

REVIEW ARTICLE

**PROCAINE, EPIGENETICS AND NEURAL THERAPY,
¿A therapeutic alternative?**

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Artículo recibido el 24 de marzo de 2011 y aceptado para publicación el 22 de julio de 2011.

SUMMARY

Procaine, epigenetics and neural therapy, ¿a therapeutic alternative?

A hallmark of human cancer from epigenetics is the silencing of tumor suppressor genes, along with DNA hypermethylation. This review describes procaine, which can produce epigenetic modification in four studies of cancer *in vitro* and *in vivo* and how, when combined with other anticancer drugs, increases the therapeutic index improving antitumor activity. The aim of this review is to present a general perspective of selected data that shows the progress of the investigation of cancer, defined as the study of reversible mechanisms interact on the DNA, altering gene expression without altering the structure genetics epigenetics. In the same way, to explain an usefulness of a drug, procaine, a local anesthetic in the demethylation of DNA and the consequent re-expression of tumor suppressor genes and its possible clinical application from the perspective of neural therapy, designed as a therapeutic alternative in that places a non-specific stimulation the patient's body to locate itself self-organize into a state of health. For this, an electronic search of Agora, E-Book, Ovid, Pubmed / Medline, was conducted using this information for analysis. (MÉD.UIS. 2011;24(2):XX-XX).

Key words: Procaine. Cancer. Alternative medicine. DNA methylation.

INTRODUCTION

Cancer is a sickness with multiple presentations, characterized by the uncontrolled and excessive growth of cells that invade and damage tissues and organs, possibly causing the individual's death¹. This represents the second mortality cause in developed countries, where one out of five people dies because

of it. Every year are diagnosed 1.2 million new cases, half of them affecting lung, prostate, mammary glands, colon and rectus ².

Tumor formation process implies the successive accumulation of genetic alterations in one or more cells during a period of time that can last many years, until the growth can become evident. Thus, the neoplastic cells are genetically unstable, acquiring these selection of cells a faster progressive growth, producing an initial unbending proliferation and a subsequent invasive capacity, which usually ends up in metastasis. The fact that all cells from a tumor come from uniquely altered cells, implies that this abnormality of origin is transmitted from the original cell to its descendants. There are two possibilities of heredity of this situation: because of a genetic change in DNA sequence or because an epigenetic change, that is, due to an alteration in the way a gene expresses itself ^{1,3}.

The tumor growth is impulsed by selective mechanisms that limit the regulation of cell proliferation. This is made evident by the genetic inactivity as well as epigenetic inactivity of tumor suppressor genes in neoplastic cells, being this last one frequently observed in most of human cancers, and it has been proven that it is closely related to DNA hypermethylation ^{4,5}.

The function of tumor suppressor genes is to control the cycle of cellular division, as well as to avoid the excessive growth and to promote maintenance of characteristics that specify the location of cells in a determined place. These genes induce the appearance of cancers when mutating and stop expressing or produce a nonfunctional protein ¹. The procaine, a drug used in alternative medicine in the area of neural therapy, can produce DNA demethylation ^{4,5} and can become a therapeutic option in cancer treatment.

The purpose of this review is to show the molecular advances in the epigenetics of cancer and to show how procaine can produce re-expression of tumor suppressor genes in different types of cancer whose epigenetic defects are potentially reversible; offering this way, an option to begin a cancer treatment or cure, or at least, making it a manageable chronic disease.

SEARCH METHODOLOGY

The information presented in this revision was gathered from an extensive search of medical literature based in Agora, E-book, Ovid, and Pubmed/Medline data files up to December 30th, 2010 utilizing the following search key words: procaine ,cancer; epigenetic, with “and” connector. The key words in Spanish were “procaína”, “cáncer”, and “terapia neural”.

English and Spanish texts were included, finding 108 articles, out of which 38 were related with cancer epigenetics and treatment with procaine; this ample information was used to generate the analysis; likewise, the existing material on neural therapy of available books in English and Spanish and the Google search motor, laying stress on articles that explained the epigenetics of cancer and on molecular changes that procaine can bring to effect on its treatment.

EPIGENETICS

It has been established that the mechanisms responsible of the genetic expression precise control, constitute an emergent field known as epigenetics. In general, epigenetic concepts include genome hereditary modification during the cellular divisions that do not imply a change in DNA sequence ⁶.

At the present time, DNA abnormal methylation, histone modification and microRNA's, are only some of the epigenetic regulation processes with effect over the regulated gene expression being studied ^{7,8}. Therefore, we can foresee an incoming period in which cancer has to be understood as a genetic and epigenetic disorder, with the purpose of attaining precocious diagnostics and more specific therapies ⁶.

DNA METHYLATION

DNA methylation is recognized as one of the more important epigenetic processes, synonymous of silencing the genetic expression. Such methylation is produced by adding a methyl group to cytosine, followed by a guanine in the DNA sequence, known as CpG dinucleotide which is concentrated in large groups called CpG islands ^{9,10}. The attachment of a methyl group dinucleotide CpG is responsible of a growing family of enzymes known as DNA Methyltransferers (DNMT)⁸⁻¹¹.

Studies on breast cancer, hepatocellular and gastric cancer, have reported that DNA hypermethylation in tumors are associated to overexpression of DNMT ^{6,12}. It was demonstrated that the DNMT1 is necessary for maintaining the aberrant methylation of the CpG island in human cancer cells, therefore, this enzyme has become one of the possible targets for developing medicaments against cancer ^{13,14}.

HISTONES MODIFICATION

Histones are recognized like DNA packing proteins and dynamic regulators of genetic activity that suffer many modifications after the chemical translation. The state of acetylation and methylation of lysine residuals, included in nucleosome histone tails, fulfill a decisive role regulating chromatin structure and gene expression.

Histone modification, together with DNA methylation, plays a vital role in nuclear architecture organization, which in turn is involved in the transcription regulation and other nuclear processes ⁷. It is evident, that changes in different histone modifications have the potential to affect the structure and integrity of the genome, and altering the normal standard of genetic expression, as well as altering of DNA methylation can be a factor causing cancer ^{6,15,16}.

PHARMACOLOGICAL STRATEGIES IN CANCER EPIGENETICS

Two groups of pharmacological inhibitors of DNMT and histone inhibitors (HDAC) have been studied with special interest. Amongst other effects, both groups of compounds can recuperate the expression of suppressor genes of tumors ⁶.

1. HDAC inhibitors
Butirate, valproic acid, Oxamflatine, pyroxamide, trichostatine A, Apicidine and trapoxine have demonstrated possessing this activity^{6,17,18}.
2. DNMT inhibitors
In this category exist several drugs like: 5-azacitidine, 5-fluor-2'-deoxycitidine, zebularine, hydralazine procainemide and procaine^{6,17,18}.

PROCAINE

The procaine hydrochloride is a local anesthetic that produces a reversible sensitivity due to a diminishing conduction of sensorium nerve impulses close to the place of application¹⁹. It is used mainly with the purpose of suppressing or blocking nociceptive impulses, either along a nerve or nervous trunk or neuronal ganglion, whether the sensorial afference rambles through somatic afferent nerves or vegetative nerves. From time to time, the blocking serves as well to suppress the efferent sympathy activity of vasoconstrictor character.

PHARMACOKINETICS

Procaine is an aminoester discovered by Einhorn that has a liposolubility of 1, relative potency of 1, dissociation constant (pKa) of 8,9, action beginning from 1 to 2 minutes, 6% attachment to proteins, tissue concentration between 1-2%, action duration from 60 to 90 minutes and maximum dose of 1000 mg²⁰. As concerned to biotransformation, procaine is acetylated in the liver and afterwards, at plasmatic level is transformed in para-amino-benzoic and diethyl-amino-ethanol, by means of a pseudo-cholinesterase and because erythrocyte stearases^{21,22}. Procaine is not only used as a drug to block the sodium channels to supply analgesia, anesthesia and antiarrhythmic action, but it has other indications that are supposedly derived from the interaction with other receptors like the N-methyl D-aspartate (NMDA)^{23,24}.

ACTION MECHANISM

Local anesthetics depress the propagation of action potentials in nerve fibers. As a response to nerve depolarization, they block the sodium channels that depend on the voltage of the cell membrane²². These data indicate that the fixation place for local anesthetics is situated in the internal part of the transmembrane region of the channel and that the nonionized form of the anesthetic acts as transporter vehicle to go through the lipidical phase of the neuronal membrane. Besides this, the ionized form is responsible for interacting with the receptor and, therefore, responsible for the pharmacological activity^{20,25}.

NEW INDICATIONS

Studies demonstrate that continuous infusion of local anesthetics procaine type, have positive effects in paralytic

Ileus and constipation^{26,27}, bronchial asthma²⁸, scleroderma²⁹, and headaches caused by scalp fibrositics³⁰. Besides this, they have antibacterial effect by inhibiting growth of different strains in vitro²⁶.

When procaine is administered intravenously to healthy volunteers, it has as a result a brief intense emotion and sensorial emotions associated with the increase of cerebral blood flux in the paralimbic region, measured with positron emission tomography (PET)^{31,32}. Likewise, it also induces the increase of corticotrophin, cortisol and prolactin, as well as a larger and faster activity of the temporal lobe in the encephalogram³¹. There is growing evidence that local anesthetics modulate a wide range of ionic channels different from the sodium channels, since apparently exert their analgesic effect because a modulator effect over the NMDA^{26,33} receptors.

ONCOLOGY PROCAINE STUDIES

The patterns of DNA aberrant methylation, including hypermethylation of tumor suppressor genes, have been described in many human cancers. These epigenetic mutations can be reversed by DNMT inhibitors like procaine, which can provide new opportunities for cancer therapy^{34,35}. To discover inhibitor alternatives of the DNMT, the strategy used is the exploration of established drugs that have already been proven for treatment of non cancerous deceases, like procaine itself.

A great advantage of this approach is that the pharmacodynamic and pharmacokinetic profiles are already known for these compounds^{24,35,36}. Next, it is described the type of cancers on which the procaine action has been investigated.

BREAST CANCER

Procaine is an inhibitor of small molecules, that can reduce the DNA methylation without incorporating itself to their structure. It can link itself to the catalytic site of DNMT enzyme for all sequences rich in CpG, which impede the union between such enzyme and its sequence targets. In human breast cancer, procaine reduces a 40% of 5-methylcytosine in hypermethylated CpG islands and restores the expression of tumor suppressor genes epigenetically silenced⁶; besides this, it has an inhibitory effect on growth, causing mitotic arrest⁵⁻¹¹. A retrospective cohort study have suggested that anesthesia and paravertebral analgesia with local anesthetics in patients with breast cancer surgery, reduced the risk of metastasis recurrence up to 94% in three years³⁷.

HEPATIC CANCER

Investigations in line of human hepatic cancer in naked mice in vitro and in vivo concluded that procaine have reduced the viable number of hepatocytes of cellular lines HuH-7 and HuH-6 in 77,4% and 86% respectively³⁸. Procaine inhibits the cell transition in phases S/G2/M, inducing an increase of population in S phase and reducing population in G2/M. Treatment with this drug led to partial demethylation and to restoring the ARNm expression³⁸.

LUNG CANCER AND NASOPHARINGEAL

Amongst other studies, it has also been demonstrated the DNA demethylation and the effectiveness of procaine in treatment of lung cancer cell lines³⁹, and how growth could be inhibited and perhaps even reactivating the expression of ARNm RASSF1A in nasopharyngeal cancer line cells^{24,40}.

PROCAINE AND OTHER CHEMOTHERAPEUTICS

Using procaine combined with cisplatin, an antineoplastic chemotherapeutic drug, has demonstrated that increases its therapeutic index –of the cisplatin- in several carcinomas, not only improving antitumor activity but decreasing its nephrotoxicity and hemotoxicity^{17,41}. It has also been demonstrated that increases the doxorubicine cytotoxicity and bleomicine in line cells of human melanoma^{42,43}.

The epigenetic re-expression of silenced tumors suppressor genes, is a rational strategy for treating human neoplasias^{17,44}; because of this, it is important the study of local anesthetics in medicine⁴⁵. Procaine is in phase II of clinical tests as DNA demethylant in epigenetic treatment of cancer¹⁸.

PROCAINE AND NEURAL THERAPY

This is a therapy of German and Russian origin. Utilized in alternative medicine and based in the discoveries of the brothers Huneke, that make reference to interferential fields or “distortion fields”; called this way because they provoke variations in the bioelectrical levels of the nerve system, but unavoidably alter the good organic system functioning and a balanced psyche⁴⁶. Besides this, the Speransky AD. explorations whose central thesis is that “stimulus or disturbance of any portion of the peripheral or central nervous system can become the starting point of neural processes that induce organic and functional changes” in any part of the organism⁴⁷. Neural therapy is fundamented in generating a non-specific stimulus in the patient’s organism so he/she will search to self organize towards a health state. The non-specific stimulus offered implies the insertion of a needle and a local anesthetic, procaine^{48,49}.

To neutralize the interferent field with procaine can generate the interruption of a damaging neural impulse generating an improvement of established symptoms⁵⁰.

The first experimental data on the relation of neoplasm and a functional state of the nervous system were presented by Spiess⁴⁹. This author demonstrated that in the case of throat human cancer, the repeated local anesthesia inhibited the tumor growth and, in some cases, it was able to make them disappear^{49,51}. In Huneke’s teaching manual on neural therapy, according to Huneke, Peter Dosh refers to some therapeutic strategies against cancer based on empiricism, having achieved cure possibilities that are not fully explained or justified, regardless to known theoretical and experimental bases⁴⁷. There are many possibilities in segmented and intravenous neural therapy to back up any other therapy anticancer, since only the procaine intravenous injection repeated at intervals, attenuates pain, dilates blood vessels, diminishes fever and inhibits inflammatory processes and improves appetite as well as the patient’s general state⁴⁷.

Any cancer treatment, from a point of view of neural therapy has sense, if the basic vegetative system blocking is broken.

This permits to reactivate firstly the necessary energy flow for organic functions, unblocking interferent fields with procaine and relating it to general measures like detoxification with food free of toxics and sanitization of intestinal flora and odontological, with the bases of neurofocal odontology⁴⁶ and psychic disinterference⁵².

With this outline as base, several reports of cancer treatment and neural therapy are found associating other therapeutic alternatives successfully, like the ones described by Dr. Josef Issels⁵³. And what is more, Dr. Robert Kidd describes in his neural therapy book, the complete cure of patients with prostate cancer, using procaine⁵⁴.

CONCLUSIONS

Procaine reduces DNA methylation in cancerous cells cultures in vitro and in vivo in liver human cancer, breast, nasopharynx and lung, being able to reactivate tumor suppressor genes silenced by hypermethylation. These properties make this anesthetic a drug potentially interesting for oncology studies, like possible antitumor therapy in combination with existing chemotherapeutic agents and in alternative medicine, like neural therapy, not only to improve the tumor initial answer but to surpass the resistance acquired to existing antineoplastic drugs. Here the importance to continue investigating these topics deeply.

Working in alternative medicine does not imply leaving aside conventional medicine but opening new therapeutic processes that renew the possibilities of the patient to live longer.

Currently, doctors of different fields of studies use it as part of their professional activity, but many other, fearing rejection, do not report statistical result in such complex pathologies as cancer. Understanding the epigenetic alterations in cancer will help to develop new therapeutic strategies like procaine in neural therapy or synergy with cytotoxic chemotherapy, carrying emergent processes to the construction of clinical hopes to reach the great objective that cancer can be curable or, at least, can become a manageable chronic disease.

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