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Review

Tranilast: A review of its therapeutic applications

Sara Darakhshan, Ali Bidmeshki Pour*

Department of Biology, Faculty of Science, Razi University, Kermanshah, Iran

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ABSTRACT

Tranilast (N-[3′,4′-dimethoxycinnamoyl]-anthranilic acid) is an analog of a tryptophan metabolite. Initially, tranilast was identified as an anti-allergic agent, and used in the treatment of inflammatory diseases, such as bronchial asthma, atypical dermatitis, allergic conjunctivitis, keloids and hypertrophic scars. Subsequently, the results showed that it could be also effective in the management of a wide range of conditions. The beneficial effects of tranilast have also been seen in a variety of disease states, such as fibrosis, proliferative disorders, cancer, cardiovascular problems, autoimmune disorders, ocular diseases, diabetes and renal diseases. Moreover, several trials have shown that it has very low adverse effects and it is generally well tolerated by patients. In this review, we have attempted to accurately summarize previously published studies relating to the use of tranilast for a range of disorders and discuss the drug's possible mode of action. The major mode of the drug's efficacy appears to be the suppression of the expression and/or action of the TGF-β pathway, but the drug affects other factors as well. The findings presented in this review demonstrate the potential of tranilast for the control of a vast array of pathological situations, furthermore, it is a prescribed drug without severe side effects.

Contents

Abbreviations: ARH, aryl hydrocarbon receptor; bFGF, basic fibroblast growth factor; cAMP, cyclic AMP; CDK, cyclin-dependent kinase; COX-2, cyclooxygenase-2; CTGF, connective tissue growth factor; CXCL, CX chemokine ligand; CXCR, CX chemokine receptor; EMT, epithelial-to-mesenchymal transition; ER, estrogen receptor; ERK2, extracellular signal-regulated kinase 2; GPX1, glutathione peroxidase 1; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; INF-γ, interferon-gamma; iNOS, inducible NO synthase; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; mRNA, messenger RNA; MRTF, myocardin-related transcription factor; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-kappa B; NO, nitric oxide; PARP, poly ADP-ribose polymerase; PCNA, proliferative cell nuclear antigen; PDGF, platelet-derived growth factor; PR, progesterone receptor; PTCA, percutaneous transluminal coronary angioplasty; Rb, retinoblastoma; ROS, reactive oxygen species; SCF, stem cell factor; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; Txnip, thioredoxin-interacting protein; TRPV2, transient receptor potential cation channel vanilloid 2; UGT1A1, UDP-glucuronysltransferase 1A1; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor.

* Corresponding author. Tel.: +98 8314274545; fax: +98 8314274545.
E-mail address: abidmeshki@razi.ac.ir (A.B. Pour).

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Introduction

Tranilast, N-(3′,4′-dimethoxycinnamoyl) anthranilic acid (N-5′), was first reported by Koda et al. to have an inhibitory effect on homologous passive cutaneous anaphylaxis when administered orally [1]. Azuma et al. [2] have suggested that the suppressive effect of the drug on homologous passive cutaneous anaphylaxis was mainly due to its inhibitory influence on the release of the chemical mediator histamine, which is induced by IgE antibodies from mast cells. Subsequently, tranilast showed promising results in the control of bronchial asthma in children [3]. Suggestions for its use in keloid and hypertrophic scar treatment were added in the late 1980s [4]. In 1987, investigators found that it inhibited the proliferation of fibroblasts *in vitro* and that it selectively suppressed collagen deposition *in vivo* [4]. Since then, tranilast has been viewed as a novel anti-proliferative drug. Following studies on tranilast have tended to focus on its effects on the functioning of fibroblasts rather than mast cells, and new applications for proliferative diseases, especially against hypertrophic scars and keloids, have been investigated [5]. The drug is licensed for use in allergic disorders such as bronchial asthma in Japan and South Korea since 1982 [6]. Henceforth, tranilast is used to treat various medical conditions and other pharmacological actions have been demonstrated, and these are referred to in this review.

Pharmacological properties

Tranilast is a derivative of the amino acid tryptophan [7]. It is a synthetic structural and functional analog of anthranilic acid that was developed by Kissei Pharmaceuticals (Japan), and it has been marketed for use in Japan and South Korea since 1982 for bronchial asthma (under the brand name Rizaben) [6]. The committee on Drugs of Japan's central Pharmaceutical Affairs Council has approved the use of this drug [5].

Tranilast is generally administered orally. Because the solubility of tranilast in water is very low, it is dissolved with the aid of a surface-active agent; in such a solution, tranilast has been widely used in the ophthalmic field as RIZABEN eye drops 0.5% solution [8], and provides effective therapy for ocular inflammation. Ophthalmic solutions of 0.5% tranilast act directly at the lesion position and there is no serious side effect by using eye drops [8].

The level of tranilast in the plasma reaches its peak within 30 min after a single oral administration in both mice and rats [9]. In humans, tranilast levels in the plasma reaches a peak 2 h after a single oral administration, and it has a half-life of 5 h [10]. After oral administration of the usual therapeutic dose of tranilast (600 mg/day), plasma concentration reaches 30–300 μM [11]. Tranilast is a relatively safe drug and several years of clinical use have established that it is well accepted by most patients, at doses of up to 600 mg/day over a period of months [5].

The pure compound is a crystalline solid or powder with a light yellow color. It is easily soluble in dimethylsulfoxide, soluble in dioxane, very slightly soluble in ether, and nearly insoluble in water. Since it exhibits poor solubility behavior in water (14.5 μg/ml), particularly in acidic conditions (0.7 μg/ml in buffer solution of pH = 1.2) [12], the daily dose of the drug is relatively high (300 mg/day). On the other hand, tranilast is photochemically unstable, because it has a cinnamoyl group in its structure [13], and although tranilast is stable in the solid state, it is photochemically unstable in the solution state under light exposure [14]. Significant