ALGOGENIC TISSUE FACTORS AND THEIR ROLES IN ORO-FACIAL PAIN

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ABSTRACT

It is well known that algogenic tissue substances (bradykinin, prostaglandins, histamine, serotonin, Substance P) are found in tissues under normal conditions in very small quantities. Cellular, vascular and nerve fiber aggression, especially inflammatory, but also mechanical -traumatic or ischemic of the oro-maxillary tissues causes the concentration of these algogenic factors to increase, inducing the stimulation of algo-conductive nerve pathways. Their presence in large quantities generates the appearance of violent pain sometimes, either through the irritating action they have on the peripheral endings, or through compression edema due to vasodilation and vascular hyperpermeabilization following tissue irritation or aggression. Current review whants to present the potential biomarkers involved in oro-facial pain by analyzing various biofluids different molecular markers who can used to identify the risk factors and predicting the progression and outcomes of painful oro-facial conditions.

Keyword: algogenic tissue substances, oro-facial pain, biomarkers.

INTRODUCTION

Periodontal disease, tooth decay,orofacial pain and oral cancer are the main globally oral conditions [1]. Management of orofacial pain has traditionally been a difficult challenge for the dental-medical profession. The management of oral rehabilitation depends on the severity of disease and the severity of oral procedures [2]. Pain is the most common reason worldwide for emergency dental visits [3]. and there is no doubt that persistent orofacial pain (POFP) can be caused by a range of conditions affecting the mouth and face and is often associated with significant disability [4,5]. The oral cavity is considered as being a mirror that reflects the health of the human body [6]. The oral cavity is colonized by a complex microbiota. Oral biofilms on dental hard and soft tissues are the main cause of dental diseases, including caries and periodontal disease [7]. Also recent studies aprove the fact that there is an impact of stress and trait anxiety on the sensory and jaw motor responses to a tonic orofacial nociceptive stimulus [8]. Dental anxiety and fear are widespread among the population and pose a significant problem in their management [9]. Another aspect is connected with oral pain in cancer patients

wich may be due to the primary disease or to various cancer treatments, including surgery, radiotherapy, chemotherapy, and targeted therapies [10]. Emerging data suggest that an overlap exists in the molecular mechanisms that generate cancer pain. Moreover, the complex micro-neuroanatomy that innervates the oral cavity likely contributes to the severity, character, and impact of pain in cancer. Patients may be afraid of dental pain, particularly in cases of dental implantology, the uses of dental implants being accepted as a safe and predictable method to assist in cosmetic and functional rehabilitation in patients with edentulous jaws 11,12] . Furthermore, it has become a demand from patients especially due to psychological factors and improved quality of live [13,14]. In the last decades, in the context of society development, theoretical and practical interest of the trinom: clinicians, reserchers, and manufacturers, has been registered to improve the success of implant treatment outcomes [15].

PLASMA KININS (BRADYKININ, KALIDIN)

These substances appear as peptide fragments as a result of the cleavage of the plasma globulin called kininogen under the action of the enzyme kallikrein. Endogenous kinin peptide fragments are released at an increased rate during trauma, inflammation, or tissue ischemia.

In this sense, bradykinin is one of the most active algogenic substances acting on the endings of A-delta and C fibers. Bradykinin is one of the most potent pain-producing agents formed under inflammatory conditions, and a multitude of its excitatory and sensitizing effects on peripheral nociceptors have been described supporting its role as a prototype of peripheral pain mediators [16]. In addition it also sensitizes some peripheral receptors with a high excitability threshold, causing them to generate pain to stimuli and stimulation intensities that under normal conditions only cause exteroceptive sensations (for example tactile) and which have nothing to do with pain, but which now become sensitive by lowering of the excitability threshold. The nociceptive action of bradykinin requires the presence of prostaglandins. As tissue mediators of pain, kinins act through type B1 receptors for kallidin and type B2 receptors for bradykinin and kallidin present on nerve endings or sensitive neurons , being strongly involved in hyperalgesia. The density of B1 receptors shows increases in inflamed tissues and, in addition, directed-chemotactic migration in the oro-facial inflamed tissue of cells possessing B1 receptors has been proven, while B2 type receptors in turn show an appreciable concentration in the vicinity of nociceptive endings [17]. There is also strong evidence in favor of the existence of a synergistic co-participation of bradykinin, Substance P and interleukin-1 in hyperalgesia [18].

HISTAMINE (BETA-IMIDAZOLYL-ETHYLAMINE) is released by mast cells in the oro-facial subjected tissues to physical or chemical aggression, representing a biogenic amine resulting from the decarboxylation of the amino acid histidine. It has strong vasoactive actions producing dilation of the vessels in the attacked tissue, increasing vascular

permeability and favoring the appearance of inflammatory edema and pain. Neuropeptides are synthesized at the level of the neuronal soma and then transferred to the terminal level by axonal transport [19]. The release of these neuropeptides leads to the degranulation of mast cells, which release histamine that can cause further activation of nociceptive terminals. In addition, nociceptive fibers can be sensitized, made more excitable, by inflammatory mediators such as PGE10 [20]. The pain signal generated at the peripheral branch of the nociceptor is encoded in action potentials that allow centralized transmission of the information.

Histamine is a key mediator in the processing of nociceptive information, acting in an antinociceptive manner in the CNS while, conversely, in a nociceptive manner in the PNS. In the PNS, histamine is released in response to tissue injury/damage, and, through the sensitization of polymodal nociceptors resulting in increased firing rates, it contributes to the generation of pain hypersensitivity [21].

NITRIC OXIDE (NO) is a neurotransmitter represented by a free radical in the form of a gaseous molecule originating from arginine in the presence of the enzyme nitric-oxide-synthetase (NOS). Damage to the peripheral sensory nerves increases the synthesis of NO which would behave in the periphery as a neurotransmitter involved in the mechanism of hyperalgesia, the administration of nitric oxide synthetase inhibitors causing marked analgesia [22,23]. In addition, bradykinin, a known mediator of pain and present in injured tissues, potentiates the release of NO which in turn hypersensitizes peripheral tissue algoreceptors to histamine.

Nociceptive processing at the level of sensitive (afferent) endings and at the level of intraneuraxial neurons (second order and third order neurons) of pain projection involves the participation of neuronal membrane receptors for pro- or anti-nociceptive ligands: excitatory amino acids (NMDA and non- NMDA), neurokinin, purines, estrogen hormones, gamma-amino-butyric acid, opiates. The most important membrane receptors with a role in sensitization of central neuronal structures are ionotropic receptors for excitatory amino acids (glutamic acid, aspartic acid, kainic acid and alpha- amino-3-hydroxy-5-methyl-4-isoxazole propionic–AMPA), metabotropic glutamate receptors and neurokinin (NK) receptors. Ionotropic receptors are directly involved in the opening of ion channels, for example Ca2+ channels, and metabotropic ones indirectly through the G protein, a pathway that uses intracellular second messengers (nitric oxide, protein kinase C [24].

SEROTONIN (5-HYDROXYTRYPTAMINE, 5-HT) comes from the amino acid precursor tryptophan. Injected intradermally, it causes a local inflammatory reaction and pain in the form of a burn. Serotonin also plays a role as a peripheral neurotransmitter of pain in neurogenic inflammation by coupling with the HT1B and HT1D receptors present on algoconductive fibers. The vasoconstrictor

actions initially induced by algogenic stimuli activate platelet aggregation, resulting in the release of serotonin followed by vasodilation and increased vascular permeability [25]. These phenomena favor the migration of serotonin into the peri-vascular space where it adds up its effects with those induced by other tissue algogenic substances, namely: substance P, bradykinin, nitric oxide, histamine or the cellular efflux of K+. Serotonin thus contributes in the periphery, together with the mentioned substances, to the production of neurogenic inflammation and the hypersensitivity of receptors and related fibers in the affected tissue area, contributing to the biochemical support of secondary pain. At the level of central neurons, on the contrary, serotonin has been known since 1953 as a pain inhibitor [26].

Some of the recent research speculate that drugs targeting the peripheral 5HT3 receptor may not

be sufficient to reduce trigeminal pain conditions not of muscle origin, such as migraine, in both men and women. The study focused on the metabotropic 5HT receptors known to be localized to the trigeminal ganglia to determine whether targeting a different excitatory 5HT receptor may reduce orofacial pain [27].

PROSTAGLANDINS (PG) play an extremely important role in the processing of pain at the peripheral and central level. The component substances of this group appear through the oxidation of arachidonic acid, their release can be stopped by blocking the enzyme prostaglandin-synthetase (cyclooxygenase-COX) with pharmacological agents aspirin-like or synthetic non-steroidal anti-inflammatory drugs [28,29].

The increased concentration of prostaglandins in the attacked peripheral tissues generates reactive inflammatory phenomena, increased pain sensitivity and hyperalgesia. The synovial fluid, for example, from the temporomandibular joint shows a significantly increased level of PGE2 during inflammatory conditions, a concentration that is directly related proportional to the clinical signs of temporomandibular allodynia and it is not a surprise under these conditions that COX2 (inducible prostaglandin synthetase) inhibitors prove extremely active from a beneficial point of view in the treatment of inflammation and acute and chronic pain [30].

CLINICAL IMPLICATIONS OF CENTRAL NEURON SENSITIZATION IN PAIN

The main characteristic of changes in neuronal activity in the sensitive trigeminal nuclear complex and in particular in the caudalis subnucleus, which is the basis of the oro-cranio-facial pain mechanism, is the sensitization/hyperexcitability of nociceptive neurons. This has four cardinal clinical signs as manifestations:

- the decrease of the excitation threshold, which clinically induces the perception of pain to stimulations of non-painful intensity, usually below the algesic threshold (installation of allodynia),

- abnormally strong painful responses to painful stimulation (appearance of hyperalgesia),

- the extension (diffusion) of pain to territories not involved in the injury

- the presence of spontaneous pain.

Different characteristics of dental pain, cephalalgias, temporomandibular pain syndrome and neuropathic pain can now be explained by the sensitization state of central trigeminal nociceptive neurons following their prolonged painful stimulation. Some examples are concludent: periorbital cutaneous allodynia that characterizes some headaches involving the convergence of nociceptive afferents of the dura mater and facial cutaneous ones in the sensitive nuclei of the trigeminal nerve; the extension of the pain of an inflamed tooth in oral areas far from the source of the pain, in the face or in the mandible, explained by the extension of the central field of thalamo-cortical projection, the decrease in the threshold of excitation and the increase in receptivity and the intensity of the responses [31].

But the prolonged stimulation of the nerve endings in the attacked tissue (for example in dental therapeutic procedures, pulping) have as an effect not only central hyperexcitability, but also peripheral hyperexcitability, the latter being amplified by central sensitization, so that over time a true algic vicious circle is established supported by the formation of abnormal and self-maintaining peripheral-central circuits. An example is that of the increase in the excitability of the temporomandibular joint and the mandibular muscles, having as the primary source an inflamed tooth. Disorders of the temporomandibular joint activity appear, which are associated with the limitation of mandibular movements with the prolongation of the contraction of the raising and lowering muscles of the mandible as a form of neuromuscular adaptation of the central-peripheral and sensory-motor reactivity and sensitivity of the trigeminal nerve. In such circuits abnormal vegetative fibers can also be trained, which amplifies the disturbances, prolongs the duration of the pain and makes the treatment more difficult [32].

The dentist and the specialists who practice oro-dento-alveolar and maxillo-facial surgery interventions must constantly bear in mind the possibility that the nociceptive and algo-conductor oro-dento-facial system may change its functional parameters by moving its "cursor" excitability on a higher level of sensitivity (by lowering the excitation threshold) with the predictable consequences, namely the installation of hyperalgesia, allodynia and widespread diffuse pain. The most favorable conditions for the installation of chronic pain are those that involve aggression of peripheral tissues, therefore a good clinical therapeutic strategy will have to avoid or reduce to the minimum possible traumatic maneuvers. The relatively recent method of inducing early analgesia (compared to the classic modality only sedative) induced with a certain time interval before a procedural/surgical intervention that generates pain ("empty" analgesia - "preemptive analgesia") proved that such a therapeutic approach is more effective in reducing the effect of tissue aggression and

significantly decreases post-operative oro-facial pain, effects that can be potentiated by the administration of analgesics in the operative wound, for example opioids (which raises the interesting topic of the existence of peripheral antinociceptive pharmacological receptors) The early pre-operative administration of a judiciously chosen analgesic and not shortly before the intervention, reduces to an important extent the related intra- and post-operative nerve influxes (as well as the pre-operative ones by deactivating the psycho-emotional circuits), including morphological, genetic neuroplastic changes (reduction of c-fos and c-june gene activity and consequently decrease in the synthesis of pain mediators), biochemical, functional, phenomena that appear surprisingly, according to recent studies, even from the first 15-20 minutes after installation post-operative pain [33].

CONCLUSION

Experiments and clinical observations have convincingly proven that the trigeminal nociceptive neuronal system is responsible to the highest degree for the processing of painful oro-cranio-facial affections. It shows an extremely plastic and functionally modifiable reaction capacity, dependent on the aggressive events that they take place at the periphery in the oro-facial tissues, as well as by the activation/inhibition of some structures and circuits involved in the central matrix network of pain ("neuro-matrix of pain") with the participation both at the periphery and at the cerebral level of a neuro equipment - chemical complex consisting of receptors, neurotransmitters, transporters of pro- and anti-nociceptive molecules, enzymes, cytokines and growth factors, which are part of the inter-neuronal signaling and modulation system.

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