Broken hearts and lost souls cause sleepless nights

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In Descartes' view of the brain, the pineal gland was deemed the "seat of the soul" and the centre of rational understanding. Whilst incompatible with our contemporary understanding, it appears that Descartes' fascination was not misplaced, as the pineal is critical to our comprehension of some sleep disorders, which Descartes may even have suffered from himself (*1*). New research by Ziegler *et al.* (*2*) highlights a novel pathway by which cardiac disease leads to immune-mediated sympathetic denervation of the pineal gland and a subsequent decrease in circulating melatonin, causing sleep disruption (Figure 1). This work adds to pineal gland research by providing a tangible link between cardiac disease and sleep disorders, and provides an additional connection between the immune system and sympathetic (dys)function.

Melatonin, a hormone released from the pineal gland, is crucial for the maintenance of a healthy circadian rhythm, with the highest levels normally observed during darkness (*3*). However, a reduction in nocturnal melatonin level has been observed in patients and animal models with cardiac disease (*4*), and is believed to be responsible for associated sleep disorders. This led Ziegler *et al.* (*2*) to investigate how a reduction in melatonin release might occur during cardiac disease.

They first assessed the simplest question: whether pineal gland mass or morphology is reduced in models or patient samples of cardiac disease, thereby reducing the capacity of the pineal to release melatonin. However, the authors found no change in pineal mass or cellular composition (*2*).

Pineal gland synthesis and release of melatonin is known to be coupled to sympathetic activity via β-adrenoceptors, and in human patients with heart disease it was found that there was a decrease of sympathetic innervation of the pineal gland (*2*). Furthermore, diurnal rhythms were disturbed after surgical removal of the superior cervical ganglia (SCG), and could be recovered by melatonin supplementation (*2*). The authors also observed a reduction in pineal-innervating sympathetic fibers in mouse models of left ventricular pressure overload (transverse aortic constriction, TAC) and heart failure with preserved ejection fraction, suggesting that the sympathetic denervation occurs across species and is due to cardiac disease.

To interpret these results, sympathetic fiber loss should be viewed in the context of global changes in sympathetic neuron function during cardiac disease. As sympathetic neurons tend to be hyperactive during cardiovascular disease (*5,6*) it is possible that the reduction in sympathetic tone will be less dramatic than the decrease in number of innervating axons suggests. Other phenomena, such as an increased release of NPY (7) or cholinergic trans-differentation during cardiac disease, may also play a role (*8*).

In order to assess how sympathetic innervation of the pineal gland might be reduced in cardiac disease, structural changes of the SCG, which provide the majority of pineal gland sympathetic innervation, were also assessed. Here Ziegler *et al.* (*2*) observed fibrotic scarring and hypertrophy of the SCG in the TAC mouse model, and post-mortem human biopsy tissue. Hypertrophy in patients was confirmed *in situ* using ultrasound measurements. This was accompanied by an increase in infiltrating macrophages and a reduction in the number of pineal-innervating melatonin receptor 1a (*Mtnr1a)*-positive neurons in the TAC model (which was assumed to reflect loss of the neurons rather than a decrease of *Mtnr1a* expression).

SCGs in the TAC mouse model showed a marked increase in macrophage number, and it was suggested that the macrophages were responsible for the loss of pineal-innervating sympathetic neurons (*2*). Consistent with this, depleting macrophages with clodronate (which may however also affect neutrophil function (*9*)) or preventing macrophage activation (with cobra venom) reduced the depletion of sympathetic fibers and fall of melatonin level occurring (*2*). However, prior work has shown that sympathetic neuron-associated macrophages interact with SCG neurons during normal physiology, including by regulating noradrenaline clearance (*10*). Thus, the relationship between pineal-innervating sympathetic neurons and the immune system may be complicated, and further work should probe how this relationship changes in cardiac disease.

A functional characterization of the *Mtnr1a*-positive SCG neuron subpopulation would be valuable, and two further questions remain. First, there are also some *Mtnr1a*-positive neurons in the stellate ganglia (*11*), that are unlikely to innervate the pineal gland, raising the question of their function. Previous work has divided sympathetic neurons according to NPY expression in both the SCG and stellate ganglia, and in this study a similar difference exists between pineal-innervating and "other" sympathetic neurons (Fig. 3B of (*2*)), so it would be interesting to understand how the *Mtnr1a*-expressing subtype described here fits within this framework. This may have functional implications since NPY and non-NPY SCG neurons have different electrophysiological properties (*12*). The second question is why pineal-innervating sympathetic neurons express less transcript encoding noradrenaline-synthesising enzymes (*TH*, *DBH*; Fig. 3B of (*2*)). Answering these questions will require a comprehensive functional study of the pineal-innervating sympathetic neurons, and studying why not only pineal-innervating SCG neurons but also some non-pineal-innervating stellate ganglia neurons (*11*) express melatonin receptor 1A receptors.

It remains to be understood how this denervation phenotype develops, whether it is specific to pineal-innervating neurons and if other end-organ targets of the SCG are denervated during cardiac disease. Macrophage infiltration appears to be absent from abdominal ganglia (*2*) and, surprisingly, as the authors discuss, the inflammation appears milder in the stellate ganglia (*13*), which provide the majority of cardiac sympathetic innervation. Why, following cardiac disease, macrophages selectively target non-cardiac innervating neurons, in a ganglion that provides a minority of the total sympathetic innervation to the heart, remains elusive.

Ziegler *et al.* (*2*) provide an exciting leap towards understanding the reduction in melatonin levels that occurs during cardiovascular disease and opens up a new mechanism by which sympathetic neurons and immune cells may interact. Understanding the mechanism and specificity of this interaction are clear future research directions that may underpin therapy. Meanwhile, as in romantic literature, broken hearts and loss of (sympathetic) contact with the (seat of the) soul, do indeed lead to sleepless nights.

Figure legend

Cardiac dysfunction (1) leads to macrophage infiltration (2) of the SCG (which provides a small sympathetic innervation to the heart). This causes a loss of neurons (3) innervating the pineal gland (4), decreasing melatonin secretion and altering sleep. Question marks denote uncertainty over how macrophages are stimulated to infiltrate the SCG. Created with BioRender.com

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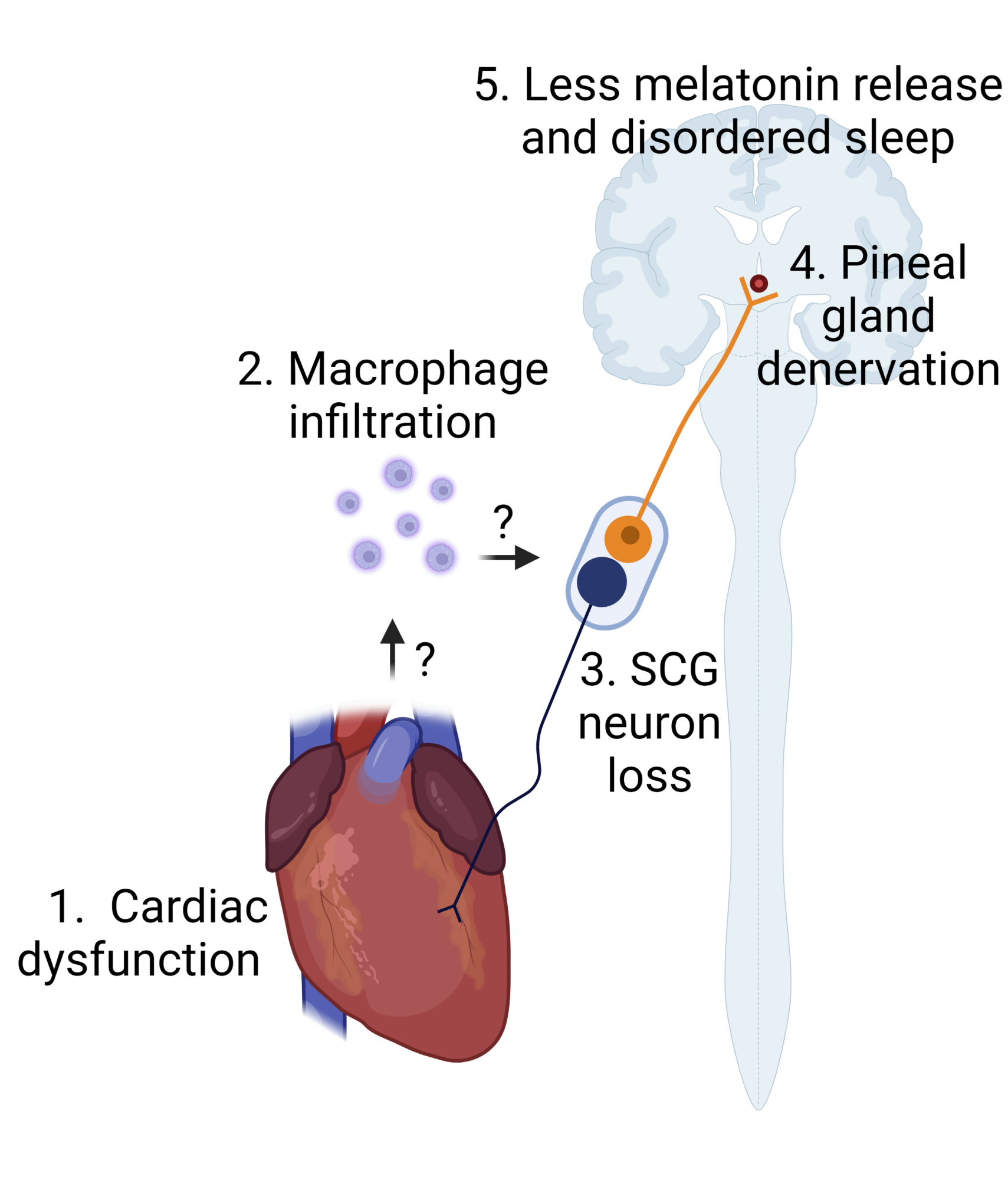
5. Less melatonin release and disordered sleep
4. Pineal gland denervation
2. Macrophage infiltration
?
?
3. SCG neuron loss
1. Cardiac dysfunction