address all etiologies. As such, developing experimental models to further understand mechanisms and potential targets of intervention are urgently needed.

In the study by Gile and colleagues, the investigators have sought to provide new information on the diurnal dysregulation hypothesis through investigation of circadian rhythm disruption in a murine model (9). Specifically, the team sought to investigate the role that inhibition of the circadian rhythm protein Period2 (PER2) plays in delirium-like states in a murine model. Study of this pathway is of notable importance due to role that sleep deprivation (a ubiquitous issue in nearly all critically ill patients) plays in the occurrence of delirium and as a potential modifiable clinical target for the bedside team (10,11).

The Biologic validity of PER2

There are certain zeitgebers (environmental time signalling stimuli such as exposure to light) that regulate the synchronization of circadian rhythms to the 24-hour cycle. Previous investigations have indicated that mistimed sleep affects molecular processes that can impact the circadian regulation of the human transcriptome (12). There have been 10 circadian

transcription factors which have been identified so far (12). Among these, PER2 protein has been described as a component of the cellular mechanism that contributes the internal 24 hour clock as well as other potential functions (13). In the study by Gile and colleagues, they have argued that in humans, “*the hippocampus appears to play a critical role in the pathogenesis of delirium*” and disruption of the *Per2* gene in this region leads to sleep disruption.

While this is a novel and provocative hypothesis, there are a few issues with this concept. First, whether *Per2* expression is altered in aging or in acute illness (both germane to delirium in the critical care environment) has not been previously addressed. Second, while sleep disturbances and disruption in circadian rhythms have been postulated in delirium, there is as of yet little or no information that gives biological validity that alterations of PER2 activity occur during delirium. A comprehensive assessment of PER2 changes during age and acute illness, therefore, are crucial to establishing an evidence base for mechanistic studies of the importance of PER2 in delirium. The current study begins this process, though one must acknowledge the limitations in studying a key molecular regulator of circadian biology at a single cross-sectional time point. Despite this description of altered *Per2* expression, it is necessary to assess the extent to which the pattern of *Per2* is altered and whether circadian rhythm is likewise altered. Third, the Authors have sought to modify PER2 activity with the flavonoid nobiletin. Although there are prior studies demonstrating that nobiletin (a protein found in citrus peel) is an enhancer of PER2 function, it has also been shown that nobiletin significantly reduces LPS-induced cytokine production and that it reverses olfactory bulbectomy-induced memory impairment in a rat model via protection against cholinergic degeneration (14,15). Therefore, to substantiate that nobiletin protects cognitive function via effects on PER2 and circadian regulation, it is important to show at molecular and behavioural levels that: a) a genuine disruption of circadian rhythm has been achieved; and b) that nobiletin mitigates this and c) that the reversal of circadian change is responsible for any observed cognitive benefits. In the absence of these observations, one can only say that nobiletin has partially reversed some modest cognitive disruption.

Indeed, the Authors have suggested that *Per2*^{-/-} mice “revealed a phenotype that shares similarities with acute delirium” at baseline, which would indicate a more chronic cognitive impairment rather than the deleterious responses to an acute stressor that typify delirium. Notwithstanding the finding that altering *Per2* expression/function affects some aspects of activity and cognition, perhaps the *Per2*^{-/-} model may be most relevant as a model of underlying vulnerability, while acute changes in circadian rhythm, triggered by acute illness or sedation speak more directly to delirium as defined in DSM-V (16).

Validity of the animal model system(s)

Although the Authors should be congratulated for approaching different etiological routes to cognitive function relevant to delirium it is important to recognise that, in doing this, they are effectively presenting multiple model systems: 1) midazolam-induced cognitive dysfunction 2) lipopolysaccharide (LPS)-induced cognitive dysfunction 3) *Per2*^{-/-}-associated cognitive dysfunction and 4) constant light exposure-induced cognitive

dysfunction. In the study by Gile et al, each of these models have undergone limited characterization.

Taking the LPS model as one example, normal healthy animals are described as demonstrating deficits at 24 hours post-LPS administration. Delirium is characterized as an acute deviation from baseline cognitive function, however, baseline cognitive performance has not been assessed in the current study: treated animals are only compared to saline-treated controls. In the absence of baseline assessment, therefore, the observation that saline-treated controls show performance of approximately 60% tends to undermine confidence in the robustness of the cognitive deficits (an animal that has no idea which way to turn will, on average, score 50%, i.e. chance responding). Given these modest deficits, that experimental groups for behaviour contain just 5 animals is a concern in the current 'reproducibility crisis' for behavioural neuroscience (17). This is perhaps best captured in the novel object recognition data (Figure 3 in Gile et al.). Here, all of the treatment groups demonstrate a degree of preference for the novel object and there are very modest differences in the extent of that preference. It is not clear that any of the treatments show novel object preference that is actually different from the saline-treated animals (i.e. normal memory performance).

Moreover, as the Authors clearly show, LPS-treated animals show profound suppression of activity in the open field at 24 hours (the same time point as the described 'delirium-like' cognitive impairment). A cognitive test that relies on the animals' spontaneous motivation to explore may likely be an unreliable indicator of cognitive impairment when activity itself is profoundly suppressed (18). Prior studies have extensively tested working memory in food-rewarded and aversively motivated T-maze tasks post-LPS and consistently find no evidence of working memory dysfunction in the hours directly after LPS, nor at 24 hours, in normal mice, although these challenges do produce acute and fluctuating deviations from baseline performance when challenged animals have prior hippocampal pathology (19–21). Those studies established good baseline performance of ~80% against which to compare post-treatment performance. In the current study, with no baseline assessment and small sample size one has to be cautious about the conclusions drawn.

Likewise, there is real benefit to studying the impact of environmental conditions (i.e. zeitgebers) to simulate sleep disruption during ICU-illness, however, it is not clear from this model of constant light exposure what impact this has had on sleep cycles and circadian disruption in a general sense. A more complete engagement with the tools of the circadian biology field will be necessary to clarify the parameters of the current model and to begin to elucidate the roles of regulators of circadian rhythm and the sleep-wake cycle in the pathophysiology of delirium. This remains a high priority as is evident from previous and upcoming clinical trials of melatonin and melatonin agonists for delirium (22–24).

Summary

The study by Gile et al, has importantly opened the box to begin to study the interplay of sedation, acute illness and circadian rhythm in the pathophysiology of delirium but further characterisation of these model systems is clearly required.

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