Extended Longevity

Scientific White Paper

Bluecosig Formula. Blood signaling and transcription adjustment by increasing Oxytocin and decreasing TGF-β1. Includes phytotherapeutic extracts of: *Caulophyllum thalictroides, Panax quinquefolius, Scutellaria baicalensis, and Curcuma longa*. Biological Actions, Molecular Mechanisms, and Their Effects.

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Bluecosig Formula is designed to support blood signaling and transcription adjustment where aging reversal or rejuvenation via blood signaling to all cells, can be realized. It is a synergistic herbal analog formulation of five (5) plant extracts including ***Caulophyllum thalictroides, Panax quinquefolius, Scutellaria baicalensis, and Curcuma longa*.** This formula is an herbal analog to the underlying research that identified two key determinants as the causal factors for aging in blood signaling: TGF- β1 which activates ALK5/pSmad 2,3 and goes up with age, and oxytocin (OT) which activates MAPK and diminishes with age.

Age-Related Blood Signaling

Herbal analogs of synthetic molecular structures can be utilized in the rejuvenation of multiple old organs. This represents significant progress in reversing human tissue aging. A few morphogenic pathways account for most of the phenotypes of aging. In a process called "heterochronic parabiosis", a young and old animal become surgically connected to share common blood circulation. This shared circulatory system restored tissue health and regeneration of the old partner; and at the same time, the young partner experienced a regenerative decline in several tissues. It has been deduced that this result arises from key signaling networks regulating stem cells. Pathway-based approaches for the enhancement of aged tissue repair have been seen by systemic delivery of OT which induces MAPK/pERK signaling, by forced activation of Notch-1, by antagonism of TGF- β /pSmad signaling, or by antagonism of the Jak/Stat pathway. The translational ramifications of this approach is the attenuation and reversal of multi-tissue attrition and decline of cognitive performance in old mammals, for a number of degenerative and metabolic age-associated diseases. Diminishing TGF- β signaling and adding OT (which activates pERK via the oxytocin receptor (OTR), achieves a broad rejuvenation of the three germ-layer derivative tissues: brain, liver, and muscle. It can be demonstrated that a reversal in several signs of aging across multiple tissues, can occur through the simultaneous modulation of two signaling pathways, one of which becomes elevated with age and the other reduced. This points toward a pharmacological approach to rapidly enhance the health and maintenance of multiple old tissues.

Oxytocin

The oxytocin signaling pathway refers to signaling pathway proteins including oxytocin, oxytocin receptors, and related regulatory factors. Oxytocin is a peptide hormone secreted by the posterior pituitary. Synthesized from the hypothalamic

paraventricular nucleus and supraoptic nucleus, it consists of 9 amino acids. It is transported to the pituitary gland at a rate of 2 mm to 3 mm per day. The physiological role of the oxytocin signaling pathway is mainly to stimulate the breast to secrete milk, promote the contraction of the uterine smooth muscle during childbirth, and promote the role of maternal love. It also can reduce the level of stress hormones such as adrenal ketones in the body to lower blood pressure. Both men and women can secrete it.

The oxytocin signaling pathway initiates a subsequent response by the binding of oxytocin and the receptor. Oxytocin is mainly synthesized in the large cells of the suprachiasmatic nucleus and paraventricular nucleus of the hypothalamus, and a small amount is synthesized in peripheral organs, a dual role of hormones and neurotransmitters. Neurosecretory granules containing oxytocin and pituitary vasopressin are widely distributed in Purkinje fibers and distributed along neurons. Oxytocin is widely distributed in organs such as uterus, ovary, testis, adrenal gland, thymus, and pancreas, and has functions of autocrine and paracrine. The Oxytocin Receptor (OTR) belongs to the type A G-protein coupled receptor (GPCR) family. Because oxytocin has high sequence homology with another neuropeptide (vasopressin, AVP, also known as arginine vasopressin), when studying novel agonists and antagonists of the oxytocin system, vasopressin receptors (ie, V1a receptor and V2 receptor) are usually used as controls for examining whether the affinity of the novel ligand to the oxytocin receptor is significantly stronger than its affinity for the vasopressin receptor.

Oxytocin signaling pathway

Oxytocin promotes uterine contraction through the activation of calcium channels associated with receptors and the release of sarcoplasmic reticulum calcium. Oxytocin binds to the receptor and is mediated by a second messenger, which is regulated by voltage or hormone regulation on the muscle cell membrane and by contractor-mediated extracellular calcium influx. Oxytocin increases the production of inositol 1,4,5-triphosphate, and the mobilization of 5-trisphosphate inositol stores intracellular calcium release in the endoplasmic reticulum and sarcoplasmic reticulum. Oxytocin causes cells to produce inward currents through receptor-activated, non-selective cation channels that depolarize cell membranes, producing action potentials and muscle contractions. Oxytocin increases the activity of mitogen-activated protein kinases through the mediation of G-protein.

Active Herbal Ingredients

Caulophyllum thalictroides, Blue Cohosh is a known oxytocin synergist with a long history of use in traditional herbal medicine. Blue cohosh is a popular herb, roots, and rhizomes which have been extensively used for women's health. Alkaloids and saponins are considered to be responsible for its pharmacological effects. Two glycosides in blue cohosh are believed to stimulate oxytocin. It is said to promote menstrual flow, stimulate circulation, and increase the flow of urine. Pharmacological studies have demonstrated that alkaloids and triterpence saponins are responsible for its major biological function as an anti-inflammatory, analgesic, antioxidant, antibacterial, anti-acetylcholinesterase, and antitumor.

Panax quinquefolius, Panax ginseng root significantly extended life span via modulation of multiple longevity assurance genes, including genes involved in insulin signaling and stress response pathways. Ginseng extract has an anti-fibrosis effect via the regulation of the TGFβ1/Smad signaling pathway in the CCl4 induced liver fibrosis model. Recent studies have demonstrated the inhibition of the expression of TGFβ1, Smad2, and Smad3.

Scutellaria baicalensis, the effect on the TGF-β signaling pathway components has been demonstrated by the SB treatment of cells and resulted in a significant decrease in expression of TGF-β isoforms, TGF-β receptors, and SMADs. It is an analog of the drug Alk5 kinase inhibitor, and can block the growth factor's receptors, stopping it from aging the body's stem cells. It can block the key TGF- β 1 pathway, which is elevated by aging, thereby rejuvenating multiple organ systems. Flavones isolated from the root also exhibit strong neuroprotective effects on the brain. Their neuroprotective potential has been shown in both oxidative stress-induced and amyloid-beta neuronal death models. Baicalein, the main flavone present, strongly inhibited aggregation of neuronal amyloidogenic proteins in vitro and induces dissolution of amyloid deposits. It has been shown to stimulate brain tissue regeneration, inducing differentiation of neuronal precursor cells.

Curcuma longa, or Turmeric root, and its curcuminoid constituents have demonstrated properties consistent with decreases in inflammatory stress signaling and increases in protective signaling. Curcumin is known to have anti-aging, anti-oxidant, anti-inflammatory, anti-arthritic, and anti-cancer effects and increases BDNF, while having a positive effect on Alzheimer's disease and depression. It is also anti-rheumatic, and anti-microbial.

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Research Paper

Rejuvenation of brain, liver and muscle by simultaneous pharmacological modulation of two signaling determinants, that change in opposite directions with age

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ABSTRACT

We hypothesize that altered intensities of a few morphogenic pathways account for most/all the phenotypes of aging. Investigating this has revealed a novel approach to rejuvenate multiple mammalian tissues by defined pharmacology. Specifically, we pursued the simultaneous youthful in vivo calibration of two determinants: TGF-beta which activates ALK5/pSmad 2,3 and goes up with age, and oxytocin (OT) which activates MAPK and diminishes with age. The dose of Alk5 inhibitor (Alk5i) was reduced by 10-fold and the duration of treatment was shortened (to minimize overt skewing of cell-signaling pathways), yet the positive outcomes were broadened, as compared with our previous studies. Alk5i plus OT quickly and robustly enhanced neurogenesis, reduced neuro-inflammation, improved cognitive performance, and rejuvenated livers and muscle in old mice. Interestingly, the combination also diminished the numbers of cells that express the CDK inhibitor and marker of senescence p16 in vivo. Summarily, simultaneously re-normalizing two pathways that change with age in opposite ways (up vs. down) synergistically reverses multiple symptoms of aging.

INTRODUCTION

In heterochronic parabiosis, a young and old animal are surgically connected to share a common blood circulation. Experiments in mice showed this shared circulatory milieu restored tissue health and regeneration of the old partner; and at the same time, the young partner experienced a regenerative decline in a number of tissues [1-5]. In parabiosis, both organs and blood are shared, but further work focusing on exchanging only blood or infusing only plasma further detailed age-related effects on different tissues [6, 7]. However, parabiosis is not clinically translatable and infusion of young blood or plasma into old mammals is controversial and fraught with multiple side-effects [1, 3, 6-10]. Blood fractionation is typically cumbersome, and it is inherently complicated by the fact that the rejuvenative activities are likely to be contained in multiple molecularly different fractions [11]. Plus, the assays for determining such activity are themselves complex, thus adding to the hurdles of a screen for active blood molecules. With these observations to consider, what would be the key set of molecular parameters that were changed by the blood heterochronicity and what would be best translational way forward?

The changes that manifest with aging include altered cell metabolism, increased Reactive Oxygen Species

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Review

Systemic Problems: A perspective on stem cell aging and rejuvenation

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Abstract: This review provides balanced analysis of the advances in systemic regulation of young and old tissue stem cells and suggests strategies for accelerating development of therapies to broadly combat age-related tissue degenerative pathologies. Many highlighted recent reports on systemic tissue rejuvenation combine parabiosis with a "silver bullet" putatively responsible for the positive effects. Attempts to unify these papers reflect the excitement about this experimental approach and add value in reproducing previous work. At the same time, defined molecular approaches, which are "beyond parabiosis" for the rejuvenation of multiple old organs represent progress toward attenuating or even reversing human tissue aging.

Prologue

How long has it been since we knew that age-imposed changes in the circulatory milieu are to blame for the progressive attrition of organs and degenerative disorders that invariably accompany human aging? Some say, we've known for millennia, from the Ancient Greeks and Medieval stories of vampires. Others say that it was McKay's 1950s experiments, where old rats were sutured with young rats to establish parabiosis, aka, a joined blood circulation that suggested better health of largely non-cellular cartilage [2].

Yet, another answer is that it has been 10 years since the paradigm-shifting observations that in heterochronic parabiosis, the young systemic milieu rapidly and broadly rejuvenates organ stem cells in muscle, brain/hippocampus and liver, while the old systemic milieu rapidly and broadly ages myogenesis, liver regeneration and neurogenesis, with the responsible biochemical pathways being re-set to their young or old states ([1], and Figure 1).

What paradigms have been shifted?

Before this work, the prevalent theories of tissue decline in aging focused on cumulative cell intrinsic changes as culprits: telomere attrition, DNA damage, oxidative damage, mitochondrial dysfunction, etc.). While all of the above continue to be true for differentiated cells, it is important to realize that organ stem cells age "extrinsically" [1, 4-7], and maintain a relative "youth" that could be due to the state of quiescence, which is default for most if not all postnatal stem cells [10]. As such, stem cell regenerative capacity persists throughout life, but sadly, the biochemical cues regulating organ stem cells change with age in ways that preclude productive regenerative responses, causing the abandonment of tissue maintenance and repair in the old [3].

Promisingly, numerous studies have demonstrated that experimental youthful re-calibration of specific bio-chemical cues will quickly (within days) rescue the effective regenerative capacity of old stem cells in *vivo*, demonstrating that old stem cells can for all practical purposes maintain old organs [4, 11-14]. Such quick and robust "rejuvenation" also suggests that not much intrinsic "aging" has been experienced by these stem cells, or that the intrinsic aging of stem cells can be rapidly reversed (within 24 hours) after exposure to youthful molecular cues, for example, by activation of Notch [4]. Conversely, progeric changes in these defined bio-chemical signals make even young stem cells behave like old in a day, before the byproducts of

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Heterochronic parabiosis for the study of the effects of aging on stem cells and their niches

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Aging is unmistakable and undeniable in mammals. Interestingly, mice develop cataracts, muscle atrophy, osteoporosis, obesity, diabetes and cognitive deficits after just 2–3 postnatal years, while it takes seven or more decades for the same age-specific phenotypes to develop in humans. Thus, chronological age corresponds differently with biological age in metazoan species and although many theories exist, we do not understand what controls the rate of mammalian aging. One interesting idea is that species-specific rate of aging represents a ratio of tissue attrition to tissue regeneration. Furthermore, current findings suggest that the age-imposed biochemical changes in the niches of tissue stem cells inhibit performance of this regenerative pool, which leads to the decline of tissue maintenance and repair. If true, slowing down stem cell and niche aging, thereby promoting tissue regeneration, could slow down the process of tissue and organismal aging. In this regard, recent studies of heterochronic parabiosis provide important clues as to the mechanisms of stem cell aging and suggest novel strategies for enhancing tissue repair in the old. Here we review current literature on the relationship between the vigor of tissue stem cells and the process of aging, with an emphasis on the rejuvenation of old tissues by the extrinsic modifications of stem cell niches.

Key words: aging, parabiosis, stem cells, niche, muscle

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The Puzzles of Stem Cell Aging

Organ systems are interconnected anatomically and physiologically, perhaps explaining why there is a general concordance of the rate of tissue aging in an individual. An emerging unified theme suggests that the aging of a tissue is generally caused by decline in the regenerative capacity of its resident stem cells. Moreover, recent data suggests that biochemical changes in the niches of tissue stem cells are responsible for such regenerative declines in old mammals. Consequentially, experimental "youthful" modifications of stem cell niches have been shown to boost the regenerative performance of tissue stem cells in the old, leading to healthier tissues. The youthful modifications of stem cell niches have been successfully achieved through heterochronic tissue transplants,[1,2] where old stem cells are exposed to young tissue niches by being transplanted there and through heterochronic parabiosis, where old stem cells are exposed to a youthful environment by virtue of the effects of the young circulation.[3-5] Interestingly, for many tissues (muscle, liver, brain, bone), the regenerative potential of the aged stem cells was determined by the age of the niche or environment rather than by the age of the stem cells themselves, such that young local and/or systemic environments promoted effective regeneration by the old stem cells.[3] The same studies have also shown that aged niches inhibit the regenerative capacity of young stem cells.[4,5]

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Development of TGF-β signalling inhibitors for cancer therapy

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Abstract

The transforming growth factor-β (TGF-β) superfamily of ligands has a pivotal role in the regulation of a wide variety of physiological processes from development to pathogenesis. Since the discovery of the prototypic member, TGF-β, almost 20 years ago, there have been tremendous advances in our understanding of the complex biology of this superfamily. Deregulation of TGF-β has been implicated in the pathogenesis of a variety of diseases, including cancer and fibrosis. Here we present the rationale for evaluating TGF-β signalling inhibitors as cancer therapeutics, the structures of small-molecule inhibitors that are in development and the targeted drug discovery model that is being applied to their development.

Key Points

- When acting as a tumour suppressor, transforming growth factor-β (TGF-β) can potently inhibit the growth of endothelial, epithelial and haematopoietic cells. However, as the tumour evolves, the cells become refractory to TGF-β-mediated growth inhibition and begin to overexpress TGF-β, creating a favourable micro-

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Inhibition of TGF-β signaling by an ALK5 inhibitor protects rats from dimethylnitrosamine-induced liver fibrosis

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1 Chronic liver disease is characterized by an exacerbated accumulation of matrix, causing progressive fibrosis, which may lead to cirrhosis. Transforming growth factor beta (TGF-β), a well-known profibrotic cytokine, transduces its signal through the ALK5 ser/thr kinase receptor, and increases transcription of different genes including PAI-1 and collagens. The identification of GW6604 (2-phenyl-4-(3-pyridin-2-yl-1*H*-pyrazol-4-yl)pyridine), an ALK5 inhibitor, allowed us to evaluate the therapeutic potential of inhibiting TGF-β pathway in different models of liver disease.

2 A cellular assay was used to identify GW6604 as a TGF-β signaling pathway inhibitor. This ALK5 inhibitor was then tested in a model of liver hepatectomy in TGF-β-overexpressing transgenic mice, in an acute model of liver disease and in a chronic model of dimethylnitrosamine (DMN)-induced liver fibrosis.

3 *In vitro*, GW6604 inhibited autophosphorylation of ALK5 with an IC_{50} of 140 nM and in a cellular assay inhibited TGF-β-induced transcription of PAI-1 (IC_{50}: 500 nM). *In vivo*, GW6604 (40 mg kg^{-1} p.o.) increased liver regeneration in TGF-β-overexpressing mice, which had undergone partial hepatectomy. In an acute model of liver disease, GW6604 reduced by 80% the expression of collagen IA1. In a chronic model of DMN-induced fibrosis where DMN was administered for 6 weeks and GW6604 dosed for the last 3 weeks (80 mg kg^{-1} p.o., b.i.d.), mortality was prevented and DMN-induced elevations of mRNA encoding for collagen IA1, IA2, III, TIMP-1 and TGF-β were reduced by 50–75%. Inhibition of matrix genes overexpression was accompanied by reduced matrix deposition and reduction in liver function deterioration, as assessed by bilirubin and liver enzyme levels.

4 Our results suggest that inhibition of ALK5 could be an attractive new approach to treatment of liver fibrotic diseases by both preventing matrix deposition and promoting hepatocyte regeneration.
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Keywords: Hepatectomy; collagen; ALK5; hepatic stellate cells; liver fibrosis; DMN; TGF-β; GW6604

Abbreviations: ALAT, alanine aminotransferase; ALK5, activin-like kinase 5; ASAT, aspartate aminotransferase; BMP, bone morphogenic protein; BrdU, bromodeoxyuridine; COL IA1, collagen IA1; COL IA2, collagen IA2; COL III, collagen III alpha chain; DMN, dimethylnitrosamine; DMSO, dimethylsulfoxide; DTT, dithio threitol; HSC, hepatic stellate cells; LAP, latency-associated peptide; PAI-1, plasminogen activator inhibitor-1; PCNA, proliferating cell nuclear antigen; TGF-β, transforming growth factor beta; TIMP-1, tissue inhibitor of metalloproteinase 1

Introduction

Transforming growth factor beta (TGF-β) is a pleiotropic cytokine involved in a variety of biological processes including development, cell growth, differentiation, cell adhesion, migration, extracellular matrix deposition, and the immune response (Massague *et al*., 2000). Dysregulation of TGF-β production or response has been implicated in pathologies such as atherosclerosis, cancer, and fibrosis (Blobe *et al*., 2000). The role of TGF-β as a potent profibrotic cytokine has been demonstrated in a number of animal models (Border & Noble, 1994; Kopp *et al*., 1996) and overexpression of TGF-β in transgenic mice results in liver and kidney fibrosis (Sanderson *et al*., 1995). In human, elevated TGF-β1 levels can be measured in the serum and urine of patients with hepatitis (Bayer *et al*., 1998) diabetic nephropathy as well as other fibrotic diseases (Broekelmann *et al*., 1991; Border & Noble, 1994; Shah *et al*., 1999). In liver biopsies from patients with chronic liver diseases of various aetiologies, TGF-β expression or mRNA levels are increased and correlate with the extent of fibrosis (Paradis *et al*., 1996; Kanzler *et al*., 2001).

TGF-β has direct and indirect effects on matrix accumulation; it triggers expression of collagen genes and limits matrix degradation by decreasing the expression of stromelysin and

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Research Article

Anti-Inflammatory Effect of Triterpene Saponins Isolated from Blue Cohosh (*Caulophyllum thalictroides*)

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Blue cohosh has been used as a medicinal herb in eastern North America. It was commonly used as traditional medicines for the treatment of menopausal symptoms, rheumatic pain, and as anti-inflammatory remedy. Particularly, extract of blue cohosh roots has been used as anti-inflammatory antipyretic in traditional medicines. In the present study, we investigated the effects of blue cohosh components on the suppressive expression of iNOS or proinflammatory cytokines after the activation of microglia with lipopolysaccharide (LPS). The expression of iNOS, TNF-α, IL-1β, and IL-6 was determined by western blotting or gene expression. Blue cohosh treatment suppressed the elevation of LPS-induced iNOS expression in a concentration-dependent manner in microglia cells. Blue cohosh constituents also suppressed the expression of TNF-α, IL-1β, and IL-6. In addition, blue cohosh extract suppressed the expression of COX-2, iNOS, and proinflammatory cytokines in adrenal glands of mice. These results demonstrate that constituents of blue cohosh exert anti-inflammatory effects through the inhibition of expression of iNOS and proinflammatory cytokines. Therefore, blue cohosh may have therapeutic potential for the treatment of inflammation-related diseases.

1. Introduction

The central nervous system includes two major cell types, neurons and glial cells which contain astrocytes, oligodendrocytes, and microglia [1]. Microglia play an important role as principal immune cells in the infectious, traumatic, inflammatory, ischemic, neurodegenerative, and neuroinflammatory conditions [2–5]. Microglia of the CNS is activated in response to brain injury. In diverse pathological conditions of brain, microglial activation is induced by various inflammatory mediators such as cytokine, neuronal death, and abnormal protein aggregation. While microglial activation is necessary and critical for host defense, overactivation of micoglia is neurotoxic. Thus, microglial activation plays an important role in the progression of neurodegenerative disease such as Alzheimer's disease and Parkinson disease [6].

Lipopolysaccharide (LPS) is representative microglial activators. The inflammatory response of activated microglia appears to be consistent although the nature of the stimuli various. Especially, LPS which is sensed by a toll-like receptor (TLR) had commonly been utilized for induction of inflammatory response [7]. LPS-stimulated microglia is known to release proinflammatory cytokines and oxidants such as TNF-α, IL-6, IL-1β, and nitric oxide [8]. Their activity is neutralized by an anti-inflammatory response that prevents excessive damage to the host. Excessive or deficient production of some cytokines can lead to disproportionate pathology or immune supression [9].

Thus it may be functionally important to tightly regulate that the degree of microglial activation could be a good therapeutic target to resist neurodegenerative disease. For the last decade, efforts have been made to develop anti-inflammatory agents that are able to inhibit microglial activation. However, the long-term administration of anti-inflammatory drugs is limited due to the side effects. Therefore, novel anti-inflammatory agents with fewer side effects are needed.

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Review Article

Genus *Caulophyllum*: An Overview of Chemistry and Bioactivity

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Recently, some promising advances have been achieved in understanding the chemistry, pharmacology, and action mechanisms of constituents from genus *Caulophyllum*. Despite this, there is to date no systematic review of those of genus *Caulophyllum*. This review covers naturally occurring alkaloids and saponins and those resulting from synthetic novel taspine derivatives. The paper further discussed several aspects of this genus, including pharmacological properties, mechanisms of action, pharmacokinetics, and cell membrane chromatography for activity screening. The aim of this paper is to provide a point of reference for pharmaceutical researchers to develop new drugs from constituents of *Caulophyllum* plants.

1. Introduction

Caulophyllum is a small genus of perennial herbs in the family Berberidaceae. The genus *Caulophyllum* is well known for its diversity and pharmacological uses in traditional medicine system since ancient times. All species in this genus are very similar [1]. *C. robustum* is native to eastern Asia, especially in China, while *C. thalictroides* and *C. giganteum* are native to eastern North America. It is worth noting that nearly all phytochemical and pharmacological studies on this genus are focused on *C. thalictroides* and *C. robustum* due to their important medical functions [2].

The roots and rhizomes of *C. thalictroides* (L.) Michx. (blue cohosh) have been used traditionally by Native Americans for medicinal purposes [3]. The primary function of blue cohosh in many native communities of North America was to induce childbirth, ease the pain of labor, rectify delayed or irregular menstruation, and alleviate heavy bleeding and pain during menstruation [4]. Between 1882 and 1905, blue cohosh was listed in the United States Pharmacopoeia as a labor inducer [5] and sold as an herbal supplement that can aid in childbirth. Dietary supplements of blue cohosh are readily available throughout the USA over-the-counter and from Internet suppliers [6]. There is considerable concern about the safety of blue cohosh with reports of new born babies having heart attacks or strokes after the maternal consumption of blue cohosh to induce labor [7–9]. There is a heated discussion about using blue cohosh as dietary supplements for women [2].

C. robustum Maxim is well-known in *Hong Mao Qi* in Chinese, which grows widely throughout north-east, north-west, and south-west China. Its roots and rhizomes have been used as folk medicine to treat external injuries, irregular-menses, and stomach-ache due to its strong and wide biological activities [10]. Modern pharmacological studies have demonstrated that alkaloids and triterpence saponins are responsible for its major biological function as an anti-inflammatory [11], analgesic [12], antioxidant [13], antibacterial [11], antiacetylcholinesterase [14], and antitumor [15, 16]. Taspine, a lead compound in anticancer agent development [17, 18], was firstly screened to possess obvious effect on tumor angiogenesis and human epidermal growth factor receptor by using cell membrane chromatography from the *C. robustum* [19].

So it is very necessary to deeply explore *Caulophyllum* plants. In the past decades, some promising advances have been achieved in understanding the chemistry, pharmacology, and action mechanisms of constituents from genus

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Review Article

The Oxytocin-Oxytocin Receptor System and Its Antagonists as Tocolytic Agents

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Oxytocin, a hormone involved in numerous physiologic processes, plays a central role in the mechanisms of parturition and lactation. It acts through its receptor, which belongs to the G-protein-coupled receptor superfamily, while Gq/phospholipase C (PLC)/inositol 1,4,5-triphosphate (InsP3) is the main pathway via which it exerts its action in the myometrium. Changes in receptor levels, receptor desensitization, and locally produced oxytocin are factors that influence the effect of oxytocin on uterine contractility in labor. Activation of oxytocin receptor causes myometrial contractions by increasing intracellular Ca^{+2} and production of prostaglandins. Since oxytocin induces contractions, the inhibition of its action has been a target in the management of preterm labor. Atosiban is today the only oxytocin receptor antagonist that is available as a tocolytic. However, the quest for oxytocin receptor antagonists with a better pharmacological profile has led to the synthesis of peptide and nonpeptide molecules such as barusiban, retosiban, L-368,899, and SSR-126768A. Many of these oxytocin receptor antagonists are used only as pharmacological tools, while others have tocolytic action. In this paper, we summarize the action of oxytocin and its receptor and we present an overview of the clinical and experimental data of oxytocin antagonists and their tocolytic action.

1. Introduction

Oxytocin (OT) is a nonapeptide synthesized by the magnocellular neurons located in the supraoptic and paraventricular nuclei of the hypothalamus and secreted to the circulation by the posterior pituitary and nerve terminals in response to various stimuli. The sequence of amino acids in the OT molecule is Cysteine-Tyrosine-Isoleucine-Glutamine-Asparagine-Cysteine-Proline-Leucine-Glycinamide, with a sulfur bridge between the two cysteines. OT and vasopressin have similar structures and differ only in two amino acids. Oxytocin is also synthesized in many peripheral tissues, for example, uterus, placenta, amnion, corpus luteum, testis, and heart [1].

Oxytocin exerts a variety of actions and is involved in a large number of physiological and pathological processes. These actions include the regulation of the hypothalamo-pituitary-adrenal axis in response to stress, pregnancy, luteal function, maternal behavior, cell proliferation, modulation of emotional relationships and sexual behavior, erectile function and ejaculation, antinociception, cardiovascular function, osteoporosis, and neuropsychiatric disorders [2–6]. However, its best-known and most well-established roles are stimulation of uterine contractions during parturition and milk release during lactation. In 1906, Sir Henry Dale found that an extract from the human posterior pituitary gland had a uterotonic effect, and Vincent du Vigneaud et al. achieved synthesis of oxytocin in 1953 [7]. Since oxytocin contributes to myometrial contractility, its receptor has been a target for tocolytic agents. While atosiban is an oxytocin receptor (OTR) antagonist used for the management of preterm labor [8], research is ongoing for the tocolytic properties of various other OTR antagonists.

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Effect of ginseng extract on the TGF-β1 signaling pathway in CCl_4-induced liver fibrosis in rats

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Abstract

Background: Liver diseases are major global health problems. Ginseng extract has antioxidant, immune-modulatory and anti-inflammatory activities. This study investigated the effect of ginseng extract on carbon tetrachloride (CCl4)-induced liver fibrosis in rats.

Methods: Male Wistar rats were divided into four groups: control group, ginseng group, CCl_4 group and CCl_4 + ginseng group. Liver injury was induced by the intraperitoneal (I.P) injection of 3 ml/kg CCl_4 (30% in olive oil) weekly for 8 weeks. The control group was I.P injected with olive oil. The expression of genes encoding transforming growth factor beta (*TGF-β*), type I TGF-β receptor (*TβR-I*), type II TGF-β receptor (*TβR-II*), mothers against decapentaplegic homolog 2 (*Smad2*), *Smad3*, *Smad4*, matrix metalloproteinase 2 (*MMP2*), *MMP9*, tissue inhibitor matrix metalloproteinase-1 (*TIMP-1*), Collagen 1a2 (*Col1a2*), Collagen 3a1 (*Col3a1*), interleukin-8 (*IL-8*) and interleukin -10 (*IL-10)* were measured by real-time PCR.

Results: Treatment with ginseng extract decreased hepatic fat deposition and lowered hepatic reticular fiber accumulation compared with the CCl_4 group. The CCl_4 group showed a significant increase in hepatotoxicity biomarkers and up-regulation of the expression of genes encoding *TGF-β, TβR-I, TβR-II, MMP2, MMP9, Smad-2,-3, -4, and IL-8* compared with the control group. However, CCl_4 administration resulted in the significant down-regulation of IL-10 mRNA expression compared with the control group. Interestingly, ginseng extract supplementation completely reversed the biochemical markers of hepatotoxicity and the gene expression alterations induced by CCl_4.

Conclusion: ginseng extract had an anti-fibrosis effect via the regulation of the TGF-β1/Smad signaling pathway in the CCl_4-induced liver fibrosis model. The major target was the inhibition of the expression of *TGF-β1, Smad2,* and *Smad3*.

Keywords: Ginseng extract, Carbon tetrachloride, Gene expression, Real time PCR

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Inhibition of Transforming Growth Factor-β (TGF-β) Signaling by Scutellaria baicalensis and Fritillaria cirrhosa Extracts in Endometrial Cancer.

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Abstract

Transforming growth factor-β (TGF-β), regulates cell proliferation, angiogenesis, metastasis, and is an inducer of epithelial-mesenchymal transition (EMT). Cancer cells exhibit activated TGF-β/SMAD signaling pathway and its inhibition is an attractive strategy for cancer treatment. The Chinese Herbs **Scutellaria baicalensis** (SB) and Fritillaria cirrhosa (FC) have been shown to be beneficial to cancer patients, but the mechanisms by which the extracts of two herbs elicit the beneficial effects are unclear. In this study, we have used human endometrial cancer cells to assess the anticancer efficacy of SB and FC on TGF-β signaling pathway components. SB and FC treatment of cancer cells resulted in a significant decrease in expression of TGF-β isoforms, TGF-β receptors, and SMADs. Both herbs effectively inhibited basal and TGF-β1-induced cancer cell proliferation and invasion, which was accompanied with abrogation of Snail, Slug, matrix metalloproteinases (MMPs), αvβ3 integrin, focal adhesion kinase (FAK), and p-FAK expression. An inhibitor of TGF-βRI blocked TGF-β1-induced cell invasion and significantly diminished antitumor effects of SB and FC. These results suggest that SB and FC block endometrial cancer growth by downregulating TGF-β/SMAD signaling pathway.

KEYWORDS: EMT; invasion; metastasis; natural products; proliferation

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Review

The Role of Curcumin in the Modulation of Ageing

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Abstract: It is believed that postponing ageing is more effective and less expensive than the treatment of particular age-related diseases. Compounds which could delay symptoms of ageing, especially natural products present in a daily diet, are intensively studied. One of them is curcumin. It causes the elongation of the lifespan of model organisms, alleviates ageing symptoms and postpones the progression of age-related diseases in which cellular senescence is directly involved. It has been demonstrated that the elimination of senescent cells significantly improves the quality of life of mice. There is a continuous search for compounds, named senolytic drugs, that selectively eliminate senescent cells from organisms. In this paper, we endeavor to review the current knowledge about the anti-ageing role of curcumin and discuss its senolytic potential.

Keywords: ageing; anti-cancer; autophagy; microbiota; senescence; senolytics

1. Introduction

Demographic data unquestionably show that the population of elderly and very elderly people is continuously increasing. The population of people aged 65 and above represents 8.7% of the total population. However, this percentage differs between continents and is around 15–16% in North America, Europe and Central Asia, but only about 5% in the Middle East, North Africa and South Asia [1]. The increase of lifespan is not really satisfactory without an improvement of healthspan. We would like to live longer, but in good health, which is necessary to enjoy the world around us. Actually, there is a great deal of evidence that the ageing process is malleable and the rate and quality of ageing can be modulated [2]. In order to be able to postpone ageing, it is urgent to reveal the mechanisms of ageing.

It is commonly accepted that cellular senescence plays a very important role in organismal ageing and age-related diseases [3]. Namely, it has been observed that senescent cells accumulate in the tissues and organs of old animals and humans, and that proliferation potential differs among cells derived from individuals of different age [4–8]. Even though the actual number of senescent cells seems not to be very high and fluctuates between a few and a dozen percent, changes in the extracellular milieu caused by the increased production of cytokines by senescent cells, and the senescence-associated impairment of regenerative processes, can lead to spectacular organismal dysfunctions. Moreover, senescent cells contribute to the onset and progression of diseases, the frequency of which increases with age. The accumulation of senescent cells has been observed in the course of almost all age-related disorders [9]. Breakthrough experiments, which have definitely proved the involvement of cell senescence in the progression of ageing and age-related diseases, came from animal studies. It has been clearly shown that the elimination of senescent cells alleviated the symptoms of ageing and age-related

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