β- adrenergic agonists: substances with anabolic effect in animals for meat production

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review

Summary

The paper reviews the literature data on the β-adrenergic agonists as a group of substances with anabolic effect in animals. The chemical structures of individual compounds are displayed as their basic properties, mechanism of action, physiological effects and adverse effects in humans and animals caused by exposure to anabolic doses of these substances. β- agonists in the body achieve the effect by binding to specific β-adrenergic receptors located on cell membranes of target tissues. Their use in anabolic dose in animals results in a significant increase in muscle mass and a decrease in body fat mass, better utilization of food, increased growth of animals and improved organoleptic properties of meat produced. In the last two decades, in some countries of the European Union, β-agonists were illegally used during the fattening of animals, with the aim to achieve significant yield in meat production and higher economic profit. A misuse of the clenbuterol as the most important representative has caused adverse effects on human and animal health. In the European Union, as well as in Croatia, the use of these substances with anabolic purposes in animals for meat production is prohibited, and the control of abuse is carried out through national residue monitoring.

Keywords: *β-adrenergic agonists, anabolic effects, animals for meat production*

Introduction

β- adrenergic agonists (β-agonists) are chemical substances that have already been used for more than 30 years in human and veterinary medicine in the treatment of chronic bronchitis, chronic obstructive pulmonary disease and asthma, as well as tocolitics in animals (Anderson et al. 2005; Barnes, 1999). Also, these substances are growth promoters in many animal species for meat production, and the effect in the body generates binding to specific β-adrenergic receptors located on cell membranes of target tissue (Mersmann, 1989; Mersmann, 1998).

The application of β-agonists in anabolic dose in animals results in a significant increase in lean body mass and a significant decrease in the amount of body fat, better utilization of food and increased growth of animals (Van Der Wal and Berende, 1983, Meyer and Karg, 1989; Meyer, 2001; Anderson et al., 2005). The application of these substances in livestock meat results in better sensory properties, with smaller portions of fat and greater proportion of muscle tissue (Bergen et al. 1987; Crome et al., 1996, Armstrong et al., 2004), which is therefore acceptable to consumers. These findings had significant negative implications for human health in the past because these substances, although toxic, were misused in the livestock industry, i.e. were applied on animals for meat production.

Since 1984 to date numerous studies of anabolic effect of β-agonists in animals of high economic interest, such as poultry, pigs, sheep and cattle have been conducted (Meyer et al., 1995, Ramos et al., 2000). The group of β-adrenergic agonists represents dozens of compounds, among which in the recent period clenbuterol has been the most studied β_2-adrenergic agonist as a long-acting substance and the main representative of this group of substances. Data show the occurrence of many short-acting substances at the market, such as salbutamol, ractopamine, cimaterol, zilpaterol, terbutaline, mabuterol and other

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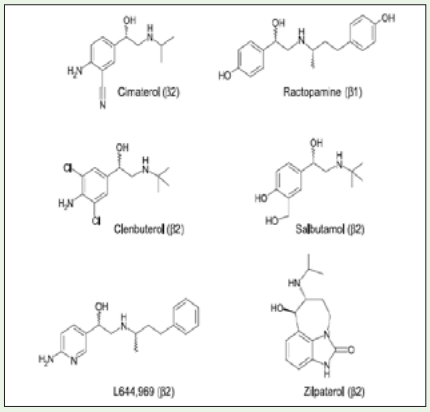

Figure 1.**Structure of several phenethanolamines β-adrenergic agonists**

β-agonists, and the achievement of increasing the share of meat protein and reducing fat content for about 40% (Courtheyn et al., 2002). However, the use of β-agonists in animals results in accumulation of residues of pharmacologically active substances in the tissues, which methods of thermal processing of meat cannot inactivate or remove (Rose et al., 1995). If such products are consumed by people, they can cause alimentary intoxication and serious consequences for human health. Illegal use of clenbuterol led to numerous cases of poisoning people who consume the meat of treated animals (Martinez-Navarro, 1990; Pulci et al. 1991; Woodward, 2005). Therefore, its use, as well as the use of all substances from the group of β-agonists, is banned in the European Union and the Republic of Croatia.

The opinions of scientists, and prescribed legislation in some countries of the world differ significantly in terms of justification for the application of certain β-agonists (ractopamine, zilpaterol) on animals for meat production in order to achieve better utilization of food and sensory characteristics of meat, as well as the possible adverse consequences may result from use of these substances.

Physicochemical properties

β-adrenergic agonists are derivatives of catecholamines, hormones epinephrine and norepinephrine, whose structure is characterized by a six-membered aromatic ring, hydroxyl group linked to the β-carbon positively charged nitrogen in the etilamine side chain and a substituent on the aliphatic nitrogen, which corresponds to the specific individual β-receptor (Smith, 1998). This structure is common to all phenethanolamines β-adrenergic agonists (Figure 1), with the exception of large groups on the aliphatic nitrogen, a common and natural adrenergic neurotransmitters, adrenaline and noradrenaline.

β-agonists are orally active compounds that can be added to food intended for animal feed. Among the β-adrenergic agonists, the most important is the group of β_2-adrenergic agonists. Biological activity of β_2-adrenergic agonists is attributed to the six-membered aromatic ring, which may be substituted with hydroxy groups, halogens, amines, hydroxymethyl groups, cyano groups, or their different combinations. At the same time, the chemical substitution (especially halogen) related to the aromatic ring significantly affects the excretion half-time extension of β_2-adrenergic agonists in mammals as well as their affinity for binding to the receptor (Smith, 1998).

Available commercial salts of β-agonists are generally insoluble in nonpolar solvents such as methylene chloride, ethyl acetate and ether, and soluble in water, methanol, ethanol and chloroform (Turberg et al., 1995). Standard materials are usually white or slightly yellowish in color, stable in boiling water (at 100 °C) and oil (at 260 °C). Research of the impact of cooking, baking, frying and microwave preparation of, for example, clenbuterol residues showed that there were no significant changes in concentration of residues of these substances, except under extreme processing conditions (Chan, 1999). β- agonists appear on the market under various trade names such as Spiropent / Ventipulmin (clenbuterol), Paylean (ractopamine) Zilpamex (zilpaterol).

β- adrenergic receptors

There are two main types of adrenergic receptors, α-and β-adrenergic receptors. They are divided further into three types: α_1-adrenergic receptors, α_2-adrenergic receptors and β-adrenergic receptors (Badino et al., 2005). β- adrenergic receptors in mammals include three receptor

subtypes (β_1-, β_2-and β_3-adrenergic receptors), which are present in all tissues related to growth, including skeletal muscle and adipose tissue (McNeel and Mersmann, 1999) (Figure 2). Recent studies indicate the possible presence of the β_4-adrenergic receptors in some parts of the cardiovascular system and adipose tissue (Badino et al., 2005).

Representation of individual receptor subtypes is different in each tissue or organ and is dependent on the type of animals, and certain tissue has primarily represented one subtype of β-adrenergic receptor (Mersmann, 1998; Mersmann, 2002). In the pigs, β_1-and β_2-adrenergic receptors are present in different proportions in the left chamber, the lungs, liver, muscle and subcutaneous adipose tissue, and β_3-adrenergic receptors in the left chamber, the lungs, subcutaneous adipose tissue, but not in muscle (McNeel and Mersmann, 1999).

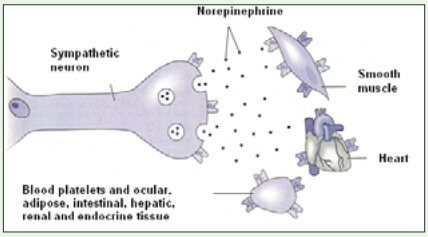

Figure 2 **Primary tissue locations of α-adrenergic and β-adrenergic receptors (Brenner, 2000)**

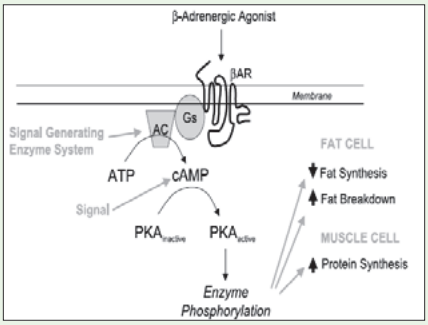

Figure 3 **The mechanism of converting the signal from the β-adrenergic receptor (βAR) (Moody et al., 2000)**

Mechanism of action

β_2- adrenergic agonists, whether the are synthetic (clenbuterol) or natural (adrenaline), act in the body through a series of biochemical reactions induced by binding of these substances for specific β_2-adrenergic receptors located on cell membranes in the tissues of mammals (Boyd et al., 1996; Beermann, 2002).

Direct binding of β-agonists for β-adrenergic receptors located on cell membranes, within cells results with biochemical signal that starts a series of reactions (Figure 3.). That leads to activation of Gs proteins and activation of adenylate cyclase (AC). Activated adenylate cyclase catalyzes the synthesis of cyclic 3.5-adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). cAMP is one of the major intracellular signaling molecules, which causes the breakdown of glycogen and increased plasma glucose concentrations (Anderson et al., 2005). cAMP stimulates the activity of protein kinase A, binding to its regulatory subunit, which then phosphorylates various intracellular proteins. Some of these proteins are enzymes that are activated by phosphorylation, for example glycogen phosphorylase and hormone-sensitive lipase, which results in an increased degradation of fat or lipolysis (Moody et al., 2000; Meyer, 2001), whereas phosphorylation causes the inactivation of some enzymes, such as glycogen synthetase.

CREB (cAMP response element binding protein) protein is a phosphorylated protein kinase A. This protein binds to cAMP in the regulatory part of gene and stimulates transcription of genes. Phosphorylation increases the transcriptional activity of CREB and providing a mechanism for the β-adrenergic receptor agonist-mediated transcription of many genes in mammalian cells (Mersmann, 1998). β-agonist stimulation of adenylate- cyclase increases the concentration of cAMP and thus lipolytic effect. Influenced by a cAMP- activated, protein kinase through phosphorylation translates triacil glycerol lipase in an active form. Reaction product, diacylglycerol, other lipases cleave to the end to glycerol and fatty acids, which enter the bloodstream (Karlson, 1993).

Physiological effects in animals

In veterinary medicine, β-agonists have an important use for therapeutic purposes as bronchodilators and tocolitics agents. However, a long- term use of β_2-adrenergic agonists can cause desensitization caused by the decrease in receptor number (Re et al. 1997; Stoffel and Meyer, 1993; Luthman and Jacobsson, 1993; Badino et al., 2005). Because of their relaxing effect on muscles, β_2-adrenergic agonists are used in human medicine in the treatment of chronic bronchitis, chronic obstructive lung disease, as well as antiasthmatics, as they relax the airways, expand them and make it easier to breathe (Anderson et al. 2005; Barnes, 1999).

Stimulation of β_1-adrenergic receptor has the effect on accelerated heart rate, lipolysis and renin secretion. The activation of β_2-adrenergic receptors leads to relaxation of smooth muscle bronchi, uterus, bowel and bladder wall and vasodilation, glycogenolysis in skeletal muscle and thermogenesis, whereas stimulation of β_3-adrenergic receptor leads to thermogenesis in brown adipose tissue and lipolysis (Young and Landsberg, 1998).

Oral treatment of β-agonists in cattle, pigs and sheep, resulting in the increased muscle mass of animals, the increase in muscle protein synthesis and reduction of their degradation, as well as their combination. Furthermore, by stimulating the degradation of triacylglycerol in adipocytes, and by inhibition of their synthesis and synthesis of fatty acids, they reduce the amount of adipose tissue in the body (Miller et al., 1988, Mersmann, 2002, Anderson et al., 2005) (Figure 4.).

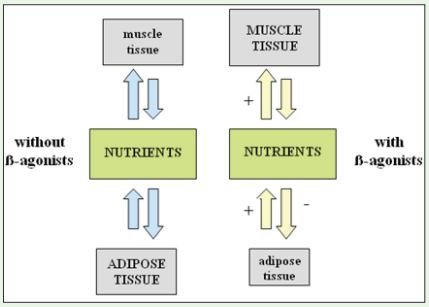

Figure 4 **Effects of β-agonists in muscle and adipose tissue of animals for meat production (Anderson et al., 2005)**

Table 1 **Parameters that influence the anabolic efficiency of β-adrenergic agonists in animals for meat production (Moody et al., 2000)**

Parameter	Requirement	Compounds studied	Species studied
Dietary protein	Greater response with higher dietary protein	Clenbuterol BRL47672 Ractopamine	Pigs, broilers
Duration of treatment	Greater response during final finishing phase	Cimaterol Clenbuterol BRL47672 Ractopamine	Pigs, cattle, sheep
Dosage	Differential effect on growth and leanness	Ractopamine	Pigs
Age or weight	Greater response with older, heavier animals	Cimaterol Ractopamine	Pigs, cattle
Genetics	Effective in both fat and lean genetics	Cimaterol Ractopamine	Pigs

The application of β_2-adrenergic agonists by stimulating protein synthesis (inhibition of proteolysis) and degradation of fat (lipolysis) can result in an increased amount of proteins and reduced amount of adipose tissue for more than 40% (Courtheyn et al., 2002). The research results of clenbuterol treatment on lambs showed increased protein synthesis by about 40%, as well as the reduced accumulation of fats by about 30% (MacRae et al., 1988). Literature data show a significant increase in lipolysis during treatment of animals for meat production induced by β_2-adrenergic agonist (Merkel et al., 1987). Also, β_2-adrenergic agonists cause hypertrophy of muscle, mainly by reducing the degradation of proteins, more than stimulation of the synthesis, and nitrogen retention (Beermann et al., 1987, Anderson et al., 1989). Parameters that influence on the result of treatment of animals for meat production are listed in Table 1.

Earlier studies indicate that anabolic treatment with certain β-agonist has the effect on changes in metabolic and endocrine systems, causing significant changes in the levels of certain parameters (Zimmerli and Blum, 1990). Their

use appears to increase the peripheral blood flow, changes in arteriovenous concentrations of substrate and its influence on the release of insulin, growth hormone, thyroid hormones and corticosteroids (Yang and McElligott, 1989; Peters, 1989). In the treatment of calves it was observed that clenbuterol causes an increase in the concentration of glucose, insulin and free fatty acids (Luthman and Jacobsson, 1993; Meyer, 2001). Anabolic sub-chronic clenbuterol treatment of pigs resulted in the significant increase in activity of specific liver enzyme alanine aminotransferase (ALT) and alkaline phosphatase (ALP) as indicators of hepatic dysfunction (Gojmerac et al., 2002).

Toxic effects

The investigations, as well as numerous cases of intoxication in humans, suggest that the use of highly active β_2-adrenergic agonists as growth promoters in cattle presents a potential risk to human and animal health (Kuiper et al., 1998). β- agonist clenbuterol, as the most toxic substance from the group of β-agonists, was the subject of considerable controversy at the beginning of the 1990s when its illegal use was associated with cases of acute poisoning in Europe.

Chronic treatment of animals with clenbuterol caused changes in metabolic activity (Zimmerli and Blum, 1990), changes in the respiratory system (dilatation of the trachea), depletion of glycogen (Biolatti et al., 1994), vacuolar degeneration of the prostate, reduced testicular growth and proliferation, and changes in weight and size of the thymus and thyroid glands (Groot et al., 1998). There are reports on degenerative changes of urethral and glandular epithelium of prostate, epithelial vacuolization of epithelium and necrosis with pycnosis of the liver and fragmentation, changes in the secretion of estradiol and progesterone (Illera et al., 2003a; Illera et al., 2003b), an increased number of mitochondria, smooth endoplasmic reticulum, Golgi apparatus and lipid droplets, as well as the reduced size of the nucleus (Blanco et al., 2002, Blanco et al., 2003).

Table 2 **Cases of human poisoning after consummation of clenbuterol contaminated meat (Pleadin and Perši, 2009)**

Country, year	Number of poisoned	The source of contamination	References
Spain, 1990.	135	beef liver	Martinez-Navarro, 1990.
France, 1990.	22	veal liver	Pulce et al., 1991.
Spain, 1992.	232	veal liver	Garay et al., 1997.
Italy, 1996.	62	beef meat	Brambilla et al., 1997.
Portugal, 1996.	-	veal liver	Ramos et al., 2003.
China, 2003.	39	pork meat	Woodward, 2005.

Several European countries reported cases of acute alimentary intoxications in humans who consumed meat or liver contaminated with clenbuterol (Table 2.). Research has shown that clenbuterol in humans causes rapid heartbeat, tremor, nervousness, general weakness, dizziness and headache (Martinez-Navarro, 1990, Paige et al., 1997, Kuiper et al., 1998).

Clenbuterol was initially developed as a long-acting β_2-adrenergic agonist for the treatment of respiratory diseases and other diseases, and later generations of β-agonists have been developed with structural differences that result in shorter elimination half-life, i.e. shorter activity, and low oral action potential in animals for meat production (Anderson et al., 2005).

The application for therapeutic purposes and control of abuse

The fact that treatment of β_2-adrenergic agonists in animals intended for meat production results in improved feed efficiency, increased growth of animals and better redistribution of muscle and adipose tissue relationship, has led to many abuses of these substances in animal production (Smith and Paulson 1997; Brambilla et al., 2000; Dunshea et al., 2005). Also, with regard to the fact that toxicological studies of individual short-acting β-agonists (ractopamine, zilpaterol) did not give significant results about the harmful effects on human health and animals, when they were applied in the prescribed anabolic dose, their use in some countries is allowed. Zilpaterol can be used for anabolic purposes in cattle in North Africa and Mexico, and the use of ractopamine is permitted in 21 countries during the fattening of pigs (Mitchell and Dunnavan, 1998, Anderson et al., 2005). For these substances, maximum residue limit (MRL) is defined as the limit in which they may be present in certain animal tissues (Heitzman, 1993; Qiang et al., 2007).

However, in the European Union from 1988 the use of all substances that have hormonal effects in animals for meat production has been prohibited (Council Directive 88/146/EC). In Croatia, the use of anabolics is also prohibited, and after a series of legislative acts nowadays there are in force the Regulation of pharmacologically active substances and their classification in relation to the maximum residue levels in the food of animal origin (Official Gazette 21/2011) and the Order which prohibits the use of certain substances having a hormonal and tireostatic effect as also beta-agonists on farm animals (Official Gazette 82/2010). Clenbuterol can be used only in therapeutic purposes for achieving broncholitic and tocolitic action in bovine and equine animals at doses of 10-20 μg twice a day (EMEA, 2000), which is 5- 10 times lower than anabolic dose (Pleadin et al., 2011). Due to the possible use of clenbuterol for therapeutic purposes, in the goal to control the possible misuse of such anabolics, the European legislation defined MRL for clenbuterol in liver of cattle and equine at 0.5 μg/kg (Smith, 2000).

Illegal use of these pharmacologically active substances indicated the necessity of development of specific and selective analytical methods for their determination, as well as the establishment of control systems (Van Ginkel et al., 1993). In order to control the illegal use of these substances in animals for meat production, samples of biological material (urine, liver, blood, muscle) taken during the fattening of animals at slaughterhouses are analyzed for the presence of β-adrenergic agonists. In Croatia, sampling is performed by authorized inspectors in all regions, according to the prescribed annual residue monitoring programs of the Ministry of Agriculture, Fisheries and Rural Development of the Republic of Croatia.

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β-adrenergische Agonisten: Stoffe mit anabolischer Wirkung bei Tieren für die Fleischherstellung

Zusammenfassung

In der Arbeit ist ein Überblick der literarischen Angaben über β-adrenergische Agonisten gegeben, die eine anabolische Wirkung bei Tieren haben. Chemische Strukturen einzelner Verbindungen wurden gegeben, ihre Grundeigenschaften wurden angeführt, sowie der Wirkungsmechanismus, physiologische Wirkungen und schädliche Folgen bei Menschen und Tieren, die durch die Auslegung den anabolischen Dosen dieser Stoffe hervorgerufen wurden. B-Agonisten im Organismus erzeugen die Wirkung, indem sie sich an spezifische β-adrenergische Rezeptoren binden, die sich an den Zellenmembranen des Zielgewebes befinden. Ihre Anwendung in anabolischer Dose hat bei den Tieren als Folge eine bedeutende Vergrößerung der Muskelmasse, eine Verminderung der Fettgewebemenge , eine bessere Nutzung der Nahrung, Stärkung des Tierwuchses und verbesserte sensorische Eigenschaften des hergestellten Fleisches.In den letzten zwei Jahrzehnten wurden in einigen Ländern der EU die β-Agonisten während der Tiermast missbraucht, mit dem Ziel, bedeutende Herstellungsbeiträge in Fleischherstellung zu erzielen, bzw. dadurch wurde ein größerer wirtschaftlicher Profit erzielt. Der Missbrauch des bedeutendsten Vertreters von Clenbuterol verursachte schädliche Folgen für die Gesundheit der Menschen und Tiere. In den Ländern der EU und in der Republik Kroatien ist die Anwendung dieser Stoffe zu anabolischen Zwecken auf Tieren für Fleischherstellung verboten. Die Kontrolle hinsichtlich des Missbrauchs wird durch staatliche Programme des Residuum-Monitorings durchgeführt.

Schlüsselwörter: *β-adrenergische Agonisten, anabolische Wirkung, Tiere bestimmt für Fleischherstellung*

Agonisti β-adrenergici: sostanze con effetto anabolico dagli animali destinati alla produzione di carne

Somario

Quest'articolo contiene un elenco di dati di letteratura degli agonisti β-adrenergici come un gruppo di sostanze che hanno un effetto anabolico dagli animali. Ci sono anche le strutture chimiche di certi composti, insieme con le sue caratteristiche base, il meccanismo d'azione eri (8,00% : 8,50%) e, gli effetti fisiologici e le conseguenze dannose per la gente e per gli animali che sono state provocate a causa dell'esposizione alle dosi anaboliche di queste sostanze. Nell'organismo i β-agonisti creano un effetto attaccandosi sui specifici recettori β-adrenergici situati sulle membrane di cellule di tessuti d'interesse. La loro applicazione nella dosi anabolica sugli animali risulta con un aumento significativo della massa muscolare, la diminuzione di quantità del tessuto grasso, il maggior sfruttamento del cibo, la crescita aumentata di animali e le migliorate caratteristiche sensoriche di carne prodotta. Negli ultimi due decenni, in alcuni paesi d'Unione europea i β-agonisti sono stati abusati durante l'allevamento di animali, allo scopo di ottenere una maggiore produttività nella produzione di carne, cioè realizzare un maggiore profitto economico. L'abuso del più importante rappresentante clenbuterolo ha prodotto le conseguenze dannose sulla salute umana e animale. Negli paesi di Unione europea, come nella Repubblica di Croazia, l'applicazione di queste sostanze sugli animali con il fine anabolico è proibita nella produzione di carne, e la sorveglianza dell'abuso si fa tramite i programmi statali del monitoring di residui.

Parole chiave: *agonisti β-adrenergici, effetto anabolico, animali destinati alla produzione di carne*

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