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Ageing is a process where the growth effect of neuronal noradrenaline changes progressively in favour of the flow mediated, neurodegenerative and inflammatory effect of plasma noradrenaline

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ABSTRACT

The noradrenaline stimulus has two components, one excitor, the other inhibitory. Neuronal noradrenaline is the excitor component and plasma noradrenaline is the inhibitory. The balance of effect between the two, the noradrenergic balance, is the controlled variable of the sympathetic system and determines the effect of noradrenaline. Neuronal noradrenaline stimulates tissues by diffusion from their sympathetic nerve endings, plasma noradrenaline does so by diffusion from their microcirculations. Changes in microcirculatory flow, by altering the flow mediated effect of plasma noradrenaline, are mainly responsible for altering the noradrenergic balance in the peripheral tissues; changes in CSF flow are speculated to be mainly responsible for doing the same in the brain, by altering the balance between synaptic noradrenaline in the brain and nonsynaptic noradrenaline in the subarachnoid CSF. When plasma noradrenaline alters the noradrenergic balance it triggers afferent sympathetic activity that alerts hypothalamic neurons to the event and they restore the balance and tissue homeostasis, within milliseconds, by adjusting the level of efferent sympathetic activity they project back to the affected tissue. Because the restoration is so rapid the effect of plasma noradrenaline is normally unobservable and dismissed as not having occurred. Because the hypothalamus is not involved with the responses of isolated canine lateral saphenous vein segments to noradrenaline, the effects of plasma noradrenaline in that preparation are not countered by reactive efferent activity and, consequently, are readily apparent in it. Quantitatively, they have been found to be a function of microcirculatory flow and noradrenaline concentration and, qualitatively, to be inhibitory, dilator, pro inflammatory and neurodegenerative. In life, due to a progressive increase in plasma noradrenaline concentration and, more so, in microcirculatory flow, the noradrenergic balance moves progressively in favour of the neurodegenerative and inflammatory effects of plasma noradrenaline. These observations are the basis of an hypothesis that ageing is caused by a genetically programmed shift in balance away from the growth and anti-inflammatory effects of neuronal noradrenaline, early in life, towards the neurodegenerative and pro-inflammatory effects of plasma noradrenalin, later in life. Death is believed to occur when plasma noradrenaline has damaged the structure of the sympathetic system so much that it can no longer create the minimum quantity of neurotransmitter needed to maintain the level of noradrenergic balance and homeostasis necessary for life.

This paper proposes that ageing reflects a changing balance between the contrasting effects of plasma and neuronal noradrenaline (NA) in the peripheral tissues, and in the brain, a changing balance between the contrasting effects of synaptic noradrenaline (SNA) and nonsynaptic noradrenaline (NSNA). That balance represents the controlled variable of the sympathetic nervous system (SNS) and changes from being in favour of the growth effect of neuronal NA (NNA) early in life to being in favour of the neurodegenerative and inflammatory effect of plasma noradrenaline (PNA) in the elderly. The body of the paper is in five parts. The first gives the rationale for the NA stimulus having two components with contrasting effects, with the balance between the two determining its effect; the second describes the first evidence I detected of NA having two independent effects;

Abbreviations: NA, noradrenaline; PNA, plasma noradrenaline; MNA, microcirculatory noradrenaline; NNA, neuronal noradrenaline; SNA, synaptic noradrenaline; NSNA, nonsynaptic noradrenaline; CLSV, canine lateral saphenous vein; SNS, sympathetic nervous system.

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the third describes the flow mediated effects of PNA stimulation on isolated segments of the canine lateral saphenous vein (CLSV) when it stimulated them by diffusion from their microcirculation (the vasa vasorum network); the fourth describes *in vivo* findings that support the validity of the experimental findings; the fifth discusses the implications the experimental findings have for understanding the nature of the ageing process. The paper concludes by suggesting how it might be possible to delay, or even reverse temporarily, the ageing process.

PART 1

Why NA has two components with contrasting effects

Every biological stimulus investigated to date has been found to have two effects, one excitor, the other inhibitory [1–4]. It is reasonable, then, to expect that NA, the stimulus of the SNS, would have two contrasting effects also, with the balance between them, the noradrenergic balance, determining the nature of the effect. The need for a stimulus to have two effects arises from its function, which is to transmit information in the form of patterns that need contrast to be detected: star patterns need darkness and sound patterns silence to be detected. Sensory physiologists use the term lateral inhibition to connote the mechanism responsible for contrast in stimuli. The SNS generates contrast in its stimuli by having NA diffuse from different diffusion sources [5], the postcapillaries of the microcirculations and the post-ganglionic sympathetic nerve endings. By doing this NA generates two diffusion patterns with different polarities that determine contrasting effects. The contrasting polarities are believed to be in planes at right angles to one another [6]. The potency of NNA stimulation is a function of impulse frequency and the quantum of NA released per impulse; the potency of MNA stimulation is a function of NA concentration and microcirculatory flow. The main cause of change in the effect of MNA is change in microcirculatory flow, not change in PNA concentration. The important implication of that is the quantitative effect of NA can change without there being any change in its concentration.

Most investigators believe PNA has no effect at basal concentration and attribute all adrenergic effects to the neurotransmitter function of the SNS [7]. They justify their belief by such evidence as that the basal concentration of PNA, at 180–250 pg/ml [8], is below the threshold needed to cause a pharmacological effect and that NA has no effect, when infused into healthy young men until its concentration reaches 1000–1500 pg/ml minimum [7]. However, basal PNA has an effect (*v.i.*) but only when it stimulates tissues by diffusion from their microcirculations. But because any effect of PNA disturbs the noradrenergic balance of the tissue it stimulates, the SNS counteracts that disturbance by generating afferent sympathetic activity that alerts neurons in the hypothalamus to the disturbance and they then adjust the level of efferent sympathetic activity they project back to the tissue so the effect of the PNA stimulus is concealed – not abolished – and homeostasis is restored to the tissue [9]. But because that adjustment occurs within milliseconds the effect PNA stimulation is not observable and hence gives rise to the impression that it has none. So, changes in efferent sympathetic activity represent reactive responses to changes in PNA stimulation and their purpose is to maintain tissue homeostasis. Consistent with that analysis, I believe the reason infused NA had no detectable effect on young men until its concentration reached 1000–1500 pg/ml [7], is because up to that concentration the hypothalamic neurons were able to replenish their neurotransmitter stores sufficiently rapidly enough to maintain homeostasis and conceal the effect of the infused NA. Above that concentration, however, they were unable to do that and the effect of the infused NA then became detectable.

PART 2

The flow dependent dilator effect of MNA stimulation in vitro and in situ

The first evidence I detected that MNA stimulation has a flow mediated effect resulted from an investigation I made of why isolated *in vitro* CLSV segments were more responsive to NA stimulating them through their lumenal surfaces than through their adventitial surfaces [10]. Because the segments were perfused at a constant flow, the perfusion pressure upstream of the segments increased as their constrictor tone increased and decreased as it decreased. In the course of the investigation I noticed the response of an occasional segment to electrical stimulation converted spontaneously from being constrictor to being dilator for a period in the course of a response [11] (Fig. 1).

A largely serendipitous decision to reposition ties put on a segment's tributaries to prevent leaks, from random, convenient distances from the tributary junctions to a common position flush with the junctions, eliminated the bimodal responses and, more significantly, strengthened the segments' constrictor responses to both electrical and exogenous NA stimulation by around 50%. Subsequent investigation revealed the reason for that was due to the tie repositioning reducing the volume of reflux perfusing the segments' microcirculations. The structural changes associated with that reflux were investigated by fixing segments with a rapidly acting fixative as their responses neared their peaks and then investigating them by serial sectioning or scanning electron microscopy. The fixative used consisted of a pH 6.6–6.8 solution of 2% glutaraldehyde and 2.5% paraformaldehyde in phosphate buffer (see Fig. 2).

Because isolated CLSV segments have no arterial inflow the only way to investigate their responses to MNA stimulation was by perfusing their microcirculations by reflux. That posed a problem initially, because of the belief then, and now, that microcirculations of healthy veins do not drain into their hosts and consequently cannot be perfused by reflux from them [12]. Consistent with that belief, every perfusion study of the venous microcirculation, over the centuries, has involved orthograde perfusion through their companion arteries. However, I demonstrated that it was possible to perfuse microcirculations of healthy veins by reflux [13]. The failure of others to do the same was found to have been due to their failure to detect the opening of venules that drain the venous microcirculation into the bases of the valves of the tributaries and veins and that are concealed in deep folds [9] created by the recoil of fibroelastic structures called aggers, discovered two centuries or more ago but now effectively forgotten [14]. Aggers are functional (Starling) valves located along the insertions of valve cusps. In tributaries they are located at the insertions of the cardinal valves, located 2 to 3 tributary diameter length from the tributary junctions [9]. Because of that location, aggers were usually located proximal to the conveniently positioned ties but distal to the repositioned ties, meaning the former did not block reflux but the latter did and eliminated the bimodal responses. When the venous tone is normal, aggers block reflux but they positively facilitate it when the venous tone rises, thus enabling overspill NA reduce the increased tone by a reflux dilator effect of MNA stimulation [14]. For reasons still not understood, aggers become functionally disabled when flow in a vein is turbulent and that allows reflux to occur even when a vein's tone is normal. Using that information I investigated the responses of unstimulated CLSV segments to MNA stimulation. To induce the turbulence needed to do that I moved a perforated polythene tube or floated a length of knotted thread in the perfusate [15]. Turbulence increases reflux for the same reason as it increases perfusion of arterial microcirculations [9,16], viz., by introducing dispersive radial components into the axial velocity vector of laminar flow.