

# Neuroprotective Effects Against POCD by Photobiomodulation: Evidence from Assembly/Disassembly of the Cytoskeleton

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**ABSTRACT:** Postoperative cognitive dysfunction (POCD) is a decline in memory following anaesthesia and surgery in elderly patients. While often reversible, it consumes medical resources, compromises patient well-being, and possibly accelerates progression into Alzheimer's disease. Anesthetics have been implicated in POCD, as has neuroinflammation, as indicated by cytokine inflammatory markers. Photobiomodulation (PBM) is an effective treatment for a number of conditions, including inflammation. PBM also has a direct effect on microtubule disassembly in neurons with the formation of small, reversible varicosities, which cause neural blockade and alleviation of pain symptoms. This mimics endogenously formed varicosities that are neuroprotective against damage, toxins, and the formation of larger, destructive varicosities and focal swellings. It is proposed that PBM may be effective as a preconditioning treatment against POCD; similar to the PBM treatment, protective and abscopal effects that have been demonstrated in experimental models of macular degeneration, neurological, and cardiac conditions.

**KEYWORDS:** photobiomodulation, PBM, postoperative cognitive dysfunction, POCD, cytoskeleton, neuroprotection

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## Introduction

Postoperative cognitive dysfunction (POCD) is a neurodegenerative condition, acquired after surgery and anaesthesia,<sup>1,2</sup> and is similar to Alzheimer's disease (AD) in symptoms and risk factors such as age and education level.<sup>1,3</sup> POCD has become a significant problem in the health-care system, in terms of both patient outcome and increased resources expended. As yet, there are a few effective therapeutic interventions. Photobiomodulation (PBM) is the use of (nonthermal) visible and infrared light to promote therapeutic benefits.<sup>4–6</sup> Recently, PBM has been shown to be effective against neurodegenerative disorders, including AD,<sup>7</sup> Parkinson's disease (PD),<sup>8</sup> and depression,<sup>9</sup> in both animal models and clinically. The concept of preconditioning in health with laser treatments has been explored over the past few years with increasing evidence of its effectiveness.<sup>10</sup> This paper reviews the effects of PBM treatment on the cytoskeleton as a mechanism behind preconditioning and its proposed use for preconditioning and neuroprotection against POCD. Cytoskeleton modulation, as well as the parallel between the evoked PBM response and endogenous mechanisms of neuroprotection in hibernation, cortical spreading depression (CSD), *N*-methyl-D-aspartate (NMDA) poisoning, and ischemic preconditioning, is reviewed. These mechanisms involve interaction between

a number of proteins and signaling molecules, including TWIK-related spinal cord potassium channels (TRESK) and transient receptor potential vanilloid 1 (TRPV1) ion channels. These proteins may interact with the cytoskeleton,<sup>11,12</sup> postsynaptic density protein 95 (PSD-95), cypin, and prion protein (PrP<sup>C</sup>), which together organize cytoskeleton structure.<sup>13–15</sup> This review discusses the role of the cytoskeleton in allostasis in response to redox stress and cellular stress,<sup>15,16</sup> which results in neuroinflammation<sup>17</sup> and protein interactions of the axonal and synaptic densities.<sup>18</sup> PBM has been shown to have a direct effect on the cytoskeleton, which is directly involved in neural blockade, in pain modulation<sup>19</sup> and most probably in the preconditioning effects of PBM, which may also be important in preconditioning against POCD. The emphasis is on the neuroprotective role of small, reversible axonal varicosities that are protective against the large destructive neural varicosities seen in neurodegenerative disease and sympathetically dysregulated pain.

## Postoperative Cognitive Dysfunction

POCD is also known, in the literature, as postoperative cognitive deficit, postoperative cognitive decline, perioperative cognition deficit, and postoperative cognitive change. It is a widely recognized clinical condition, involving the loss



of cognition following anaesthesia and surgery. Although POCD has been extensively reviewed,<sup>1,20–24</sup> it has no universally accepted definition. In fact, there is no International Statistical Classification of Disease code for POCD, Diagnostic and Statistical Manual of Mental Disorders code, gold standard diagnostic criteria, and recognized biomarker.<sup>22</sup> However, the perception of POCD as a problem and a consequence of anaesthesia and surgery has been recognized since 1860 when Bigelow first used anesthetics.<sup>25</sup> POCD has been increasingly documented since 1955<sup>26</sup> and has been well described as an objective diagnosis.<sup>27</sup> An operational understanding of POCD is its manifestation as an acute but often subtle deterioration in cognition, with a loss of the ability to perform tasks involved with everyday living. It may affect a spectrum of cognitive abilities, including memory, speed of information processing, orientation, concentration, psychomotor ability, fine motor coordination, and attention span. POCD is observed in patients as the inability to accomplish simple cognitive tasks, such as crosswords,<sup>1</sup> and is diagnosed using a variety of neuropsychological tests. Definitive diagnosis requires that the tests be performed preoperatively, in order to obtain a baseline from which a decline can be determined. Postoperative tests are best performed one week after surgery, after any postoperative delirium has passed, and after the cessation of any drugs and pain that might cause interference in the testing. Most studies<sup>20,27,28</sup> agree that the major factors that influence POCD are increasing age (>60 years, although some studies use >65 years or even >70 years), preoperative cognitive condition, and education. Cognitive reserve and trajectory are perhaps the most important factors that influence the risk of POCD.<sup>29</sup> Additional factors include length and complexity of the surgery (with cardiac surgery possibly being more risky than noncardiac surgery),<sup>20,28</sup> a history of alcohol abuse,<sup>30</sup> previous stroke,<sup>28</sup> diabetes mellitus, hypertension, atherosclerosis,<sup>31</sup> and postoperative complications, especially respiratory complications and postoperative infections.<sup>27</sup> A recent study has also identified gender as a factor, with females being at greater risk than males,<sup>32</sup> as is the case with AD.<sup>33</sup> Although POCD in the very young is less studied, most evidence, such as that obtained from twin studies<sup>34</sup> and cohort studies,<sup>35</sup> suggests that it is much less of a problem. However, Yin et al determined that propofol could impair short-term memory in children.<sup>36</sup>

Although there have been numerous studies that have reported POCD, many of these are anecdotal, are case studies, or are poorly controlled and inadequately tested. Some clinicians and researchers consider that there is a lack of statistical evidence to separate POCD from normal cognitive decline and reviews of case-controlled studies using stringent criteria have shown mixed results in the past.<sup>22</sup> For example, a review of 25 randomized controlled trials did not demonstrate unequivocal POCD response in patients<sup>37</sup> and a meta-analysis of 26 randomized controlled trials found no evidence of POCD.<sup>38</sup> Part of the difficulty in the study of POCD is the

variety of testing regimes and diagnostic tools that have been used in various studies and the consequent inability to compare between studies. Other difficulties include the lack of appropriate control groups in many studies and the difficulty in determining the normal cognitive trajectory of surgery patients in the studies.<sup>22</sup> In addition, many of the studies in the past have been small, lacked power, and were retrospective. Despite these problems, there is compelling evidence that POCD exists as a genuine phenomenon<sup>21,37,39</sup> with a strong public and medical awareness of the consequences of the disorder. Recent prospective studies of POCD have indicated that the risk of POCD posed by anaesthesia/surgery was 1.35<sup>40</sup> and 1.99<sup>41</sup> compared with the general population. In recent years, a number of prospective, long-term, and cohort studies have been initiated in order to provide more definitive information and predictions for POCD.

The general acceptance of POCD as a real and measurable disorder has resulted in increased attention and research into the implications of POCD. Each day, millions of people around the world undergo anaesthesia and surgery. Increasing life expectancy and the consequent increase in the elderly population, the advances in surgical procedures, the decline in mortality rates, and the shortening of postoperative recovery times point to an increasing number of surgical procedures performed on the elderly, the population most at risk of POCD. For example, statistics from the Australian Institute of Health and Welfare (<http://www.aihw.gov.au/>) indicate that in 2010, 32% of all anesthetics were given to >65 years old (13.5% of population). With the predicted percentage of >65 years old in the population in 2051 increasing to 24.2%, anesthetics given to >65 years old is predicted to be 48% of all anesthetics administered. In addition to being major recipients of surgical procedures, elderly patients are at greater risk of cognitive decline and dementia, pointing to an increasingly important role for POCD in the postoperative recovery of elderly patients.

The reported incidence of POCD varies widely with different studies, most probably reflecting methodological differences. Incidence can range from 10% to 40% after one week and up to 15% after three months postoperatively in noncardiac surgery. The International Study of POCD (ISPOCD) has concluded that 26% of patients older than 60 years developed POCD at one week postoperatively and 10% had POCD at three months.<sup>27</sup> Although it has been commonly accepted that cardiopulmonary bypass surgery has a higher risk of POCD than noncardiac surgery,<sup>20,28</sup> this might in fact be due to the generally less rigorous criteria used in many cardiac surgery studies,<sup>22</sup> the differences in diagnostic criteria<sup>21</sup> or to specific factors common to cardiac surgery. Evered et al<sup>42</sup> found that at three months, the number of patients with POCD were independent of whether the surgery was cardiac or total hip replacement and, in general, the number of patients with POCD at three months are similar in both groups.<sup>23</sup>



POCD may be short-lived and reversible or may last for months or possibly years, with the potential to affect clinical outcomes for up to five years postoperatively.<sup>43</sup> While up to 47% of elderly patients could demonstrate some cognitive decline after 24 hours, this decreases to much lower levels by the time of discharge.<sup>21</sup> Early POCD, lasting up to three months, may in fact be a common problem, affecting not only up to 10% of elderly surgery patients but also young patients, but in whom recovery is much faster.<sup>21</sup> Recovery from POCD sets this condition apart from other neurodegenerative diseases (AD, PD, etc.) and the recovery is similar (albeit much slower) to the recovery in cognitive decline that occurs within hours after CSD that accompanies migraine with aura and cluster headaches.<sup>44</sup>

POCD may also be progressive, with some patients who do not show early POCD at one week, progressing to POCD at three months. POCD might also be cumulative, with more episodes of anaesthesia/surgery leading to a greater incidence of POCD.<sup>31</sup> Even if there is complete recovery from POCD, the effects of short-term POCD impact on patients' quality of life and the ability to continue in employment. There is, therefore, a socioeconomic burden, including increased hospital stays, increased out of hospital care, job loss, and dependence on social payments.<sup>45</sup> There may also be an increase in mortality, with POCD patients 1.63 times as likely to die as non-POCD patients.<sup>45</sup>

Persistent POCD is more contentious. Some studies have shown evidence of persistent POCD in a small number of patients. The ISPOCD showed that after one to two years, 1% of patients showed persistent POCD.<sup>46</sup> Some early studies indicated that dementia was still apparent after five years,<sup>47</sup> with one study showing high levels of long-term POCD (42%) at five years.<sup>48</sup> The ISPOCD long-term study found, however, no significant relationship with dementia after 11 years,<sup>49</sup> and other studies have shown little evidence of cognitive decline after a number of years when compared with nonsurgery patients.<sup>50–52</sup>

The cause or causes of POCD have remained elusive, despite intensive research over the past 25 years. As with other forms of dementia, the cause of POCD is almost certainly multifactorial. Part of the difficulty in determining etiological factors involved in POCD is in the separation of anaesthesia, surgery, and perioperative care; it is not usual to give anaesthesia without surgery and surgery is most usually performed under anaesthetic. The time in hospital may also be a factor, the so-called hospital stay syndrome.<sup>53</sup> Other contributing factors to POCD may include perioperative conditions, inflammation, pain, and comorbidities, although a number of specific factors, such as changes in cerebral blood flow, cardiopulmonary bypass, hypoxemia, and microemboli, have been all but discarded as sole causes.<sup>23</sup> In reviewing available evidence, Krenk et al<sup>21</sup> suggest a multifactorial pathogenesis with the potential involvement of postoperative sleep disturbance (exacerbated by opioid analgesia), inflammatory stress response, pain, and environmental factors. Fast-track

hip and knee replacements, which included patient education and preparation, as well as shorter hospital stays, were shown to result in decreased short-term POCD, but not long-term POCD.<sup>54</sup>

POCD shows some similarities with other forms of dementia, such as AD, which it mimics in a number of ways<sup>3,55,56</sup> and POCD may in fact be triggered by AD pathways.<sup>55</sup> Mild cognitive impairment (MCI) is a subjective decline in cognition and can be a precursor to AD, with a substantial minority with MCI (depending on age) progressing to AD.<sup>57</sup> MCI is prevalent in the elderly population with between 14% and 18% of people over 75 showing symptoms.<sup>23</sup> Since a substantial proportion of elderly patients undergoing surgery will have MCI, it is possible that anaesthetics and surgery could aggravate or *unmask* MCI and lead to progression to POCD and ultimately to AD. Aging of proteins and an increase in misfolded and unrectified proteins lead to an increase in protein-folding neurodegenerative diseases (such as AD, PD, Huntington's disease (HD), and prion diseases) and are most probably also linked with POCD.<sup>13,58</sup> There is currently a great deal of research into the link between POCD, anaesthesia/surgery, and dementia, especially AD, since any connection would indicate a far greater and longer lasting impact of POCD.

The exact mechanism of action of anaesthesia is still unclear. General anaesthetics have a number of common receptors in the central nervous system, including either blocking NMDA receptors (eg, ketamine and nitrous oxide)<sup>59</sup> or enhancing gamma-aminobutyric acid type A (GABA<sub>A</sub>) receptors.<sup>60</sup> The fact that these receptors are known to affect memory<sup>61,62</sup> raises the possibility of a direct link between anaesthetics and POCD. Cell culture studies indicate that a number of anaesthetics cause apoptosis<sup>39</sup> and mounting evidence from animal studies has strengthened the link between anaesthetics and dementia including POCD.<sup>55,63–65</sup> For example, anaesthesia has been shown to cause cognitive deficit and neurodegeneration in developing (rat) brains,<sup>66–68</sup> and vanilloid anaesthesia has been shown to lead to long-term memory impairment in adult and aged rats<sup>69</sup> and mice,<sup>70</sup> as well as a transient decrease in the expression of hippocampal neuronal nitric oxide synthase (nNOS) and PSD-95 in aged rats, together with cognitive impairment.<sup>71</sup> Anaesthesia and cognitive deficit in animal studies has been linked with NMDA receptor expression,<sup>72</sup> disruption of calcium homeostasis,<sup>73</sup> and neuroinflammation (see the following sections). Although many studies emphasize the potential link between anaesthetics and cognitive decline, Callaway et al found no link between sevoflurane and long-term cognitive impairment in aged rats<sup>74</sup> and found that the effects of desflurane were dose dependant and not long lasting.<sup>75</sup>

A number of neurodegenerative diseases (AD, PD, HD, tauopathies) have in common the disruption of the cytoskeleton, with the disassembly of microtubules (MTs) and the concomitant accumulation of tau fibrils and  $\beta$ -amyloid (A $\beta$ ). Anaesthetics are known to interact with the cytoskeleton,<sup>64,76–79</sup>



can bind to tubulin and cause MT disassembly,<sup>80</sup> and so are appropriate targets as potential causative agents of POCD. Craddock et al<sup>80</sup> have identified multiple (32) binding sites for volatile anesthetics on  $\alpha$ - and  $\beta$ -tubulin and consider that anesthetics are prime candidates as causative agents of POCD, via altered tubulin and phosphorylation of tau, leading to MT instability. Animal studies have also suggested that anesthetics (propofol, halothane, sevoflurane, and isoflurane) can increase AD  $\beta$ -amyloid<sup>24,63,81–83</sup> and increase tau phosphorylation<sup>70,84,85</sup> with the anesthetic sevoflurane shown to produce transient hyperphosphorylation of tau in mice on a single application and persistent tau hyperphosphorylation and memory impairment with repeated exposure.<sup>84</sup> The anesthetic propofol was also shown to induce tau hyperphosphorylation in a mouse hippocampus model of AD.<sup>86</sup> On the other hand, exposure of presymptomatic AD mice to anesthetics (halothane, isoflurane) did not accelerate the progression of the disease but, on the contrary, appeared to result in the preconditioning against neurodegeneration, due to increased phosphorylation of tau.<sup>87</sup>

Despite anecdotal and some epidemiological evidence of a link between anesthetics and AD,<sup>88</sup> PD,<sup>89–91</sup> and POCD,<sup>92</sup> clinical evidence does not, on the whole, support the animal studies. Large studies such as the ISPOCD<sup>93</sup> as well as meta-analyses<sup>94,95</sup> have found no link between anesthetics and POCD or AD, including comparisons between general and regional anesthetics.<sup>93,96</sup> However, an expert group attending the *British Journal of Anaesthesia Salzburg Seminar* in 2012 reviewed the available data on POCD and concluded that there was mounting evidence to indicate that general anaesthesia can negatively affect cognition especially in the elderly (as well as the very young).<sup>70,97</sup> Although there is little direct evidence that the type of anesthetic is a risk factor,<sup>37,70</sup> it is possible that the route of anesthetic and depth of anaesthesia may have an impact on POCD. The use of the bispectral index to guide anesthetic titration has been found to reduce the occurrence of POCD in some studies.<sup>98,99</sup> There are also indications that it is not simply anesthetic use that leads to POCD. Surgery-induced nociception without anesthetics was shown to induce POCD in mice.<sup>100</sup>

There are a number of studies that have shown that surgery/anesthetics can lead to increases in the biomarkers for AD,<sup>85,101</sup> including  $\beta$ -amyloid<sup>102,103</sup> and phosphorylated tau,<sup>101,103</sup> strengthening the case for some involvement of anesthetics with the risk of AD.<sup>89,90</sup> The presence of brain  $\beta$ -amyloid has in fact been found to be a good predictor of POCD risk in cognitively normal patients.<sup>104</sup> A consensus statement issued from an international workshop on anesthetics and AD<sup>105</sup> concluded that there was sufficient evidence to warrant further investigations into the onset and progression of AD and neurodegeneration after anaesthesia and surgery and that clinical trials should be emphasized, which are led by anesthetists. Anesthetic delivery to patients undergoing surgery has always been a highly individualized process. This individual approach

is amplified in elderly and other at-risk patients. There as yet have been no studies of POCD in groups that require different anesthetic regimes, such as redheaded women.<sup>106</sup> The focus of research on POCD is moving from anaesthesia and surgical techniques that are common to all patients and moving toward individual patient-centered factors.<sup>2</sup>

The molecular mechanism of POCD (as with other neurodegenerative diseases) has been difficult to pin down. Induced POCD in mice has been shown to reduce NMDA receptor B levels,<sup>100</sup> which, along with PSD-95, is implicated in synaptic plasticity and learning.<sup>107</sup> Recently, aspartic acid, an agonist and activator of NMDA receptors which implicated in AD,<sup>108</sup> has been identified as a possible biomarker of POCD in aged rats.<sup>109</sup> POCD was found to be linked with endogenous melatonin levels and possibly circadian rhythms in patients who had undergone abdominal surgery.<sup>110</sup> Proteomics has provided a window into possible molecular mechanisms of POCD and other neurodegenerative diseases. Li et al, in a study of aged rats with cognitive dysfunction following anesthetic and surgery, identified 21 proteins that were altered (upregulated or downregulated) following surgery/anaesthesia.<sup>111</sup> Four of these proteins were involved in oxidative stress, seven proteins with mitochondrial energy production, and three proteins were implicated in neuroinflammation. Kalenka et al<sup>112</sup> found that 17 proteins differentially expressed in rat hippocampus after isoflurane anaesthesia, including proteins involved in stress response and cytoskeleton integrity. In a clinical proteomic study, 58 separate polypeptides were found to have changed expression in patients identified with POCD following surgery.<sup>113</sup> Interestingly, in a proteomic study of twins with no symptoms of AD, mitogen-activated protein kinase (MAPK) was found to be related to early cognitive decline over a 10-year period.<sup>114</sup>

Neuroinflammation may play a role in POCD,<sup>2,115–118</sup> as pain<sup>119</sup> and alleviation of each may reduce short-term POCD.<sup>118,120</sup> Injury and insult lead to the formation of an inflammasome, which initiates an inflammatory cascade involving inflammatory cytokines, including interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and nuclear factor kappa enhancer of activated B cells (NF- $\kappa$ B), regulated by alpha-melanocyte-regulating hormone ( $\alpha$ -MSH). The involvement of the inflammatory response in POCD is suggested by a number of animal studies. Anaesthesia alone and anaesthesia combined with surgery can induce IL-1 $\beta$ <sup>121–125</sup> and TNF- $\alpha$ <sup>123</sup> in mouse and rat models of POCD. Isoflurane without surgery has also been shown to increase TNF- $\alpha$ , IL-6, and IL-1 $\beta$  in mice.<sup>126</sup> Li et al,<sup>111</sup> identified three proteins that were involved in neuroinflammation.

The link between inflammatory cytokines and POCD is also suggested by clinical studies, which parallels the suggested association between inflammatory cytokines and AD.<sup>127</sup> High-mobility group box 1 and IL-6 were found to be significantly correlated with POCD in patients who had undergone major surgery,<sup>128</sup> while Ji et al<sup>129</sup> found that IL-1 $\beta$  (but not IL-6)



was associated with POCD in total hip replacement surgery. Inflammation markers IL-6, IL-1 $\beta$ , TNF- $\alpha$ , S-100B, and tau were also found to increase after surgery.<sup>103</sup> Recent studies have also shown some link between POCD in patients and levels of insulin-like growth factor 1 (IGF-1) and IGF-1 binding protein 7, both were believed to be important in memory consolidation and AD.<sup>17</sup> IL-6 has been suggested as playing a crucial role in the neuroinflammatory response leading to POCD.<sup>130</sup> Inflammatory cytokines have also been associated with POCD after cardiac surgery<sup>131</sup> and levels of S-100, an indicator of traumatic brain injury, was found to be an indicator of POCD.<sup>132,133</sup> In addition, in a meta-analysis of studies investigating the inflammatory response of patients, IL-6 and S-100B were identified as being correlated with POCD.<sup>134</sup> The inflammatory cascade is, in part, controlled by the melanocortin system including  $\alpha$ -MSH, which downregulates inflammatory cytokines.<sup>135</sup> Melatonin is important as a risk factor of AD<sup>136</sup> and possibly POCD.<sup>110</sup> The melanocortin system also has a PrP<sup>C</sup> regulatory involvement<sup>137</sup> and Mariante et al<sup>138</sup> contend that PrP<sup>C</sup> is involved in a regulatory loop of inflammatory processes linked with systemic or cellular stress.

There is a need to identify patients at risk of POCD, but as yet, no common genomic indicators of POCD have been unambiguously identified. This includes apolipoprotein E (*ApoE*), which has been associated with POCD in some studies<sup>139</sup> but not in others,<sup>140,141</sup> although a recent prospective study has shown that patients carrying the *ApoE4* genotype (the highest genetic risk factor for AD)<sup>142</sup> had an increased risk of POCD.<sup>143</sup> A review of the literature has identified a number of potential markers of POCD,<sup>144</sup> including C-reactive protein (CRP), P-selectin (SELP), complement component 3 (C3F), inducible NOS (iNOS), and cytochrome P450. The presence of brain  $\beta$ -amyloid has also been found to be a good predictor of POCD risk in cognitively normal patients<sup>104</sup> and a link has also been established between A $\beta$ 42/tau ratio (an indicator of AD) in the cerebrospinal fluid of patients prior to surgery and POCD.<sup>129,145</sup> Proteomic studies have suggested that fibrinopeptide A is a potential biomarker.<sup>113</sup>

Neuroprotection by preconditioning is the use of sublethal insult to provoke a protective response and has had some success in the prevention of ischemic stroke, AD, and PD in animal models.<sup>146</sup> Neuroprotection against POCD has had mixed success. Bilotta et al,<sup>37</sup> based on a review of clinical trials, suggest that neuroprotection against POCD could be achieved with a number of drugs, such as atorvastatin. There is some evidence that amantadine, which increases glial-cell-line-derived neurotrophic factor and decreases neuroinflammation, might reduce the effect of POCD.<sup>147</sup> IL-6 receptor antagonists have also been found to act as a preventative measure against POCD.<sup>130</sup> Remote ischemic preconditioning, however, was not found to be effective as neuroprotection against POCD,<sup>148</sup> nor was propofol (used to suppress electroencephalogram bursts),<sup>149</sup> reduction in C5 complement,<sup>150</sup> platelet activating factor antagonist<sup>151</sup> or the corticosteroid dexamethasone.<sup>152</sup>

Presurgical cognitive intervention has been shown to have some effect on reducing POCD.<sup>153</sup> Interestingly, the administration of melatonin prior to isoflurane anaesthesia in rats was shown to reduce cognitive impairment.<sup>154</sup>

PBM has been shown to have an effect on neurodegenerative diseases in animal models, including AD, PD, and depression.<sup>7,9,155,156</sup> Purushothuman et al<sup>7</sup> propose that the ability of PBM to reduce hyperphosphorylation of tau is neuroprotective in AD. It has also been shown that laser light is absorbed by  $\beta$ -amyloid,<sup>157</sup> and Grillo et al<sup>158</sup> have shown a decrease in  $\beta$ -amyloid with PBM. It is therefore proposed that the success of PBM in the preconditioning against AD and the treatment of PD suggest that it might also be an effective preconditioning agent against POCD.

### Photobiomodulation

PBM has been defined as a “nonthermal process involving endogenous chromophores that elicit photophysical (linear and nonlinear effects) and photochemical events at various scales, resulting in beneficial photobiological responses.”<sup>74</sup> This is most often low-level laser therapy (LLLT) but may also be a noncoherent light-emitting diode (LED). Light was used in 1903 as a therapy for skin lesions, with an article published by Finsen in the *Lancet* in 1903<sup>159</sup> reporting the *striking results* of the use of red light treatment to prevent the disfigurement of smallpox scars, providing that the intervention was at an early stage of the disease. Additionally, Finsen was awarded the Nobel Prize in 1903 for the use of ultraviolet (UV) light for the treatment of lupus vulgaris. Phototherapy as a treatment fell from favor until 1968 when Mester et al first showed that laser could stimulate wound healing and hair growth in mice.<sup>160</sup> Another early use of laser therapy was the treatment of wound and skin lesions (radiation ulcers following the Chernobyl nuclear accident using argon lasers (450–530 nm).<sup>161</sup> Over the past 45 years, PBM in the visible to infrared wavelengths (between 400 and 1072 nm) has become increasingly accepted as a therapeutic intervention, with randomly controlled clinical trials as well as animal models demonstrating a significant role for LLLT in the treatment of many conditions in veterinary as well as human patients. It has also become apparent that there is a biphasic dose response for LLLT, following the Arndt–Schulz curve,<sup>162</sup> where increasing dose corresponds to an increasing effect up to a maximum (a *dose window*), after which further increasing dose evokes a negative response. PBM is currently used to treat a variety of radiation and chemotherapy-induced ulcers,<sup>163</sup> as well as oral and other wounds<sup>4,164</sup> and wound infection.<sup>165</sup> The use of PBM therapy can protect against damage to the skin by UV light as well as a number of other skin conditions, including vitiligo, psoriasis, and herpes simplex.<sup>166</sup> LLLT is used for sports injuries,<sup>167</sup> tendon repair,<sup>168</sup> remodeling collagen fibers in tendon injuries,<sup>169</sup> for lymphedema management,<sup>170</sup> and for acceleration of tooth movement during orthodontics.<sup>171</sup> PBM has been used in the treatment of cardiac disease and cardiac



protection in animal models via the modulation of iNOS and induction of mesenchymal stem cells.<sup>172–175</sup>

PBM has also been successfully used in the treatment of both acute and chronic pain in the periphery<sup>176,177</sup> and in centrally mediated pain states including chronic neck pain.<sup>178–181</sup> The ability of photons introduced as LLLT to modify bioelectrical signaling in peripheral nerves has been unequivocally demonstrated in animal and human models.<sup>19,182</sup> This is of primary importance in pain treatment as suppression of action potentials in nociceptors is one of the mechanisms for the direct analgesic effects of LLLT.<sup>177</sup> Nociceptors are selectively affected by laser irradiation, and it has been proposed that this effect underpins the pain-relieving effects of LLLT in the treatment of acute and chronic pain<sup>182</sup> and the basis of the local anesthetic effect of LLLT, which can be effective as a pain block in such things as dental extraction.<sup>183</sup>

Most recently, there has been increasing evidence from animal studies for the use of PBM in cognitive and neurodegenerative diseases, such as depression,<sup>9,184</sup> traumatic brain injury,<sup>185</sup> AD,<sup>7,158,186–189</sup> and PD.<sup>8,155,156,189,190</sup> PBM has the added benefit of a wide dose window to achieve the effect and no identified harmful effects, within the correct dose parameters and following the contraindication recommendations of not directing PBM into eyes, over a carcinoma site or over a fetus.<sup>191</sup>

LLLT has also been shown to have a role in neuroprotection<sup>190</sup> and preconditioning against such conditions as muscle fatigue, inflammation, and pain, as reviewed by Agrawal et al,<sup>10</sup> macular degeneration,<sup>192,193</sup> preconditioning in cardiac protection,<sup>172</sup> PD<sup>190</sup> and AD.<sup>7,186</sup> In addition to targeting the site of the disease, this preconditioning and protection can also involve an abscopal (indirect) effect, where the effect is elicited by irradiating an area of the body remote from the site of disease or injury.<sup>189,194</sup> This has been shown to occur in patients with macular degeneration, where the nonirradiated eye experienced the same protection as the irradiated eye.<sup>193</sup> The abscopal effect has also been shown for cardiac disease in rats, where LLLT to a remote site (tibia) elicited a response in protection against cardiac infarct,<sup>173</sup> upregulating iNOS and mobilizing c-kit<sup>+</sup> cells to be recruited to the heart damage site.<sup>172,174</sup> This abscopal effect has been shown to be at least as effective as PBM at the site of injury.<sup>174</sup> Tibial bone marrow as a target also improved cognition in a mouse model of AD.<sup>188</sup> LLLT delivered to the skull in mice was also shown to improve AD  $\beta$ -amyloid and cognition.<sup>186</sup> Johnstone et al<sup>8,155</sup> have shown neuroprotection in a rat model of PD, where remote preconditioning produced a similar effect on *trans*-cranial LLLT. They propose a systemic effect with circulating cellular or molecular factors to induce the abscopal neuroprotective effect. Keszler et al suggest that direct application of LLLT to patients' hearts may not be necessary for the protection against cardiac ischemia due to this systemic effect.<sup>175</sup>

Current known mechanisms of LLLT action have been well reviewed<sup>4,195,196</sup> and include roles for cytochrome-*c*-oxidase

and mitochondrial energy production,<sup>196</sup> retrograde mitochondrial signaling,<sup>197</sup> NOS modulation,<sup>173,181,196,198,199</sup> electron transfer via a redox reaction<sup>200</sup> resulting in antioxidant enzyme activity,<sup>201,202</sup> restoration of balance between pro- and antioxidant mediators by increasing peroxisome proliferator-activated receptor expression and glutathione concentration,<sup>203</sup> modulation of hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ),<sup>204</sup> reduction in TNF- $\alpha$ ,<sup>205</sup> modulation of inflammatory cytokines and ILs, NF- $\kappa$ B,<sup>206,207</sup> IL-6, and IL-1 $\beta$ ,<sup>208</sup> modulation of growth factors IGF-1, and transforming growth factor beta-1 (TGF- $\beta$ 1),<sup>201</sup> modulation of opioid and its precursor molecule proopiomelanocortin (the melanocortin signaling system),<sup>209</sup> and cytokine abscopal effects.<sup>155</sup> LLLT is known to downregulate the inflammatory process<sup>210</sup> by increasing antioxidants and decreasing oxidative stress,<sup>211</sup> via the mechanisms described earlier and by increasing superoxide dismutase.<sup>201,203</sup> PBM also directly affects the cell signaling molecule MAPK.<sup>167,212</sup>

In addition to the photon receptors for the mechanisms described earlier, which includes the known chromophores of melanin, flavins, porphyrins, and cytochrome C oxidase,<sup>196</sup> there may be a second group of interactions where physical perturbations by photons cause conformational changes in receptor proteins<sup>4,194,213</sup> especially in redox-sensitive proteins. This perturbation involves a molecular switching mechanism<sup>214</sup> which includes the receptor tyrosine kinases,<sup>195,215</sup> ion channels such as TRPV1 channels, which can respond to visible and infrared light,<sup>216,217</sup> and potassium channels.<sup>218</sup> Various opsin proteins, which belong to the G-protein-coupled receptor family, also act as photoreceptors. These include rhodopsin molecules in rod cells of the retina and in the skin,<sup>219</sup> photopsins in cone cells of the retina, melanopsins in retinal ganglion cells, encephalopsins (OPN3) in the brain,<sup>220</sup> and neuropsin (OPN5) in spinal tissue (eye, brain, testes, spinal cord).<sup>221</sup> Light also regulates neuronal activity in the eye by direct allosteric modulation of GABA and NMDA receptor proteins, which directly influence neuronal signaling, depending on the redox state of the receptor.<sup>222,223</sup> This group of interactions with receptors would involve physical perturbation of the molecular structure in the skin and neural membranes to facilitate the physiological function.<sup>4,194</sup>

There has been less attention to the role of cytoskeleton modulation as a primary LLLT mechanism. Evidence for the role of LLLT in cytoskeleton modulation, pain attenuation, and neurotransmission blockade has been demonstrated by Chen et al<sup>224</sup> and Chow et al.<sup>19,177</sup> As the cytoskeleton is both a receptor and an initiator of signal transduction, cytoskeleton modulation by PBM is a candidate for the observed abscopal effects of LLLT.

## MT and Cytoskeleton Modulation

The cytoskeleton is an important component of all cells and consists of the MT network, neurofilaments, and actin filaments. MTs provide structural support, connect targets, and



act as a track to direct vesicle and organelle traffic within the cell. MTs are composed of  $\alpha$ - and  $\beta$ -tubulin dimers and have *dynamic instability*, where they grow and shrink, switching between assembly (*rescue*) and disassembly (*catastrophe*) according to the need, and are thus in equilibrium with unpolymerized  $\alpha$ - and  $\beta$ -tubulin. This process allows rapid reorganization of the MT cytoskeleton. In neurons, MTs are found in the dendrites, cell body, and axon. In dendrites, MTs are short and have a mixed polarity. In axons, MTs form bundles of various lengths but with the same polarity,<sup>225</sup> which is critical for neurite polarity and neurite growth<sup>226</sup> as well as anterograde and retrograde transport.

The control of this dynamic instability is very complex and as yet poorly understood but appears to be regulated in part by multiple posttranslational modifications to the tubulin protein (eg, tyrosination, polyglutamylation, acetylation, SUMOylation)<sup>225</sup> and in part by MT-associated proteins (MAPs),<sup>227</sup> which bind either tubulin or assembled MTs and are thus either stabilizing or destabilizing for MTs. MAPs, such as tau (in axons) and MAP2 (in dendrites), bind directly to MTs and form transient interactions that stabilize the MTs into the parallel arrays seen as bundles. Other MAPs can promote assembly (eg, MAP4) or disassembly (eg, stathmin) of MTs. Phosphorylation of tau is necessary for MT stabilization, but under normal conditions tau phosphorylation is limited.<sup>228</sup> With increased phosphorylation, the extent of binding to MT decreases. A number of neurodegenerative diseases (such as AD, PD, and other tauopathies)<sup>229,230</sup> are characterized by hyperphosphorylation of tau, where up to 100% of the available sites in the protein are phosphorylated. This destabilizes MTs and leads to the formation of intracellular aggregates (neurofibrillary tangles).<sup>229</sup> An example of this is children in Mexico City, who are exposed to heavy pollution, can develop hyperphosphorylation of tau and protein changes (aggregates) in the brain, particularly if they have *ApoE* variant gene, which is associated with adult AD.<sup>231</sup> Tau may also provide a link with the plasma membrane and play a role in signal transduction.<sup>232</sup>

Other molecules that may influence MT dynamics include PrP<sup>C</sup> and PSD-95. PrP<sup>C</sup> is known to bind to tubulin, stathmin, and tau<sup>233–235</sup> and has been proposed as a major player in MT assembly/disassembly.<sup>236</sup> Schmitz et al<sup>237,238</sup> have shown that PrP<sup>C</sup> plays a direct role in the organization of the cytoskeleton, as well as cognition and behavior, as a result of its relationship with neurofilaments and MTs. Dysregulation (upregulation) of PrP<sup>C</sup> expression leads to hyperphosphorylation of tau and malformed *stumpy* neurites.<sup>239</sup> PrP<sup>C</sup> overexpression is also believed to be involved in the  $\beta$ -amyloid formation and cognitive dysfunction of AD via its interaction with nicotinamide adenine dinucleotide phosphate (NADPH) oxidase at the membrane, inflammatory cytokines, and the subsequent alteration of actin filaments.<sup>240</sup> Interaction between PSD-95 and cypin has also been proposed to regulate MT organization in dendrites.<sup>14</sup>

MTs are central in cellular signaling and a major target of signaling pathways to maintain the balance in their dynamic instability and thus control cellular (neuronal) function. They are also an effector of downstream signaling, interacting with other signaling molecules such as NF $\kappa$ B, extracellular signal-regulated kinase 2, and MAPK and organizing signal pathways.<sup>241</sup> Linden et al<sup>242</sup> have suggested that PrP<sup>C</sup>, with its membrane scaffolding connection to the extracellular matrix, links  $\alpha$ -tubulin,  $\beta$ -tubulin, and MT and is thus involved in multicomponent signal transduction with a wide range of allosteric effects in physiology and pathophysiology. PrP<sup>C</sup> acts as a redox sensor molecule for oxidative stress and triggers downstream processes.<sup>243</sup> Goswami<sup>11</sup> has suggested that a component of MT signaling is centered around TRPV1 channels, which are redox sensors for infrared stimuli.<sup>244</sup> Potassium leak channel TRESK may interact with cytoskeleton<sup>12</sup> and is believed to be one of the two-pore domain potassium (K<sub>2P</sub>) ion channels that are important as targets for anaesthesia.<sup>245</sup>

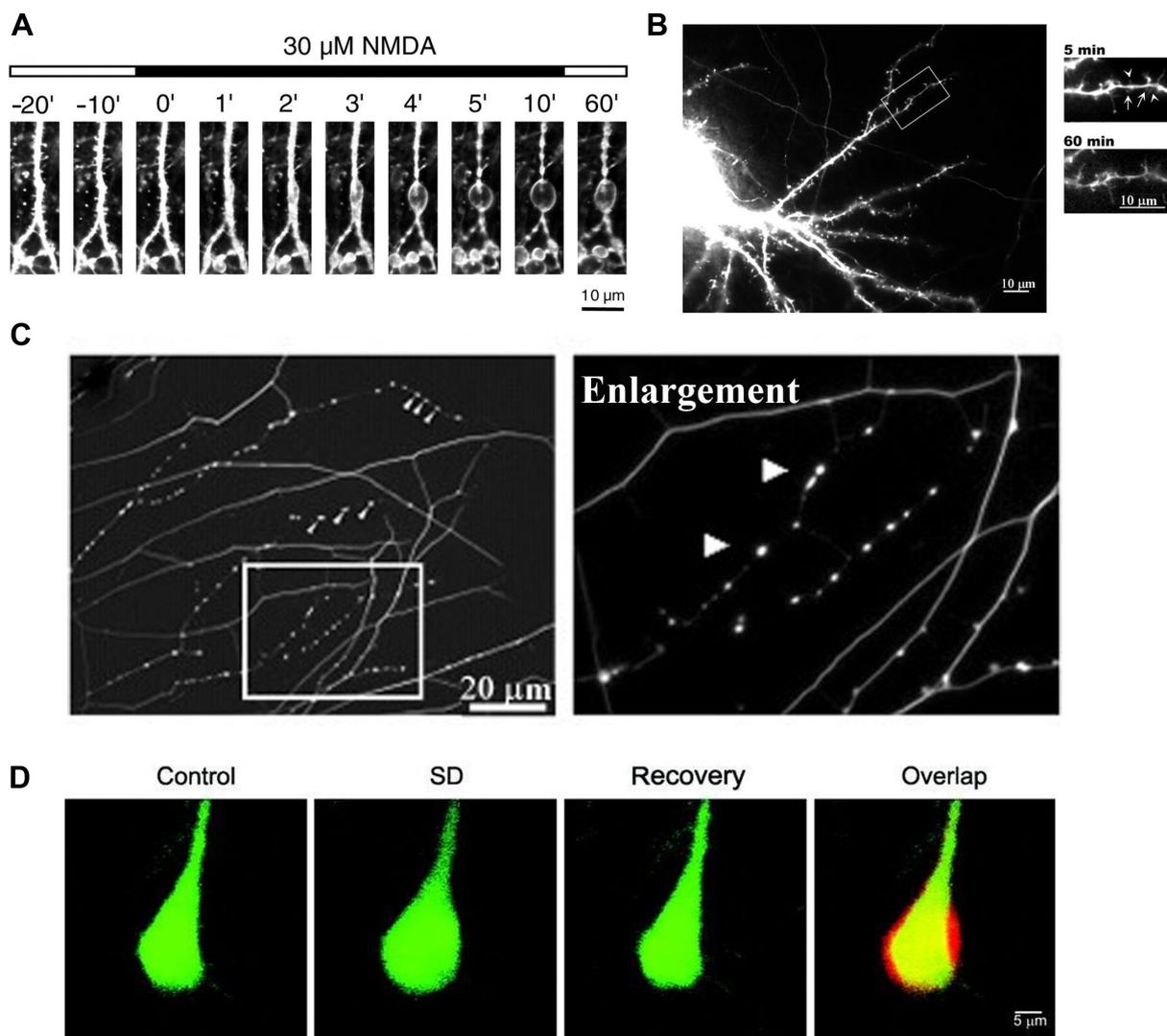
MTs act as the scaffold for anterograde and retrograde axonal transport of organelles, vesicles, and proteins using kinesin and dynein motor proteins. The normal functioning of neurons depends on the integrity of the cytoskeleton for fast axonal flow. Because MTs are subject to constant catastrophe and rescue and because MT bundles are of different lengths, axons can normally cope with intermittent disruptions to the MT cytoskeleton. Varicosities or focal swellings form when complete breakage of the MT cytoskeleton leads to a buildup of cargo at the breakage point.<sup>246</sup> Disruption of the cytoskeleton and varicosity formation has a profound effect on the bioelectrical function of nerves. Mitochondria, which deliver the adenosine triphosphate (ATP) required for many enzymes and the generation of action potentials, are not able to move along the cytoskeleton. Ion channels such as TREK<sup>247</sup> and other signaling molecules such as nerve growth factor (NGF) and brain derived growth factor (BDGF) are also not able to move along the MT in retrograde or anterograde cargo transport, which has marked effects on signal transduction.<sup>248</sup>

Assembly and disassembly of the neural (synaptic) proteins is also observed as a common process during hibernation in mammals,<sup>249</sup> where it is involved in reversible neuroplasticity and resistance to neural damage. During hibernation, cell bodies and dendritic spines shrink, synapses are lost, and synaptic proteins and MTs<sup>250</sup> are disassembled. These proteins are stored in the axon until required for reassembly, rather than being degraded and then resynthesized de novo.<sup>249</sup> Proteome variations during hibernation and arousal indicate that cytoskeleton changes are the dominant protein changes.<sup>251</sup> MT disassembly is regulated by tau phosphorylation, which, in this case, does not form the fibrils that are typical of the tau hyperphosphorylation seen in AD.<sup>252</sup> This regular disassembly/reassembly of proteins leads to some memory loss in hibernating ground squirrels when compared with non-hibernating squirrels.<sup>249</sup> Human hypothermia with circulatory arrest and subsequent resuscitation can also commonly accompanied by

some memory loss,<sup>253</sup> similar to POCD. Using this hibernation evidence, Arendt and Bullmann have proposed a model for cytoskeleton modulation in the process for neuroplasticity in the hippocampus and other cortical synapses.<sup>254</sup>

The appearance of varicosities in axons appears to be an endogenous mechanism that protects nerves from damage, occurring as a response to multiple stimuli and stressors, including mechanical stress, axonal damage, heat and cold, toxins, and anesthetics. Originally considered as only a sign of neuropathology, it is now apparent that varicosities are reversible and neuroprotective.<sup>14,255</sup> There are numerous examples of neuroprotective varicosities. In the central nervous system, sublethal hypoxia can lead to reversible dendritic *beading*, which can be blocked by NMDA antagonists.<sup>256</sup> Ikegaya et al<sup>255</sup> have shown that small reversible dendritic varicosi-

ties are produced endogenously as a response to a stressor and can act as a neuroprotection against greater damage to the neuron (Fig. 1A). Prevention of this response led to increased neuronal damage, collapse of normal neural function, and cell death. This same response has been demonstrated more recently by Tseng and Firestein,<sup>14</sup> where a toxic assault (NMDA poisoning) resulted in the production of small protective varicosities (Fig. 1B), which, as long as the response was early, rapid and reversible, prevented the formation of larger, destructive neuronal swellings and neuronal death. Varicosity formation depends on the induction of nNOS and the interaction between PSD-95, cypin, and tau. Increased cypin and decreased PSD-95 resulted in an increased number of small protective varicosities, while decreased cypin and increased PSD-95 resulted in the opposite<sup>14</sup>



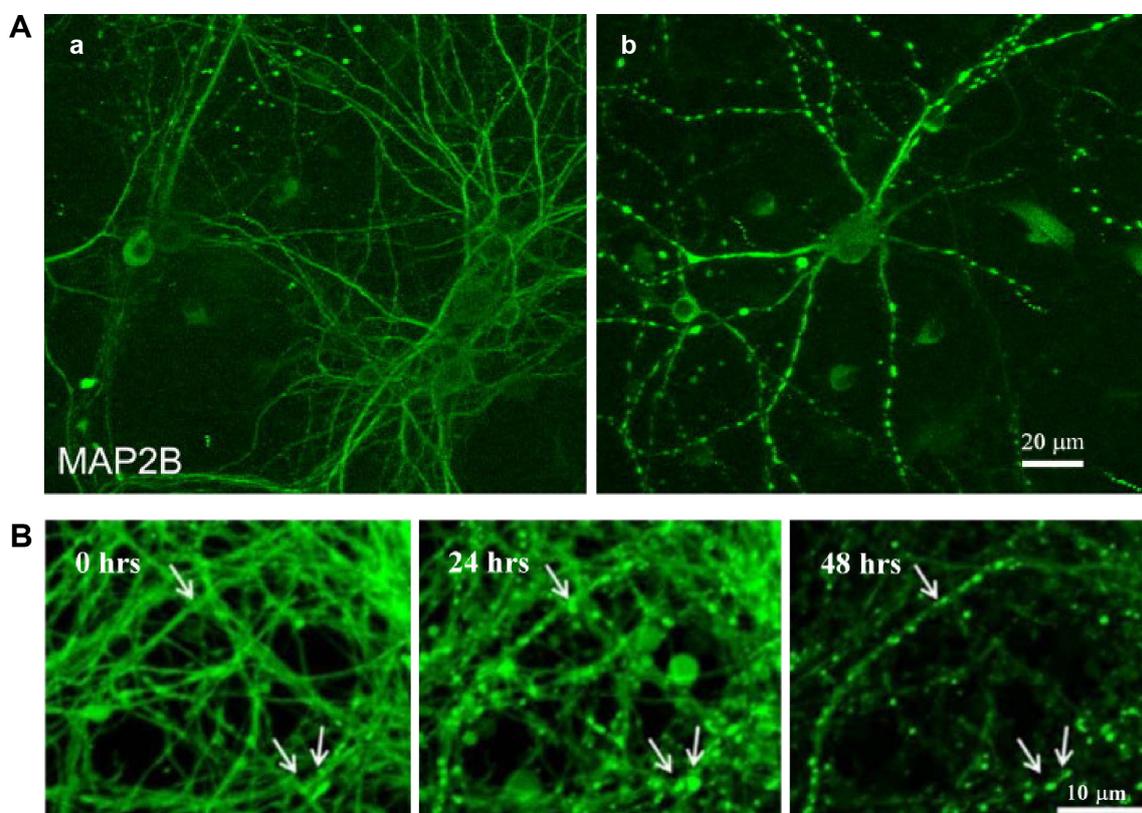
**Figure 1.** Formation of neuroprotective endogenous varicosities: (A) confocal laser microscopy images of formation of dendritic varicosities in rat hippocampus neurons treated with 30  $\mu$ M NMDA;<sup>255</sup> (B) immunofluorescent images of formation of dendritic varicosities (arrows) in rat embryo hippocampus neurons, immediately after exposure to 30  $\mu$ M NMDA (5 minutes) and reversal of varicosities after recovery (60 minutes);<sup>14</sup> (C) immunohistochemistry image stained for tubulin, showing varicosity formation in embryonic DRG neurons in response to resiniferatoxin activation of TRPV1;<sup>18</sup> (D) two-photon laser scanning images, showing the transient increase in mouse neuron volume before (control), during spreading depression (SD) and after recovery from SD, including a merged image (overlap) showing the overlap (yellow), before volume (green), and during CSD (red).<sup>259</sup>

This was suggested as a pathway in which MT cytoskeleton is regulated by sublethal changes to dendrites. PSD-95 (as well as nNOS) is also implicated in the remyelination process of regeneration of peripheral axons in a rat injury model.<sup>257</sup> The dopamine metabolite *N*-arachidonoyl-dopamine applied to dorsal root ganglia (DRG) neurites resulted in varicosity formation (Fig. 1C) implicating TRPV1 in the formation process.<sup>18</sup> Endogenous dopamine metabolites are relevant to anesthetic induced responses.<sup>258</sup>

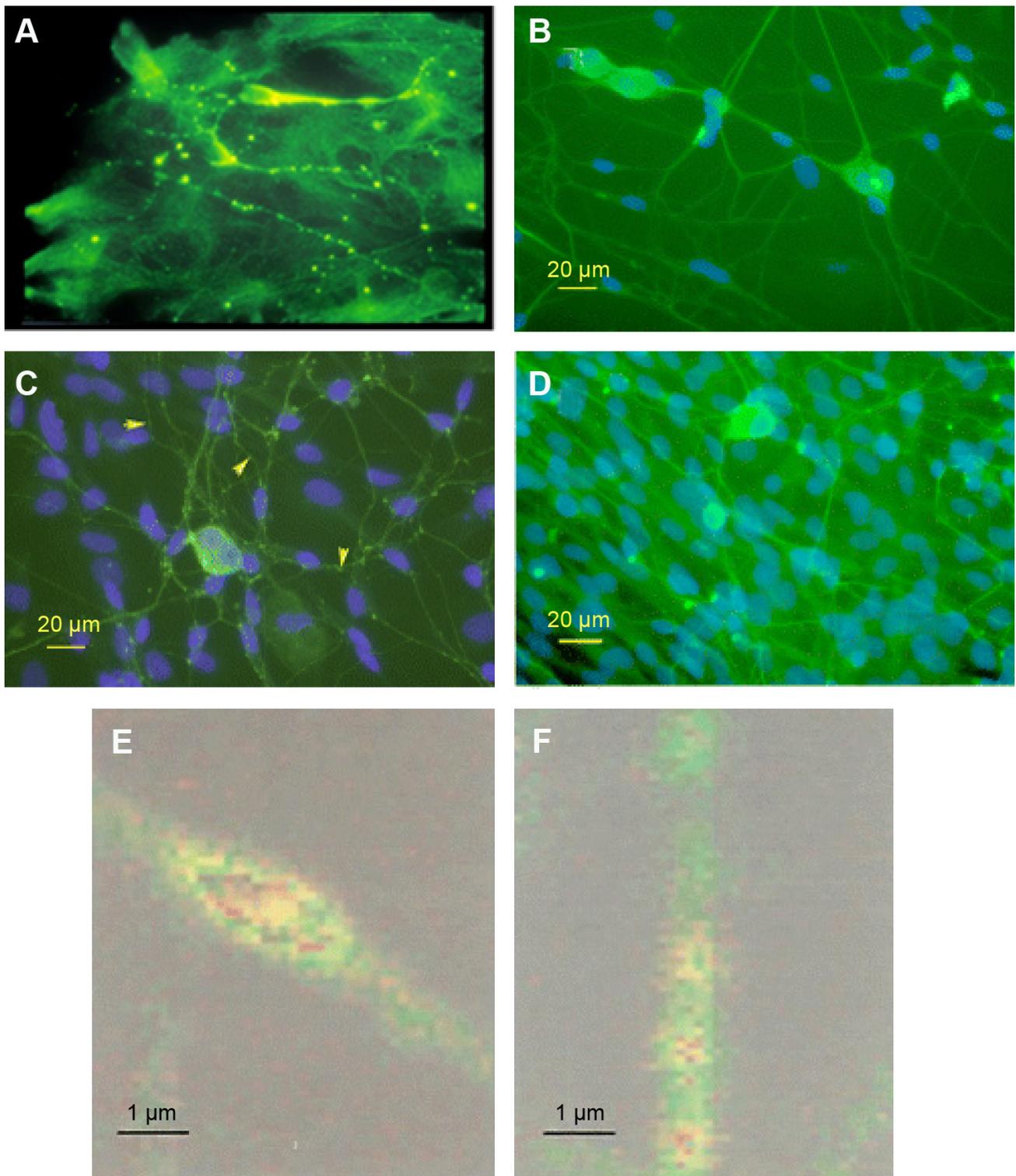
Neuroprotective cytoskeleton modulation is also present during the CSD associated with migraine with aura and cortical trauma (involving TRESK polymorphisms), where neurons undergo a transient volume increase<sup>259</sup> (Fig. 1D). These are seen as part of the neuroprotective process that protects the cortex, as an adaptive response to cortical injury and to provide tolerance to subsequent ischemic episodes.<sup>260,261</sup> nNOS increases during CSD,<sup>260</sup> and the genes upregulated in this neuroprotective response are iNOS and HIF-1 $\alpha$ .<sup>262</sup> This is an example of an immune memory process, as reviewed by Szentivanyi et al,<sup>263</sup> and may be a similar mechanism to that involved in peripheral nerve injury and varicosity formation. Reversible varicosity formation has also been noted for a number of conditions, such as ischemia<sup>264,265</sup> and toxic assault,<sup>266–268</sup> depending on the severity and/or duration of the stimulus.

Preconditioning of neurons can also involve the formation of small protective varicosities. Subjecting cell cultures of rat neurons to ischemic preconditioning<sup>269</sup> resulted in the formation of small varicosities in dendrites via a PSD-95 pathway (Fig. 2A). These were also reversible within four hours and may have had a role in neuroprotection against NMDA receptor-mediated toxicity. The use of black widow spider venom to speed recovery from botulism neurotoxin resulted in rapid varicosity formation (Fig. 2B) that (under sublethal conditions) were reversible within 48 hours.<sup>270</sup>

In a strikingly similar process to endogenously induced varicosities, PBM has also been shown to cause MT disruption and varicosity formation in the cytoskeleton of neurons.<sup>19,224</sup> This has been demonstrated in cultured rat and murine DRG neurons for a number of wavelengths, including 650 (Chow, unpublished), 808,<sup>19</sup> 830,<sup>224</sup> and 1064 nm (Chan, unpublished). This MT disruption leads to a pain blockade effect. Immunohistochemistry of DRG neuronal cultures shows the interruption of cytoskeletal integrity within 5–10 minutes following 30 or 60 seconds of laser irradiation. This effect can be seen with confocal microscopy as the formation of varicosities along the axon (Fig. 3A and B) and disruption of fast axonal flow (Fig. 3E). Specifically,  $\beta$ -tubulin from the MTs accumulates in the varicosities as do mitochondria,



**Figure 2.** Formation of preconditioning neuroprotective varicosities: (A) immunofluorescent images of neuronal cultures, showing control (a) and the formation of varicosities (b) following ischemic preconditioning using nonharmful oxygen and glucose deprivation for 30 minutes;<sup>269</sup> (B) confocal laser microscopy images of stem cell-derived neurons stained with calcein green, showing the formation of varicosities (arrows) within 22 minutes of the application of black widow venom still apparent after 24 hours, but reducing after 48 hours.<sup>270</sup>



**Figure 3.** Confocal laser microscopy of axonal varicosities (arrows) produced by LLLT in cultured rat DRG neurons at wavelengths of 1064 nm (A) (Chan, unpublished) and 830 nm (B–F);<sup>19</sup> (B) varicosity formation after 120 seconds of LLLT; (C) control; (D) reversal of varicosities 24 hours after irradiation; (E) magnified image of an axon showing a single varicosity formed after 30-second irradiation with mitochondria stained red; (F) control.

from which ATP is rapidly depleted. Importantly, this disruption is temporary and reversible, with the axon returning to its previous state within 24 hours (Fig. 3C). Other effects of LLLT on unmyelinated nerve fibers include the fragmentation of the neurite in the growth cone,<sup>224</sup> a decrease

in the number of neurofilaments, and increases in the number of MTs.<sup>271</sup>

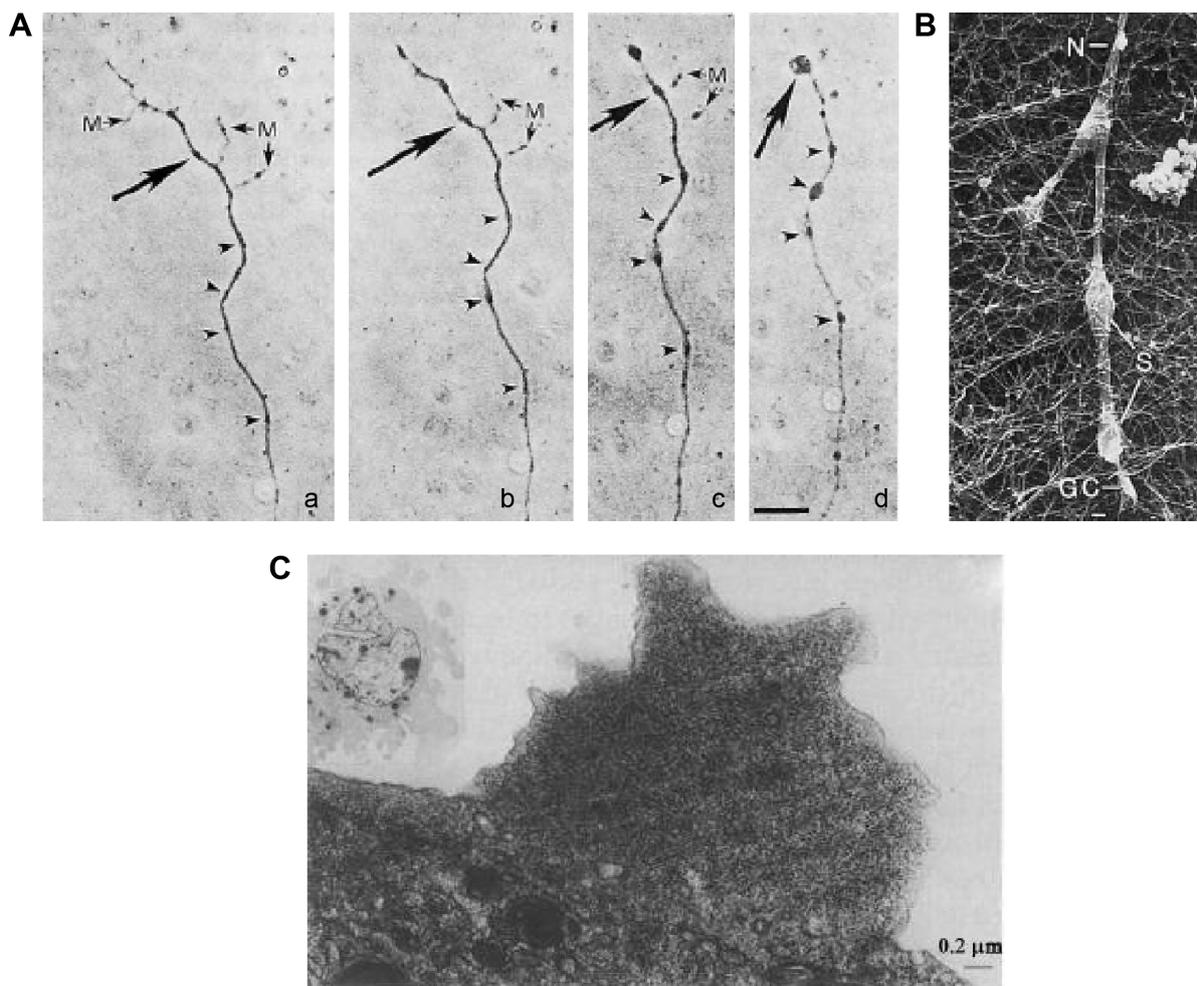
Interestingly, MT disassembly is also evident in cells, including neurons and lymphocytes, as a response to local<sup>177,79</sup> and general<sup>272</sup> anesthetics. This is characterized by the

formation of varicosities in axons, in response to local anesthetics<sup>79</sup> (Fig. 4A and B) and cell shape changes in macrophages<sup>273</sup> and the formation of *blebs* in 3T3 cells (Fig. 4C).<sup>77</sup>

There is a question as to the primary target of LLLT in neurons which will cause the cytoskeletal disruption and varicosity formation. Several of the proteins involved in the dynamic instability of MTs (including PrP<sup>C</sup> and PSD-95) have the capability to undergo conformational change, which could lead to MT instability. PBM could induce such a structural change by direct absorption of the light energy by the proteins or by the redox-sensing proteins responding to reactive oxygen species (ROS), such as nitric oxide. A potential mechanism for neural protection could also be postulated based on TRESK ion channels. The volume increase following cytoskeleton modulation and varicosity formation caused by LLLT will result in neural membrane stretch. Membrane tension is known to reversibly increase TRESK K<sup>+</sup> currents in the DRG.<sup>274</sup> This has a dampening effect on excessive neuron activation following injury and inflammation by reducing

neural excitability.<sup>275</sup> The inflammatory response is reduced by the downregulation of the calcium-activated cell stress cascade, including the unfolded protein response. This would have the effect of producing a preconditioning effect to allow the neuron a more efficient response due to immune memory.<sup>262</sup> TRESK is phosphorylated by MT affinity-regulating kinase<sup>276</sup> and also responsible for the phosphorylation of tau.<sup>277</sup> In addition, TRESK has a physical link with tubulin and possibly MTs, at least in vitro.<sup>12</sup> This suggests a (hypothetical) scaffold of TRESK/PrP<sup>C</sup>/MT, which could react to photons (PBM) either directly or via another mechanism to facilitate MT disassembly and varicosity formation.

A number of chemicals are known to destabilize MT in a similar manner to PBM. Drugs such as colchicine and nocodazole bind to tubulins and, therefore, prevent assembly into MTs. Taxol and other taxane drugs bind to and stabilize MTs preventing depolymerization, while demecolcine depolymerizes MTs.<sup>278,279</sup> As previously noted, anesthetics are also known to interact with the cytoskeleton<sup>76–78</sup> and



**Figure 4.** Varicosities and MT changes due to anesthetics: (A) light photomicrographs of the effect of  $2 \times 10^{-3}$  M procaine on varicosity formation in cultured neurites from time zero to (a) two hours (b), three hours (c), and four hours (d);<sup>79</sup> (B) scanning electron micrograph of swellings (S) in the neurite in response to  $1 \times 10^{-3}$  M procaine;<sup>79</sup> (C) electron micrograph showing the formation of *blebs* on 3T3 cell surface, due to the disruption of membrane-associated MT and microfilaments after treatment with 0.6 mM tetracaine.<sup>77</sup>



can bind to tubulin and cause MT disassembly.<sup>80</sup> Halothane interferes with MT reassembly in peripheral nerves in animal models,<sup>280</sup> and chronic exposure can cause behavioral impairment and neuronal damage including reduced dendritic branching.<sup>281</sup> Propofol causes reversible retraction of neurites in cultured rat neurones, mediated by GABA<sub>A</sub>R. Isoflurane can affect MT and neuronal filaments in astrocytes.<sup>64</sup> The anesthetic sevoflurane has been shown to produce transient hyperphosphorylation of tau in mice on a single application, while repeated anesthetic led to a persistent tau hyperphosphorylation and a significant memory impairment (POCD).<sup>84</sup> The anesthetic propofol was also shown to induce tau hyperphosphorylation in a mouse hippocampus model of AD.<sup>86</sup>

Although small, reversible varicosities are seen as a response to stress and are neuroprotective, continuation of the assault or continued dysregulation of cytoskeleton assembly/disassembly results in destructive cytoskeleton breakdown. Axonal trauma can trigger major MT breakage, inhibiting cargo transport to a greater extent than can be accommodated by normal catastrophe and rescue.<sup>282</sup> Damage by trauma may not be readily repaired by the normal endogenous mechanisms, leading to a more long-term impact on neuron function and possibly damaged MTs, further accelerating the problem.<sup>65</sup> This is exemplified by traumatic peripheral axonal injury (dynamic stretch injury)<sup>246</sup> that results in axonal swellings (Fig. 5A). These axonal swellings are also seen in head injury trauma (Fig. 5B).<sup>246</sup> In addition to the pathological conditions in the peripheral axon, the same physiological mechanism can occur in the axonal synapse and hippocampus, which involves synaptic plasticity and long-term potentiation in memories and learning, both linked with PSD-95.<sup>107,283</sup>

Chung et al<sup>284</sup> demonstrated pathological varicosities in sympathetic chronic pain when somatosensory nerves communicate with sympathetic nerves in the DRG (Fig. 5D). Focal swellings or spheroids are also evident in ischemia,<sup>285</sup> epilepsy,<sup>286</sup> and brain tumor.<sup>287</sup> Varicosities (also called focal swellings, beading, or spheroids) are hallmarks and often early indicators of neurodegenerative diseases,<sup>288</sup> such as AD<sup>182,285,289–291</sup> (Fig. 5F), PD<sup>292,293</sup> (Fig. 5C), prion disease,<sup>294</sup> multiple sclerosis,<sup>295</sup> Wallerian degeneration,<sup>296</sup> rett syndrome,<sup>297</sup> and children exposed to high levels of air pollution, who show signs of early AD.<sup>231</sup> Overexpression of PrP<sup>C</sup>, which imitates prion disease,<sup>239</sup> results in small contorted *stumpy* neurites with obvious swellings (Fig. 5E).

In summary, PBM may work well in a number of complementary ways to promote neuroprotection. PBM produces cytoskeleton modulation and neuroprotective varicosities that inhibit or reduce cargo transport and fast axonal flow, in the same way as has been demonstrated for pain blockade.<sup>19,182</sup> These varicosities mimic endogenous varicosities, and thus PBM may stimulate the body's own neuroprotective mechanism. Small reversible varicosities have been previously suggested as a neuroprotective mechanism in animal models<sup>14,255</sup>

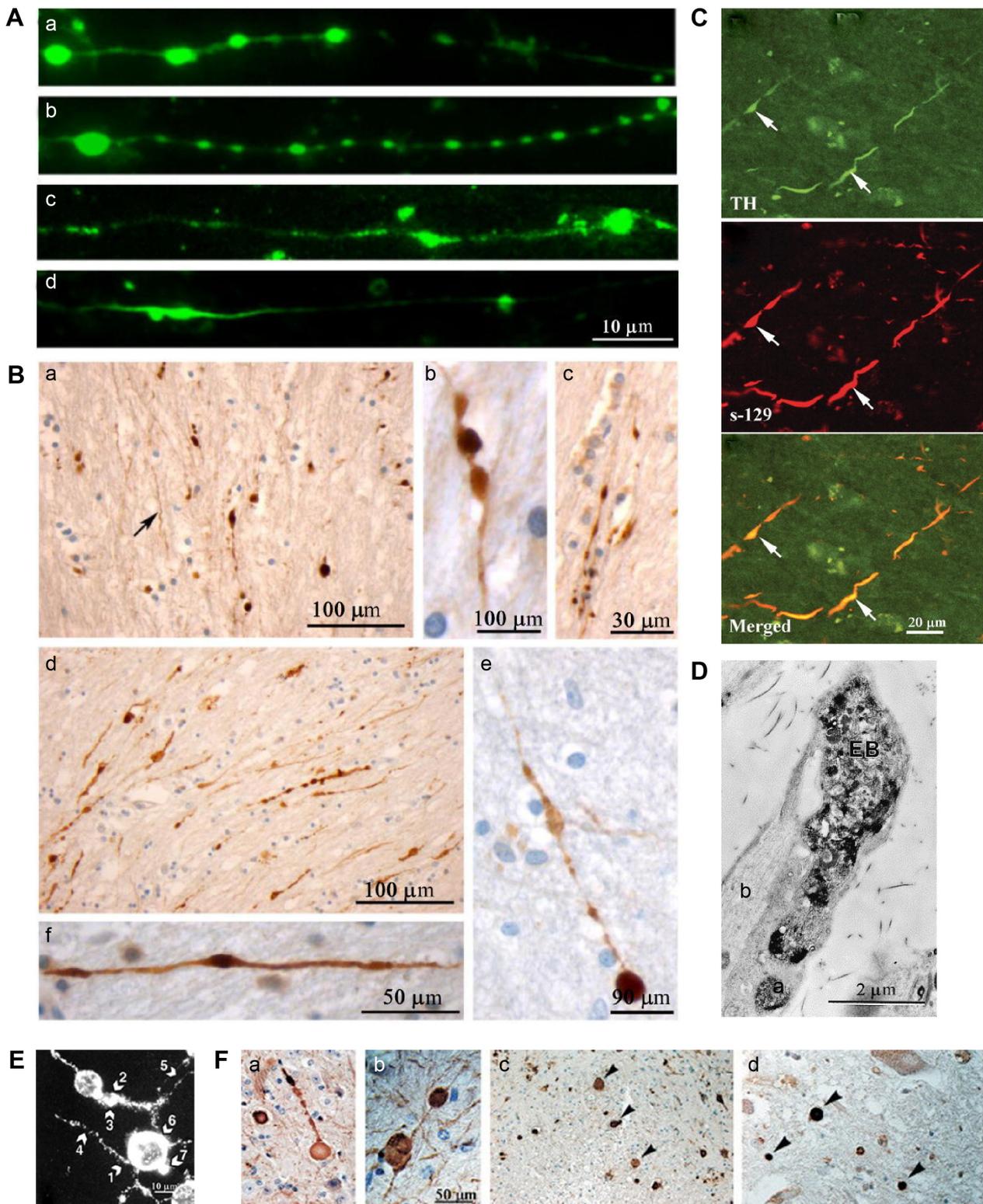
and have been invoked as part of neuroprotection against ischemia.<sup>269</sup> This PBM stimulation may operate via photon activation of redox signaling (mitochondrial or NADPH at the cell membrane) or via direct protein conformational changes (possibly in TRPV1)<sup>18</sup> and cell signaling to the cytoskeleton via a (hypothetical) TRESK-PrP<sup>C</sup>-tau-tubulin scaffold and would include the molecules PSD-95, cypin, and MAPK (also known to be modulated by PBM)<sup>212,298</sup> and the transient phosphorylation of tau.<sup>14</sup> This immune memory effect<sup>262</sup> could protect neurons against anesthetic attack on the cytoskeleton. PBM also has the effect of modulating the inflammatory response, by the regulation of the expression of iNOS<sup>196,199</sup> and HIF-1 $\alpha$ ,<sup>204</sup> the downregulation of the inflammatory cytokines IL-6, IL-1 $\beta$ , and TNF- $\alpha$ ,<sup>208</sup> and the upregulation of growth factor IGF-1,<sup>201</sup> all suspected to be involved in POCD. PBM also modulates the cellular redox balance by decreasing oxidative stress and increasing levels of antioxidants,<sup>203,211</sup> as well as the upregulation of mitochondrial function, biomarkers of which were found to be important in POCD.<sup>111</sup>

## Conclusion

Despite early equivocal studies, POCD is recognized as a significant problem in the modern health-care system, affecting elderly patients undergoing anesthetics and surgery. Although most POCD appears to be reversible within weeks or months, it nonetheless has an effect on the quality of life of patients and an impact on health-care resources. There is also a possibility of long-term effects of POCD, including AD, in certain patients. The impact of POCD will increase into the future as medical and surgical procedures continue to improve and surgery becomes lengthier and more common. With an aging population, the patients most vulnerable to POCD are also the group with the greatest increase in surgical procedures.

The cause of POCD appears multifactorial but may involve similar mechanisms to AD, with which it shares some characteristics and common molecular markers. Anesthetic use and neuroinflammation are implicated, with many markers for neuroinflammation apparent in animal and clinical studies.

MTs, and the cytoskeleton generally, have a role in signal transduction, both as an initiator and a conduit. The dynamic stability of MTs, together with their function in directing neurite growth and in cellular signaling, gives the cytoskeleton a role in the stability of the neuron and they therefore have an allosteric role more generally in the nervous system. This would include reaction to the stimuli of injury and inflammation, including anaesthesia and surgery, which is in addition to any direct effect that anesthetics have on the cytoskeleton of neurons. Assembly and disassembly of the cytoskeleton is central to neuroplasticity and involves molecular switching. Disassembly and subsequent reassembly of MT is responsible for the neuroprotective effect in hibernation, in the CSD-associated migraine with aura, in the cortical



**Figure 5.** Pathological varicosities: (A) immunofluorescent images of axonal swellings produced during dynamic stretch injury of cultured neurons, stained for tubulin (a), tau (b), amyloid precursor protein (c), and neurofilament (d);<sup>246</sup> (B) immunohistochemical stain against amyloid precursor protein, showing axonal varicosities in the corpus callosum of traumatic brain injury cases, caused by motor vehicle collision (a, e, f), falls (b, c), and blunt force trauma (d);<sup>246</sup> (C) confocal laser microscopy images of putamen tissue from Parkinson's disease cases, showing varicosities, stained for tyrosine hydroxylase (TH),  $\alpha$ -synuclein (s-129), with a merged image;<sup>292</sup> (D) electron micrograph of TH immune reactivity showing an axonal (synaptic) varicosity in rat DRG as a result of sensory and sympathetic interactions;<sup>284</sup> (E) immunostained image of varicosity formation in a neuronal cell culture after exposure to prion protein peptide 106–126, showing varicosities (arrows 1–5);<sup>239</sup> (F) immunohistochemical stains showing varicosities and spheroids in a mouse model of Alzheimer's disease, stained for neurofilament (a, b, c) and the spinal cord of an early onset Alzheimer's disease case, stained for amyloid precursor protein (d).<sup>289</sup>



adaptive response to injury, and in neuroprotection against toxic assault, such as NMDA and possibly anesthetics. Given the role of MT in such neurodegenerative diseases as AD, PD, and tauopathies, it is not unreasonable to suggest that similar mechanisms could be important in POCD.

Since there is no available treatment for POCD, preconditioning and neuroprotection would appear to be the optimum intervention for its prevention. Although neuroprotective drugs and cytokine antagonists have shown some success in animal models, it is suggested that PBM would be a viable option in preconditioning against POCD. PBM has been shown to directly affect MT and to cause small, reversible varicosities that affect cellular signaling, fast axonal transport, and pain blockade. This could occur via photoreceptors at the membrane such as opsins (neuroopsin), NADPH, or TRPV1, which could in turn interact with tau and the MTs via ROS or via signal transduction involving PrP<sup>C</sup> and/or PSD-95. The varicosities produced by PBM mimic the endogenously produced varicosities that are known to be neuroprotective against the large, destructive varicosities, swelling, and greater damage to the neuron. Thus, PBM-generated varicosities act to precondition neurons against damage in an analogous mechanism to the varicosities produced during ischemic preconditioning. PBM is known as a preconditioning treatment in other diseases and conditions, such as macular degeneration, cardiovascular disease, and muscle performance. Taken together with the success of PBM in the prevention and treatment of animal models of neurodegenerative disease, it is proposed that the use of PBM preoperatively would have a preconditioning role for the prevention of POCD in patients undergoing surgery, especially in elderly, vulnerable patients.

Since POCD is not responsive to treatment, there is a need to identify patients at risk of POCD, including identifying MCI and serum markers of POCD risk. This would enable patients who would benefit from PBM preconditioning to be identified, especially those elderly patients with patterns of vulnerability to POCD, AD, and other forms of dementia. This would, however, not preclude the more widespread use of PBM on elderly surgical patients. PBM has the benefit of no identified harmful effects within the correct dose parameters and following contraindication recommendations. Elderly surgical patients who would most benefit from PBM preconditioning could include patients with conditions known or suspected to be related to POCD or AD (including preexisting cognitive decline, MCI, type I and type II diabetes, alcohol abuse, hypertension, and atherosclerosis); patients with markers and potential markers of AD and POCD (including  $\beta$ -amyloid, *ApoE4*, A $\beta$ 42/tau ratio, CRP, SELP, C3F, iNOS, cytochrome P450, aspartic acid, and melatonin); patients with melanocortin signaling variations (such as redheaded women); patients with photophobia, CSD migraine with aura, and cluster headaches; and other patients with TRESK polymorphisms.

## Author Contributions

Wrote the first draft of the manuscript: ADL. Contributed to the writing of the manuscript: ADL, RC, BTB, and EV. Agreed with the manuscript results and conclusions: ADL, RC, BTB, and EV. Jointly developed the structure and arguments for the paper: ADL and BTB. Made critical revisions and approved the final version: ADL, RC, BTB, and EV. All the authors reviewed and approved the final manuscript.

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