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Mini Review

The Potential to use Chloroquine and other 4-Aminoquinoline Analogues to Modulate Persisting Inflammation in Old Age

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Abstract

Low-amplitude persisting systemic inflammation is frequently found in elderly people and is causally linked to several markers of frailty, including sarcopenia, low mood and higher dependency, as well as higher all-cause mortality. Older patients with such "inflammation" have raised baseline blood levels of several pro-inflammatory cytokines, such as tumor necrosis factor alpha and interleukin-1 beta, and chronically raised C-reactive protein. There is a clear need to identify interventions, including drugs that can ameliorate such inflammation by helping to re-set the innate immune system to a less inflamed baseline. Several classes of drugs have such properties. In this review the authors have summarized the background science with respect to the relationship between ageing, inflammation and frailty, then described the established role of methyl-xanthines, particularly theophylline, as immune modulating drugs before positing a case for the use of 4-aminoquinolines, such as chloroquine, in a similar role. The probable mechanisms of anti-inflammatory action for those classes of drugs are compared, leading to a proposal that formal clinical trials should be conducted of chloroquine as an adjunctive immune modulator for "inflammaging" and persisting post-acute inflammation in old age.

Introduction

A strong imperative is emerging to search for pharmacological agents that can effectively modify the consequences of persisting low amplitude systemic inflammation, particularly in aged people in whom it has been shown to be causally associated with a pre-frail or overtly frail condition, and is a probable direct etiological factor in the development of sarcopenia [1,2]. This is especially so for the many patients who are physically or mentally unable to perform exercise of sufficient regularity, work-rate and duration to benefit from the anti-inflammatory effects of aerobic exercise [2,3]. This is a familiar clinical phenotype in geriatric medicine and represents a major challenge to clinicians, health service planners and economists. Our proposition is that opportunities should be taken to identify pharmacological and non-pharmacological interventions that can help to reduce the burden of frailty and preserve function. To that end, a case can be made for taking a fresh look at a number of drugs, many of which are in common use for other purposes, that have been shown to modulate inflammatory cellular and biochemical responses, largely by resetting immune networks toward a less inflamed baseline state. To date, these effects have been arguably explored most avidly for methyl-xanthines and statins [4-7]. In this paper the authors will summarize the prevailing evidence for 4-aminoquinolines (4AQs), mainly chloroquine and hydroxychloroquine that have been shown to have immune modulating effects similar to methyl-xanthines, though apparently through different mechanisms. We draw on that evidence to propose a need for properly conducted clinical trials of 4AQs to ascertain any measurable clinical benefits.

Ageing of the Innate Immune System

Innate immunity in older people is fundamentally the same as that in younger adults but does exhibit some different characteristics, particularly with respect to baseline settings and response amplitudes. For example, commonly measured biochemical markers of inflammation, such as interleukin-1beta (IL-1β), interleukin-6 (IL-6) and Tumor Necrosis Factor Alpha (TNFα) at baseline between acute inflammatory episodeshave been shown to be often2-4-fold higher in theperipheral plasma of aged subjects, and to become increasingly so with advancing age, most steeply inpeople older than 80 years, when compared to young and middle-aged adults [1,8,9]. In one high quality study of healthy individuals across the adult age range there was mean baseline venous plasma TNFα concentration of 0.6 pg/ml in adults below the age of 30 years compared to a mean of 1.5 pg/ml in those above the age of 70 years [10]. This is one of the manifestations of the clinical state frequently referred to as "inflammaging", a term that is now widely used in clinical geriatric medicine and by researchers focusing on the immunology of ageing [1]. In many individual patients this state can

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be attributed to clinically obvious co-morbid chronic inflammatory diseases such as Rheumatoid Arthritis (RA) or Chronic Obstructive Pulmonary Disease (COPD) [9]. Similar raised plasma levels of the biochemical indicators of inflammation, particularly TNFα and IL-β have been reported in elderly people with other conditions that appear to shift the innate immune web towards a relatively pro-inflammatory setting; common examples are central obesity, atheromatousarterial disease, and type 2 diabetes [11-13]. Further, a sustainedlow-level rise inplasma pro-inflammatorymarkers has been found in people with Alzheimer's Disease (AD), and in association with a sedentary lifestyle, chronic renal disease and osteoarthritis [11,14-16].For reasons that are uncertain, some but not all well elderly people have raised baseline plasma inflammatory markers that appear to have no identifiable pathological cause, and age itself appears to be accompanied by an up-regulated baseline inflammatory state [17,18]. Taking C-Reactive Protein (CRP), a non-specific marker of inflammation, as an example, healthy young adult participantswere found to have mean venous blood CRP levels of 0.9 mcg/ml compared to 3.0 mcg/ml in healthy people over the age of 65 [17]. Baseline peripheral blood IL-6 and IL-1β also appear to be significantly correlated with age [19]. These observations have relevance for clinical practice and pathophysiological research because persisting low-amplitude inflammation, as measured by such blood markers, is associated with higher all-cause mortality, lower muscle strength as assessed by handgrip and quadriceps femoris performance, impaired instrumental function, there by affecting activities of daily living, and lower subjective well being, mood scores and self-reported health status [20,21]. The observed plasma levels of inflammatory markers, such as CRP, IL-1β, IL-6 and TNFα vary between studies, depending on assay methods, but overall the adverse outcomes considered were broadly associated with 1.5 to 3-fold elevation above those found in healthy age-matched controls. Another factor of importance to clinical geriatric medical practice that is relevant to the argument we are positing in this paper is the persisting pro-inflammatory state that often does not resolve, or does so slowly and incompletely, after an acute inflammatory event such as pneumonia or septicemia. This clearly has implications for the rate and completeness of clinical recovery and the return to pre-event mobility and instrumental function, and therefore offers a clear and clinically important target for research into effective drug interventions [22-29].

It is likely that disease progression in a number of chronic pathological states is to some extent driven by persisting inflammation and not just indicated by the presence of raised inflammatory markers [25]. It appears that a complex interactive relationship exists between cause and effect. An illustrative example is the endothelial inflammation found in atheromatous disease which has been extensively researched and is frequently cited as being typical of the inter-relationship between inflammation, age-related changes and pathological mechanisms [26]. In many elderly people, the inflammatory response to an acute stimulus, such as infection or injury, settles back to baseline more gradually than it does in younger adults. Therises in plasma TNFα, IL-1β and IL-6 last longer and the corresponding rise in the anti-inflammatory cytokine interleukin-10 (IL-10) occurs later and is of lower amplitude. This effect of ageing on innate immune responses has been most clearly shown for pneumococcal and Gram-negative endotoxin antigens [27,28], in which cases an approximately doubling of the time taken to return to pre-stimulus baseline levels in elderly subjects, after comparable pro-inflammatory peak levels. This observation strongly suggests that regulatory anti-inflammatory function is impaired, with a consequent delay in re-establishing a baseline surveillance state of the innate immune system. It is a plausible argument that this altered mechanism is a likely reason for the slower post-acute functional recovery and persisting low-level inflammation often seen in olderpatients after acute inflammatory illnesses [2].The evidence for cytokines having a central role in age-associated inflammation is certainly well established.

Sustained Inflammation and Frailty

Systemic inflammation is closely, and probably causally, associated withsome clinically important features of frailty, including sarcopenia, cachexia and low mood [2]. The molecular mechanisms are inevitably complex, incompletely understood and likely to be dependent on the patho-physiologicalcontext in individuals. Various components of the innate and adaptive immune systems, notably chemokines, the catecholamine-cortisol axis, complement reactions, interferons, immune cells and other somatic cells communicate with and influence each other in a non-linear manner best pictured as a network or web. A full account is outside the scope of this paper, but the authors have published detailed descriptive reviews elsewhere [2-4]. Effective drug treatments for the subtle dys-immune state described above are therefore likely to be those that causea corrective multi-component shift in the innate immune network, a process often termed immune modulation, and consequently ameliorate the inflammatory burden that contributes to frailty.

Drugs that Modulate Systemic Inflammation: Particularly Theophylline

Drugs in several pharmacological classes have been shown to dampen systemic inflammation through a range of complex mechanisms that are only partially understood. The list includes, but is not limited to, statins, methyl-xanthines, salicylates, 4AQs, beta-adrenoreceptor blockers, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDS), metformin and mono-clonal antibodies (MCAs) [2]. Though many of these are licensed for use as anti-inflammatory agents, some are not despite having received considerable attention to explore immune modulating properties and therapeutic potential. For example, theophylline, a methyl-xanthine drug used as a broncho-dilator in patients with asthma and COPD, was noted to improve certain outcomes in patients with COPD, for example improved walking performance, even when there was little or no measurable change in spirometry or arterial blood gas tensions. Further, this occurred at plasma levels well below (<10 mg/L) those likely to cause toxic effects [30]. Follow up studies found that the anti-inflammatory properties of theophylline acted not only locally on airways but also systemically [31,32]. Despite a series of studies, the set of mechanisms through which theophylline modulates innate immune reactions remain incomplete. Further, the patterns and sequences of reactions that constitute the innate immune web and are likely to varyfrom episode to episode, within and between individuals, and with the prevailing pathophysiological context. Importantly however, theophylline has consistently been found to reduce post-acute TNFα and IL-1β, and increase IL-10, by around 25-50 per cent. Similarly, in vivo testing of comparable concentrations of pentoxifylline, another methyl-xanthine, caused a progressive fall in the release of pro-inflammatory IL-1β, IL-6, IL-8 and TNFα of between 20 and 80

percent by peripheral venous blood monocytes over 4 days [32]. This effect appears to be mediated by activation of histone deacetylase-dependent gene switches to set a more anti-inflammatory phenotype [31-33]. These properties are apparently due to theophylline-induced re-direction of the immune web toward an anti-inflammatory state in macrophages and other immune cells. Such cells have been shown to possess several dose-dependent gene switches that up- and down-regulate various cytokines. This is therefore a plausible explanation for the observation that patients with COPD treated with the addition of theophylline to a standard regimen had lower baseline CRP levels and better functional scores compared with control subjects. It also appears that theophylline at normative therapeutic doses reduces inflammation without compromising an appropriate inflammatory response to infection. In a critical care context, it has been shown that a reduction in mortality occurs in patients with severe sepsis treated with theophylline. These effects can be viewed as the clinical manifestations of immune "modulation" [5,7,34-43].

A Possible Role for Chloroquine

Chloroquine and other 4AQs analogues are in established use as anti-inflammatory drugs, mainly in the field of rheumatology for the management of conditions such as rheumatoid arthritis and systemic lupus erythematosus. The anti-inflammatory properties of 4AQs were discovered as a beneficial side effect when chloroquine was in widespread deployment as an anti-malarial drug. Subsequent research established the efficacy of 4AQs in a range of disorders and some progress has been made to identify the mechanisms of action. Early research suggested that the principal anti-inflammatory action was mediated by the changes in macrophage and other monocyte intra-lysosomal pH, and consequent effects on antigen proteolysis and enzymatic activation, as chloroquine and its analogues are concentrated in lysosomes [44].The accumulation of chloroquineinlysosomes appears to be irreversible and elevates lysosomal pH by trapping of H+ ions in association with chloroquine molecules. Hydroxychloroquine, also alysosomotropic amine, has a similar effect on cellular function. By that apparent mechanism, chloroquine and its analogues interfere with lysosomal pH, which in turn inhibits phagocytosis, antigen processing and proteolysis and, thereby indirectly, chemotaxis, antigen presentation and the phenotypic expression of inflammation. Further research showed that chloroquine and its analogues reduce the release, and probably the production, of the pro-inflammatory cytokines TNFα, IL-1β and IL-6 by monocytes in vitro, and in vivo during treatment of patients with inflammatory conditions [45]. However, confirmatory in vitro studies have shown that it is likely that the chloroquine-induced reduction of production by monocytes is due to slower conversion of TNF precursors to the active molecule, whereas the reduced production of IL-1β and IL-6 appears to be caused by a pH-dependent inhibition of cytokine release from cells consequent mainly upon reduced molecular stability but possibly due to acid-base effects on gene transcription [45,46]. These effects appear to be mediated by alterations in antigen processing, as described above, and by an acid-base sensitive reduction in messenger-ribonucleic acid (mRNA) involved in IL-1β and IL-6 transcription [46], rather than through an epigenetic gene-switching mechanism. It appears, therefore, that the biochemical mechanisms of the immune modulating properties of 4AQs (for example chloroquine) and methyl-xanthines (for example theophylline) are different.

The Need for Research

We have, in previous papers, contended that a case can be made for well conducted studies of the use of low-dose theophylline to modulate persisting inflammation, when it is inappropriately prolonged after stimuli such as sepsis, particularly in pre-frail or overtly frail elderly patients [2,4]. We also advocate similar well designed trials of 4AQs, especially chloroquine and hydroxychloroquine. A role for the use of 4AQs might consequently be established in the reduction ofpost-acute and chronic inflammation in an attempt to ameliorate the progression from pre-frailty to established frailty, either as a sole treatment or as an adjunct to use of, for example, methyl-xanthines. The principal targets for further research should be specifically: 1) to conduct placebo-controlled trials of anti-inflammatory doses of chloroquine or hydroxychloroquine, given orally, as short-term (4-6-weeks) adjunctive treatment in elderly patients recovering from sepsis or trauma. 2) To establish whether chronic low-grade inflammation, as measured by peripheral blood biochemical markers such as TNFα and IL-1β can be modified by such treatment, and functional outcomes improved. 3) Include as defined outcomes measures of mortality, mobility scores, functional scores, return to independent living, measurements of muscle strength and other indices of sarcopenia, cognition, mood, wellbeing scores, and duration of hospital treatment.

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