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Cellular changes in the enteric nervous system during ageing

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ABSTRACT

The intrinsic neurons of the gut, enteric neurons, have an essential role in gastrointestinal functions. The enteric nervous system is plastic and continues to undergo changes throughout life, as the gut grows and responds to dietary and other environmental changes. Detailed analysis of changes in the ENS during ageing suggests that enteric neurons are more vulnerable to age-related degeneration and cell death than neurons in other parts of the nervous system, although there is considerable variation in the extent and time course of age-related enteric neuronal loss reported in different studies. Specific neuronal subpopulations, particularly cholinergic myenteric neurons, may be more vulnerable than others to age-associated loss or damage. Enteric degeneration and other age-related neuronal changes may contribute to gastrointestinal dysfunction that is common in the elderly population. Evidence suggests that caloric restriction protects against age-associated loss of enteric neurons, but recent advances in the understanding of the effects of the microbiota and the complex interactions between enteric ganglion cells, mucosal immune system and intestinal epithelium indicate that other factors may well influence ageing of enteric neurons. Much remains to be understood about the mechanisms of neuronal loss and damage in the gut, although there is evidence that reactive oxygen species, neurotrophic factor dysregulation and/or activation of a senescence associated phenotype may be involved. To date, there is no evidence for ongoing neurogenesis that might replace dying neurons in the ageing gut, although small local sites of neurogenesis would be difficult to detect. Finally, despite the considerable evidence for enteric neurodegeneration during ageing, and evidence for some physiological changes in animal models, the ageing gut appears to maintain its function remarkably well in animals that exhibit major neuronal loss, indicating that the ENS has considerable functional reserve.

Introduction

It is established that the mammalian enteric nervous system (ENS) undergoes developmental changes postnatally (e.g. de Vries et al., 2010; Foong et al., 2012). It is also clear that the cells of the adult ENS exhibit plasticity and continue to undergo changes later in life, due both to the highly dynamic nature of the gastrointestinal (GI) system, and to cellular changes that take place as part of the process of ageing.

Throughout life, particularly that of longer-lived animals, the gastrointestinal (GI) system is exposed to dietary variation and also to changes in the microbiota, to disease, inflammation and, in humans, medication. The properties of intestinal cells may be affected as a result of these changing conditions in the gastrointestinal environment. In addition, in long-lived animals, and in animals living in protected laboratory environments, cellular changes that occur simply as a result of ageing will affect the cells of the gut, although different cell types, such as muscle, epithelial cells and neurons, are likely to be affected in different ways. These age-associated cellular changes may impact upon specialised functions, and hence affect GI physiology. There is also evidence from animal models that external factors, including diet, can alter 'normal' (i.e. non-pathological) ageing of the ENS.

Understanding the contribution made by normal cellular ageing to the age-associated physiological changes that take place in the gut is important, because gastrointestinal disorders increase in prevalence in older people, and some conditions, such as constipation (see Gallagher and O'Mahony, 2009 Rao and Go, 2010), faecal incontinence (see Chatoor et al., 2007) and gastric reflux (see Franceschi et al., 2009) are very common among the elderly population. These conditions have a serious impact on the quality of life of the elderly, affecting their independence, and also have a significant impact on healthcare costs. Age-associated enteric neurodegeneration (see Bitar et al., 2011; Camilleri et al., 2008; Phillips and Powley, 2007; Saffrey, 2004; Wade and Cowen, 2004; Wiskur and Greenwood-Van Meerveld, 2010) and ageing of the other cells of the gut, such as smooth muscle cells (see Bitar et al., 2011; Bitar and Patil, 2004) are believed to be major contributory factors to the these age-associated GI disorders.

Here, the changes that occur in the cells of the ENS during ageing and the implications of these changes for GI function are reviewed. Ageing of intestinal smooth muscle (see Bitar et al.,

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2011; Bitar and Patil, 2004), endocrine cells (see Sandstrom and El-Salhy, 2001) and intestinal epithelial stem cells (Kirkwood, 2004) are reviewed elsewhere. Very few studies have investigated changes in the properties or numbers of Interstitial cells of Cajal and Fibroblast-like cells during ageing.

Changes in GI physiology in the ageing human population are well-known, but identifying the contribution made by cellular ageing to these changes is difficult, because of the many confounding factors that may also influence GI function in humans. For example, co-morbidity (e.g. vascular disease), medications (e.g. anti-cholinergic medications), change in diet and immobility may all influence GI physiology (e.g. see Rao and Go, 2010). The complications associated with discrimination between changes that are genuinely due to ageing, and those due to extraneous conditions, such as those listed above however, make carefully-maintained laboratory animals a valuable resource for studies of GI ageing; confounding factors such as variations in diet and medication are eliminated or reduced to a minimum.

Most work on ENS ageing has been carried out on the myenteric plexus, and analysis of age-related neuronal changes has focused predominantly on changes in the numbers of neuronal cell bodies, although some studies of the density of the myenteric plexus network and nerve fibre density in smooth muscle have also been performed. Cellular and biochemical properties that have been reported to be changed during ageing of other cell types and markers of cellular senescence have also been investigated in enteric neurons and are discussed here.

The changes that occur in GI neurophysiology of animals during ageing are being increasingly studied, although the GI changes that are common in ageing humans, such as constipation and incontinence, have not been widely looked for in the animals that have been used for the study of ENS ageing. Nevertheless recent evidence indicates that ageing mice do exhibit changes in the size and frequency of stools (Patel et al., 2012), indicating that they undergo changes that are at least similar to some of the exhibited by ageing humans. Physiological and pharmacological studies of the ageing ENS are not discussed here.

Plasticity of the ENS during ageing

The ENS is at all times a highly plastic system in terms of its physical characteristics, because the shape of enteric ganglia changes during and between the distensions that occur during peristalsis and other gut movements (Gabella, 1990). However, in addition to these continual dynamic changes, the size of the GI tract changes during the lifespan. The intestine undergoes considerable growth during adult life. For example, Gabella (1989) reported that the length of the guinea-pig small intestine increases by 27%, and its circumference by 30% during ageing. This growth results in an increase of 70% of serosal area under the conditions studied. Interestingly, the maximum dimensions were measured in middle-aged animals (Gabella, 1989). A number of others have also measured an increase in length and/or circumference with age (e.g. Choi et al., 2008 Gamage et al., in press Phillips and Powley, 2001; Peck et al., 2009). An increase in circumference may be due to changes in the thickness of the mucosa or muscularis externa, or both. Increases in the thickness of the muscle layers during ageing have been reported in several studies (e.g. Peck et al., 2009; Southwell et al., 2010), but not in others (e.g. Marese et al., 2007). With respect to the mucosa, it has been reported that there are changes in villus width and depth (Drozdowski and Thomson, 2006). Increases in the length and circumference of the intestine and changes in the volume of the different layers of the gut would be expected to have an impact on the arrangement of the enteric plexuses, and potentially on the density of nerve fibres in different layers. It is therefore likely that continued growth, and possibly some rearrangement, of enteric nerve fibres occurs throughout periods of gut growth, which take place during a considerable period of the lifespan.

During such periods of gut growth, some types of myenteric neuron, such as intrinsic sensory neurons, and those interneurons that project longer distances in the plexus, would need to increase the length of their processes to maintain contact with their target cells. Such a response may not be needed by all myenteric neuronal subpopulations however, since an increase in smooth muscle volume for example, could result from an increase in the size or number of muscle cells, and since they are well-coupled (Hoyle and Burnstock, 1989), effective transmission could perhaps continue even if the density of fibres decreased. Nevertheless, it would seem that the ENS, and enteric neurons in particular, must remain plastic during adulthood.

Changes in the gross morphology of the myenteric plexus during ageing

Changes in the general morphology of the enteric ganglia during ageing have been described in some studies. Gabella (1989) has reported that there is greater separation between myenteric ganglia in old guinea-pigs, and that myenteric neurons appear to be less densely packed within the ganglia. Abalo et al. (2005) described a reduction in size of myenteric ganglia of guinea-pig ileum with age, and that myenteric ganglia occupied a reduced area. No change in the number of ganglia per unit area during ageing was measured in the same study. A change in the size and the appearance of myenteric ganglia with age has also been described in humans (Hanani et al., 2004); in samples from older individuals the overall ganglionic area was found to be larger, and gaps or spaces were observed within the ganglia. Ganglia from older individuals had increased numbers of spaces, and also an increased proportion of ganglia with spaces, in both the ileum and colon. The extent of these changes correlated with advancing age, and was greater in the colon than the ileum. No difference between males and females was measured. The authors speculated that the spaces could occur due to a stretch effect resulting from gut growth, but pointed out that this was unlikely, because normal ganglia, without spaces, were seen adjacent to abnormal ganglia.

Changes in the general morphology of enteric neurons during ageing

The size, general shape and distribution of myenteric neurons have also been reported to change during ageing. Gabella (1989) reported that myenteric neurons were smaller in the ageing guinea-pig small intestine and Gomes et al. (1997) also measured a reduction in myenteric neuronal perikaryon area in ageing human colon. Santer and Baker (1988); however, found no change in the size of myenteric neurons in the rat small or large intestine, while others have measured an increase in neuronal cell body size in older rats (Phillips et al., 2003). Some of the discrepancies between these results may be due to the methods used (see section on challenges of analysis of changes of neuronal numbers in the ageing gut).

The shape of neurons in the ageing guinea-pig gut has been reported to be different from that in younger animals; neurons in ageing animals were found to have a 'horny' profile (Gabella, 1989). Some single neurons, which were larger and with a smooth profile, were found to be present at the edges of myenteric ganglia in old animals in the same study. Such peripherally-located

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