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Neuropeptide Y: Biomarker and intervention for surgical recovery

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We read with interest Enman et al.'s recent publication on Neuropeptide Y (NPY) as a therapeutic target for stress-related psychiatric diseases (Enman et al., 2015). They observe that NPY has the potential to provide novel pharmacological therapy for stress-related psychiatric diseases and may have few peripheral side-effects and drug–drug interactions. Moreover, despite its short half-life, NPY has a lasting effect. Enman et al. discuss a number of animal studies in order to lay the rationale for NPY as a pharmacological therapy for stress-related disease and cite two clinical trials that are currently underway.

Their paper provides an excellent review of NPY and its role in anxiety, depression and post-traumatic stress disorder (PTSD). Insight into the role of NPY in the neurobiology of stress is developed through the discussion of multiple animal models. Rodents that are genetically deficient in NPY are phenotypically anxious but this phenotype can be modified through the administration of NPY, especially when administered in specific parts of the brain (namely the amygdala, the hippocampus, the locus coeruleus, and the lateral septum). Animal models demonstrate that the roles of NPY receptor subtypes do not all have beneficial behavioural effects. Activation of Y1 and Y2 receptors resulted in undesirable effects. Furthermore, NPY does not readily cross the blood brain barrier. These qualities of NPY pose additional challenges in the formulation of an NPY therapeutic agent.

More broadly, the animal model evidence Enman et al. present may be applied to examine how NPY modifies the neurobiology of stress via the Hypothalamus-Pituitary-Adrenal (HPA) axis. Enman et al. provide a putative model of this modification and suggest that it may occur directly on the corticotrophin releasing hormone (CRH)-ergic or the GABA-ergic neurons of the hypothalamus, the noradrenergic neurons of the locus coeruleus, or via glutaminergic neurons projecting from the basolateral amygdala into the hypothalamus. Regardless of the neural circuitry, it is clear that NPY acts on the HPA axis before the adenohypophysis releases ACTH.

Enman et al. highlighted the role of HPY as a "functional brake" on the excitatory effects of pro-stress neurotransmitters, such as CRH and Norepinephrine (NE). While NPY possesses an inhibitory role, such as inhibiting the release of NE, its effects may be counterintuitive. The inhibition of NE prevents its depletion by preventing excessive secretion while maintaining its effectiveness for maximal impact (Li et al., 2012; Han et al., 1987). NPY, therefore, achieves potentiation through inhibition (Han et al., 1987). Understanding the function of NPY in such a context may explain the mechanism of diminished CRH levels following electroconvulsive therapy (ECT) as reported by Enman et al. The reported decrease in CRH following ECT may have resulted not only from inhibition by NPY, but also from its potentiating effects, such as preventing excessive secretion of pro-stress neurotransmitters while increasing its effectiveness. The potentiating effects of NPY may be relevant to psychological resilience.

While Enman et al. make a strong case that NPY is a potential pharmacological target, there is yet another a large body of evidence that suggests NPY could be a useful endogenous biological marker for psychological resilience (Russo et al., 2012). Psychological resilience is characterised by the ability to accept circumstances that cannot be changed and adapt to significant changes in the environment (Folkman, 2010). As such it is intimately related to stress and state anxiety. Along with other potential biomarkers, namely the androgens dehydroepiandrosterone (DHEA) and testosterone, studies consistently show that NPY levels are elevated in psychologically resilient individuals. Its precise role in resilience

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is not clear, but it is likely to act through modification of the HPA axis.

The clinical implications are manifold, especially in surgical recovery. Surgery is a highly stressful event both physiologically and psychologically, and it has been proposed that there is a psychological mediation of recovery (Kehlet & Slim, 2012; Janis, 1958), which is supported by a substantial amount of evidence (Walburn et al., 2009; Mavros et al., 2011; Munafo & Stevenson, 2001). Some patients exhibit a diminished stress response to surgery and more rapid recovery than others. These patients are surgically resilient (Graham & Becerril-Martinez, 2014).

NPY offers a potentially valuable resilience biomarker. As such, we believe that it could provide a stable endogenous biological marker for resilience that would potentially be clinically valuable to measure prior to surgery (Graham & Becerril-Martinez, 2014). This would allow the development of patient-specific enhanced post-operative recovery protocols, which would enhance the current surgical paradigm of fast-track or enhanced recovery through individualising patient allocation (Kehlet & Slim, 2012). Ensuring patient expectations are well managed and that patients undergoing elective surgery are relatively fit and healthy prior to surgery may prove to be a more clinically prudent than administering NPY to patients without any pre-operative stress-related psychological disease.

We agree with Enman et al. to some extent insofar as NPY is a potential therapeutic target. Resilience itself has been shown to be an effective therapeutic target in patients without a psychiatric disease, and we argue that such strategies can be used to personalise peri-operative care and improve surgical outcomes. An NPY-based screening test to identify surgical resilience pre-operatively would have a large impact in elective surgery allowing for targeted prehabilitation interventions and possibly also in recovery strategies after emergency or trauma surgery. A number of studies have reported behavioural/psychological (Morgan et al., 2000), physical (Coiro et al., 2011; Han et al., 2011), and dietary interventions (Huang et al., 2011) that increase NPY levels. Beyond screening, interventions may be considered to enhance levels of NPY in a perioperative surgical context.

It is clear that NPY has much clinical potential. While it may be beneficial as a therapy for stress-related psychiatric diseases, NPY has a much broader potential when considered from the perspective of psychological resilience. More research is needed on NPY as a screening biomarker, and possibly intervention, in surgical resilience.

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