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New Perspectives in Chronic and Neuropathic Pain in Older Population

Antonella Paladini[1], Franco Marinangeli[1], Stefano Coaccioli[2], Mariella Fusco[2], Alba Piroli[1], Varrassi Giustino[2]*

[1]University of L'Aquila, Medical School, Department of MESVA, 67100 L'Aquila, Italy
[2]Paolo Procacci Foundation, Via Tacito 7, 00193 Roma, Italy

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***Corresponding author:** Varrassi Giustino, Paolo Procacci Foundation, Via Tacito 7, 00193 Roma, Italy, Tel: + 39 348 6068472; E-mail: Giuvarr@gmail.com*

Chronic and neuropathic pain has always been a major health problem, especially in elderly population. An increasing number of data has demonstrated not only its importance from the physical and psychological point of view, but also for the economic and social aspects [1,2]. For centuries the attention of the researchers was focused on the study of neurons and their functions, initially they explained how pain is transmitted to brain. At the moment the clinicians know almost everything about the ascending and descending systems of pain control. They know about the extremely high number of receptors, from time to time they suggested about the importance in the perception, transmission and reduction of pain. Also the potentiality for therapy and reduction/abolition of pain are increasing in number, but still the number of patients over 65y with moderate to severe pain is increasing. Actually, it is enormous. Looking at the data of recent literature, there is an apparent prevalence of chronic pain of 50% in older adults living on their own, and over 75% in those living in care facilities [3,4]. Moreover, there are many data showing the strict interrelationship of chronic pain with other chronic diseases [5].

Cares for such group of patients are always difficult. In fact, not only chronic pain is very seldom their only health problem [5], but also there are diagnostic difficulties and scarcity of efficacious therapies [4,6]. The evaluation of pain could be difficult because of concomitant pathologies, pains from different origins, and also because of interferences from multiple therapies which could alter the clinical situation [7]. Moreover, diagnostic tools, like the different pain scales, may be of scarce help, because of significant reduction of sight and hearing, and/or possible cognitive disturbances [5,7]. Despite, older adults are the most important consumers of pain killers; this group of drugs is fully efficacious in less than 50% of the cases [8]. All these aspects explain why the prevalence referred above is only apparent, and not completely reliable.

With such results, it seems like the efforts of the researchers who are fully concentrated on neurons and their functions have not been very successful. Actually they have completely ignored for many centuries that the nervous system is not only composed by neurons. There are other cells which might be essential for the complete and optimal function of the nervous system. Data coming out of the basic research are increasingly showing the importance of microglia and astrocytes [9,10]. Microglia, that represents the most powerful immunity part of the CNS, changes completely its functionality with the age [9]. In older people microglia is mainly present as a phenotype called *primed* [10]. The *primed* microglia is more reactive to stimuli and not sensible to the natural homeostatic regulation [11]. As a consequence, the *primed* microglia might be responsible for the central sensitization [12], and facilitate the central and/or the neuropathic pain. Moreover, its hyper-production of pro-inflammatory substances and proteolytic enzymes seems responsible for the progressive impairment of the A δ fiber [13]. Also the mast cells seem to be very important for the nervous system functions decline. In older adults, they are hyper-present and hyper-reactive in the endoneural space, and are de-granulating more than younger subjects [14]. All together it certainly has a significant role in the decline of the somatosensory function of elderly people. Moreover it is a determinant factor for the low grade inflammation, which is typical for chronic diseases, including chronic pain [15,16,17]. In such situation a low, continuous increase of inflammatory mediators has been described [18]. This is responsible for a reduced impermeability of the nervous system to toxic substances [19,20], increasing the possibility of nervous sensitization and chronic pain.

Because of such a neuro-physiological change, chronic pain in elderly people is controlled with difficulty. NSAIDs are not always efficacious [4,6], and may cause many side effects [21]. Opioids are effective on μ receptors, but also stimulate the non-neuronal cells of the nervous system, like microglia, astrocytes and mast cells, increasing the peripheral and central neuro-inflammation [22,23]. In fact, some of the side effects of opioid therapy are demonstrated as a consequence of non-neuronal cells activation [24].

The findings of non-neuronal cells involvement in the development of chronic and neuropathic pain makes them an important target to prevent the onset and progression of these

 ***Corresponding author email:** Giuvarr@gmail.com*

conditions, especially in older adults. There are endogenous lipidic molecules able to promote a reduction of inflammation as well as of neuroinflammation, mainly by regulating non-neuronal cells. One of them is Palmitoylethanolamide (PEA). PEA is produced/hydrolyzed by glial cells and mast cells [25-27]. It down-modulates mast cell activation [28,29], and controls glial cell behavior [30-33]. PEA levels are altered in brain areas involved in nociception as well as in spinal cord following neuropathic pain induction [33], and in other conditions associated with the pain development [31,34]. Finally, the exogenous administration of PEA has been reported to reduce pain behaviors and to inhibit somatosensory activation and correlated events in acute and chronic/neuropathic models of pain [35]. Also, it has been demonstrated a relief of pain, a reduction of disability, and an improvement of neurological functions in different human conditions associated to chronic/neuropathic pain [36]. Since PEA has basically no adverse effects at pharmacological doses, while possessing a double therapeutic effect (i.e., anti-inflammatory and pain-relieving), as demonstrated in an extensive review article [37], and in a recent meta-analysis [38] its use might result a suitable and innovative support for the treatment of persistent pain in the elderly population.

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