

# Beta-Adrenergic receptor modulation of adipocyte metabolism and growth

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**ABSTRACT:**  $\beta$ -Adrenergic receptor ( $\beta$ AR) agonists reduce body fat in mammals and birds. Synthetic lipid metabolism is decreased in  $\beta$ AR agonist-treated animals or in agonist-treated adipocytes in vitro. Degradative lipid metabolism is increased by  $\beta$ AR agonists in adipocytes in vitro and in vivo. The  $\beta$ AR agonist effects are blocked by  $\beta$ AR antagonists. In mammalian tissues, there are at least three distinct  $\beta$ AR subtypes;  $\beta$ -1 ( $\beta$ 1AR),  $\beta$ -2 ( $\beta$ 2AR), and  $\beta$ -3 ( $\beta$ 3AR). Individual tissues have different proportions of subtypes. For example, greater than 85% of the  $\beta$ AR in rat heart is  $\beta$ 1AR, in guinea pig lung is  $\beta$ 2AR, and in rat adipose tissue is  $\beta$ 3AR. Subtype distribution within a tissue varies with species (e.g., human heart has 65%  $\beta$ 1AR and porcine adipocytes have less than 10%  $\beta$ 3AR). There is species variation in the amino acid sequence of a  $\beta$ AR subtype. Thus, it is expected that some  $\beta$ AR agonists would have different effects in the same tissue in different species because of different  $\beta$ AR subtype distribution and(or) amino acid sequence. In support of these concepts, the

pharmacology of  $\beta$ AR agonists and antagonists in adipocytes is in many cases species-specific. Cloning of individual  $\beta$ AR subtypes allows determination of the pharmacology of subtypes from that species. For example, the pharmacology of the cloned porcine  $\beta$ 1AR,  $\beta$ 2AR, and  $\beta$ 3AR indicates selected agonists or antagonists can be used to assess the proportion of  $\beta$ AR subtypes. Nucleic acid sequences of the subtypes were used to prepare probes to quantify the subtype mRNA. The pharmacological and mRNA data agree rather closely and indicate porcine adipocytes contain over 70%  $\beta$ 1AR. The effects produced by a  $\beta$ AR agonist (or antagonist) on adipose tissue in vivo depend not only on the species and the adipocyte  $\beta$ AR subtype distribution, but also on the pharmacokinetics and pharmacodynamics of the compound in that species, including blood flow to the tissue, and the multiple metabolic and endocrine effects of the compound in other tissues of the body. In short, it is expected that individual  $\beta$ AR agonists would have somewhat different effects in different species.

Key Words: Adipocytes, Beta-Adrenergic Receptors, Growth, Metabolism

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## Introduction

Understanding the mechanisms by which  $\beta$ -adrenergic receptor ( $\beta$ AR) agonists modulate adipocyte metabolism and growth requires familiarity with the family of membrane-bound  $\beta$ AR subtypes. This paper describes the physiological functions and biochemical characteristics of these receptors, including subtypes, tissue distribution, and species variation. This information provides the basis for discussing animal responses to oral administration of  $\beta$ AR agonists and effects on adipocyte metabolism and fat deposition. Secondary vs primary mechanisms of action are also discussed.

## $\beta$ -adrenergic Receptors

The  $\beta$ AR are cell-surface receptors that interact with stimulatory G-proteins ( $G_s$ -proteins) to activate the enzyme adenylate cyclase. Adenylate cyclase synthesizes cAMP, the intracellular messenger for responses to  $\beta$ AR. The physiological ligands for the  $\beta$ AR are the neurotransmitter norepinephrine and the adrenal medullary hormone epinephrine. Norepinephrine, in addition to being a central nervous system and peripheral sympathetic nervous system neurotransmitter, is present in the plasma and can act as a hormone. There are a large number of synthetic analogs of norepinephrine and epinephrine, some of which are agonists (bind to the receptor to activate it and stimulate  $\beta$ AR-mediated activity), some of which are antagonists (bind to the receptor, but do not activate it, and thus compete with agonists and inhibit  $\beta$ AR-mediated activity), and some of which are partial agonists (bind to the receptor and partially activate it). The  $\beta$ AR are present on almost

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every cell type and control an exceptionally large number of physiological and metabolic functions. Examples are regulation of heart rate and contractile force, blood pressure, bronchial muscle tension, uterine contraction, and glycogen and lipid degradation. As functions of norepinephrine, epinephrine, and synthetic analogs were explored, incredible complexity arose that gave rise to the concept of more than one type of receptor. First,  $\alpha$ -adrenergic receptor ( $\alpha$ AR) and  $\beta$ AR functions were separated, then the  $\beta$ AR was separated into two subtypes, the  $\beta$ 1AR and  $\beta$ 2AR. Later, the  $\alpha$ AR was separated into subclasses and, finally, evidence was accrued for a  $\beta$ 3AR.

The  $\beta$ AR is a continuous protein chain, > 400 amino acids in length. It contains seven relatively hydrophobic segments that traverse the cell membrane (transmembrane domains) and are connected by three extracellular and three intracellular segments or loops. Also, there is a N-terminal extracellular tail and a C-terminal intracellular tail. The ligand-binding site is composed of amino acids contributed by several of the transmembrane domains. The binding of the G-proteins occurs primarily through intracellular loop 3. Phosphorylation is one mechanism by which receptor activity is diminished, and there are phosphorylation sites on the C-terminal segment. Selected reviews about  $\beta$ AR structure and function include: Stadel and Lefkowitz (1991), Caron and Lefkowitz (1991), and Strosberg (1992, 1993, 1997). Reviews with emphasis on agricultural species are Mersmann (1989b, 1998), Mills and Mersmann (1995), and Moody et al. (2000).

### Animal Responses

The use of  $\beta$ AR agonists to alter body composition of growing animals raised for meat production was reported in the 1960s (Cunningham, 1965). Beginning in the early 1980s, synthetic  $\beta$ AR agonists were shown to affect body composition in several species, including cattle, chickens, pigs, sheep, and turkeys (Ricks et al., 1984). It was not until late 1999 that a  $\beta$ AR agonist, ractopamine, was approved in the United States for use in one of these species, the pig. Oral administration of any of a number of  $\beta$ AR agonists usually causes an increase in daily gain accompanied in many cases by a slight decrease in feed intake with a consequent improvement in efficiency of gain. The striking observation is that  $\beta$ AR agonists preferentially increase skeletal muscle protein mass, which is usually accompanied by a decrease in adipose tissue mass, with little or no change in internal organ size. All of these responses are quite variable and depend on the species, perhaps the breed, the animal age, the sex, the specific  $\beta$ AR agonist used, the dose, the diet, and many other factors that vary in the numerous published studies. There are multiple studies of the effects of  $\beta$ AR agonists on animal growth; among the summaries of these results are Hanrahan (1987), Bergen and Merkel (1991), Beerman (1994), and NRC (1994). A rather complete tabular sum-

marization of studies in various species using a variety of  $\beta$ AR agonists is noteworthy (Moloney et al., 1991), as is a summarization of multiple studies on one agonist, ractopamine, in pigs (Watkins et al., 1990). Attempts to amalgamate data across species and agonists, albeit a gross oversimplification, indicate a hierarchy of responses across species with sheep  $\geq$  cattle  $\geq$  turkeys > pigs > chickens (Mersmann, 1998; Moody et al., 2000). Perhaps one contributing factor to this hierarchy is that some species are closer to their maximal growth response because of intense selection for growth rate; consequently they respond to a lesser extent (e.g., chickens respond much less than sheep).

### Factors Leading to Variable Responses

In addition to the variable response observed in different species, even when administered the same  $\beta$ AR agonist, there is considerable variation caused by the use of different  $\beta$ AR agonists. This is to be expected because an individual agonist has not been tailored to all the species in which it has been studied. The rate of absorption, the metabolism of the agonist by various organs, and the excretion rate of the agonist or its derivative(s) dictate the concentration achieved and maintained over time in the plasma, and ultimately at the target organ sites. The many aspects of these pharmacodynamic properties of the agonist, coupled with the blood flow to the target organs, dictate the pharmacokinetic properties of the agonist. For a given  $\beta$ AR agonist, many of these pharmacodynamic properties are expected to vary among species.

The pharmacodynamic properties of a particular  $\beta$ AR agonist administered to a particular species are expected to be influenced by genetic-, sex-, and age-caused variation in drug metabolism and delivery systems. Furthermore, the  $\beta$ AR population on target organs or cell types may be expected to vary not only with species, but also with age and perhaps with breed or sex. Variation in the  $\beta$ AR number on a target cell would be expected to cause variation in the response to a  $\beta$ AR agonist. Examination of the response to a  $\beta$ AR agonist within a species must use a dose  $\times$  response design because the response of one variable (end point) may have a different relationship to dose than the response of another end point. Thus, for ractopamine-fed pigs, the half-maximal response for improvement in gain is achieved at  $\sim$ 1.5 mg/kg feed, whereas the half-maximal response for improvement in dressing percentage is achieved at  $\sim$ 10 mg/kg feed (Moody et al., 2000). Likewise, comparison of a given  $\beta$ AR agonist across species can only be validly accomplished when the studies utilize a dose  $\times$  response design because a dose that may be maximal in one species may be far less than maximal in another species. Factors influencing response to  $\beta$ AR agonists have been discussed previously (Mersmann, 1989b, 1995, 1998).

Dietary components may influence absorption of the drug, they may modify the transport of the drug, or they

may increase or decrease the metabolism or excretion of the drug. With an anabolic agent such as a  $\beta$ AR agonist, the protein content of the diet must supply sufficient essential amino acids for optimal protein synthesis to allow expression of the anabolic properties of the  $\beta$ AR agonist on muscle synthesis (Mitchell et al., 1991; Dunshea, 1993; Moody et al., 2000).

### Fat Deposition

Mammals fed  $\beta$ AR agonists generally have decreased carcass fat, as indicated by backfat thickness or trimmed fat from commercial cuts (Moloney et al., 1991). As genetic selection for lean carcasses has continued, there is less subcutaneous fat, particularly in pigs. Thus, because the control pigs have less fat, a treatment to reduce fat deposition is more difficult to detect. Regardless, in most  $\beta$ AR agonist-treated animals, there is a numerical decrease in carcass fat, even if the data do not always achieve statistical significance. When comparative slaughter techniques are employed to calculate deposition rates, the rate of muscle or protein deposition is increased, whereas the rate of fat deposition sometimes is not significantly reduced (Mitchell et al., 1991; Dunshea, 1993; Chwalibog et al., 1996). If measured at a constant time (age), the  $\beta$ AR agonist-treated animals weigh more and have more muscle mass; thus, even an unchanged rate of fat deposition translates to a lesser percentage of fat per animal. If measured at constant weight, the  $\beta$ AR agonist-treated animals have more muscle mass; even with an unchanged fat deposition rate, there is less fat mass because the  $\beta$ AR agonist-treated animals grow faster and are measured at a younger age. The overall conclusion is that  $\beta$ AR agonists decrease carcass fat in growing mammals and birds.

### Adipose Tissue Lipid Metabolism

The  $\beta$ AR agonists markedly increase adipocyte degradative lipid metabolism. Activation of the  $\beta$ AR causes an increase in cAMP that activates protein kinase A, which in turn phosphorylates hormone-sensitive lipase. Phosphorylated lipase is the activated form that initiates the degradative process, lipolysis. Fatty acids are produced and, to a large extent, exported from the adipocyte to be used as oxidative fuels by other tissues. Fatty acid synthesis and the esterification of fatty acids into triacylglycerol, the primary energy storage molecule in the adipocyte, are both inhibited by  $\beta$ AR agonists. Thus, an increase in catabolic and a decrease in anabolic lipid metabolic processes in the adipocyte would both lead to decreased hypertrophy of the adipocyte with a consequent decrease in fat deposition. Much of these data have been summarized (Smith, 1987; Mersmann, 1989b, 1995, 1998; Mills and Mersmann, 1995).

The synthetic  $\beta$ AR agonist isoproterenol and the physiological agonists norepinephrine and epinephrine

each increase adipocyte degradative lipid metabolism and decrease synthetic lipid metabolism in vitro. One enigma is that, overall, the  $\beta$ AR agonists that cause changes in body composition, including decreases in fat deposition, are not particularly potent or effective agonists to modulate adipocyte lipid metabolism in vitro (Mills and Mersmann, 1995). These results may represent artifacts of the studies in vitro because the  $\beta$ AR agonist clenbuterol, which does not increase porcine adipocyte lipolysis in vitro, increases plasma fatty acid concentrations when infused in vivo (Mersmann, 1987; Hu et al., 1988). An increase in plasma nonesterified fatty acids usually results from an increase in adipocyte lipolysis.

### $\beta$ AR Subtypes

There are three well-documented  $\beta$ AR subtypes:  $\beta$ 1AR,  $\beta$ 2AR, and  $\beta$ 3AR. Evidence for these subtypes initially came from classic pharmacological studies of organ, tissue, and cell systems using not only norepinephrine and epinephrine, but also numerous synthetic agonists and antagonists. These approaches were followed by ligand binding to membranes from various tissues. It became obvious that certain tissues contained primarily one receptor subtype. For instance, rat heart contains mostly  $\beta$ 1AR (> 90%), guinea pig bronchi contain mostly  $\beta$ 2AR (> 85%), and rat adipocytes contain mostly  $\beta$ 3AR (> 90%). These tissues, or membranes prepared from them, were prototypes used to study an individual  $\beta$ AR subtype with minimal interference from other subtypes. The individual  $\beta$ AR subtypes were eventually cloned and expressed in cells without endogenous  $\beta$ AR so that the properties of a single  $\beta$ AR subtype could be studied without interference from other subtypes. Using prototypical tissue or membrane preparations and, later, cloned subtypes expressed in cells, individual agonists and antagonists could be classified regarding their specificity for a subtype. A few agonists and antagonists were discovered that had considerable specificity for a single subtype. Thus, CGP 20,712 is considered a  $\beta$ 1AR antagonist, ICI 118,551 is considered a  $\beta$ 2AR antagonist, and BRL 37,344 is considered a  $\beta$ 3AR agonist. These subtype-specific agonists and antagonists have become classic reagents to classify the  $\beta$ AR subtypes in other tissues and species. However, such results must be considered tentative because the subtype specificity of these classic reagents is based solely on their interaction with prototypical receptors. Usually nothing is known about the subtype specificity of the classic agonist or antagonist in the species of interest. Overviews of the  $\beta$ AR subtypes with emphasis toward agricultural species are Mills and Mersmann (1995), Mersmann (1995, 1998), and Moody et al. (2000).

The  $\beta$ AR subtypes have now been cloned from a number of species. These include the porcine  $\beta$ 1AR (Cao et al., 1998),  $\beta$ 2AR (Liang et al., 1997), and  $\beta$ 3AR (Smith and Mills, personal communication) and the bovine

$\beta$ 1AR (Ha et al., 1999),  $\beta$ 2AR (Einspanier et al., 1997), and  $\beta$ 3AR (Pietri-Rouxel et al., 1995). The  $\beta$ 1AR is the largest of the three subtypes with approximately 460 amino acids. The  $\beta$ 2AR has approximately 420 amino acids and the  $\beta$ 3AR has approximately 410 amino acids. The homology for the three subtypes within a given species is usually between 45 and 60%, whereas the homology for a given subtype is rather high across species (usually > 70%). Although there is strong homology for a given subtype across species, the variation in amino acid sequence allows for considerable variation in ligand binding or functional properties of these homologous receptors. Consequently, it should not be assumed that a classic agonist or antagonist designated as specific for a  $\beta$ AR subtype (based on activities with prototypical receptors) will have the same subtype specificity in another species. For example, cloned human, mouse, and bovine  $\beta$ 3AR expressed in Chinese hamster ovary (CHO) cells respond to propranolol (a classic  $\beta$ AR antagonist) in different ways; propranolol is an antagonist for the mouse  $\beta$ 3AR but a partial agonist for the human and bovine  $\beta$ 3AR (Pietri-Rouxel et al., 1995).

### Tissue Variation in Distribution of $\beta$ AR Subtypes

Although the prototypical tissues contain a predominant proportion of a single  $\beta$ AR subtype (e.g., rat heart has > 90%  $\beta$ 1AR), other tissues have a more equal distribution of the  $\beta$ 1AR and  $\beta$ 2AR subtypes. The  $\beta$ 3AR has a limited tissue distribution, being present at high concentration in adipose tissue of some species (e.g., rats but not humans or pigs), and is expressed at substantial levels in selected areas of the gut (Mersmann, 1998). Considering only the  $\beta$ 1AR and  $\beta$ 2AR, in humans there is approximately 35%  $\beta$ 1AR in adipose tissue, 27%  $\beta$ 1AR in the lung, and 20%  $\beta$ 1AR in the liver (Sano et al., 1993).

The  $\beta$ AR subtypes may change with growth/age of the animal. For example, undifferentiated preadipocytes from the rodent-derived clonal cellline 3T3-F442A have predominantly  $\beta$ 1AR with essentially no  $\beta$ 3AR, whereas the differentiated adipocytes have > 90%  $\beta$ 3AR (Fève et al., 1991). Thus, the age of an animal may dictate the response to an exogenous  $\beta$ AR agonist because the  $\beta$ AR are less developed, or the proportion of the  $\beta$ AR subtypes may be altered during development. Of course, many other physiological responses of the animal may change with age to modify the pharmacodynamic and pharmacokinetic properties of a  $\beta$ AR agonist in vivo.

### $\beta$ AR Subtypes in Agricultural Species

Compared with a prototypical tissue wherein a single  $\beta$ AR subtype predominates (e.g., rat heart with  $\geq$  90%  $\beta$ 1AR), the proportion of that receptor subtype in the same tissue from another species may be lower. For example, based on mRNA concentrations, the pig heart

has 72%  $\beta$ 1AR and pig lung has ~ 67%  $\beta$ 1AR, rather than the > 85%  $\beta$ 2AR in the prototypical guinea pig lung (McNeel and Mersmann, 1999). Based on ligand-binding studies, bovine muscle has almost exclusively  $\beta$ 2AR (Sillence and Mathews, 1994), whereas bovine (Sillence and Mathews, 1994; Van Liefde et al., 1994) and ovine (Bowen et al., 1992) adipose tissue have predominantly  $\beta$ 2AR. These ligand-binding results must be considered tentative because a single classic  $\beta$ 1AR and  $\beta$ 2AR antagonist was used to classify receptor subtypes and there has been no verification that the antagonists used have any specificity for the bovine or ovine  $\beta$ 1AR or  $\beta$ 2AR. Extensive pharmacological measurements using porcine adipose tissue, isolated adipocytes, and ligand binding to adipocyte membranes have clearly indicated that the  $\beta$ AR present do not respond to classic  $\beta$ AR subtype-specific agonists or antagonists, as do prototypical  $\beta$ AR subtypes (Mersmann et al., 1993; Mills and Mersmann, 1995). The cloned porcine  $\beta$ 1AR (Cao et al., 1998) and  $\beta$ 2AR (Liang et al., 1997, 2000) have been expressed in CHO cells so that the pharmacology of a single porcine  $\beta$ AR can be assessed. The uniqueness of the pharmacology of these porcine  $\beta$ AR subtypes has been verified; the classic  $\beta$ 1AR antagonist CGP20712 is highly specific for the porcine  $\beta$ 1AR, but the classic  $\beta$ 2AR antagonist ICI 118,551 has no specificity for the porcine  $\beta$ 2AR, whereas a classic  $\beta$ 3AR agonist, BRL 37,344, is relatively specific for the porcine  $\beta$ 2AR (Scott Mills, personal communication). These results clearly indicate the species specificity of the pharmacological response of a  $\beta$ AR subtype and also force the conclusion that use of classic  $\beta$ AR subtype-specific agonists or antagonists to classify  $\beta$ AR subtypes in other than the prototypical species produces, at best, tentative conclusions.

Using compounds specific for the cloned porcine  $\beta$ 1AR and  $\beta$ 2AR, it has been estimated that porcine adipocytes have ~75%  $\beta$ 1AR (Scott Mills, personal communication). Using quantitative measurement of the mRNA for porcine  $\beta$ AR subtypes, it has been estimated that porcine adipocytes contain ~73%  $\beta$ 1AR, ~20%  $\beta$ 2AR, and ~7%  $\beta$ 3AR (McNeel and Mersmann, 1999). Based on mRNA concentrations, the proportion of  $\beta$ AR subtypes in other pig tissues was estimated (McNeel and Mersmann, 1999), but these results have not been verified by ligand binding. There are no reports of  $\beta$ AR subtypes in cattle or sheep tissues using appropriately controlled mRNA measurements or ligand binding assessments using agonists or antagonists verified as specific for the  $\beta$ AR subtype of interest.

### Secondary Mechanisms

In addition to direct effects on adipocytes, systemically delivered  $\beta$ AR agonists can have a number of secondary effects that could alter adipocyte metabolism and consequently growth. Blood flow to a variety of tissues is increased in the presence of a  $\beta$ AR agonist; this has been demonstrated in cattle (Eisemann et al.,

1988), sheep (Beermann et al., 1987), and pigs (Mersmann, 1989a). The concentration of a number of hormones may be altered; some of these can directly or indirectly affect the adipocyte. For example, the lower plasma insulin in sheep chronically fed a  $\beta$ AR agonist might lead to decreased lipogenesis and increased lipolysis (Beerman, 1987). Metabolic rate may be increased by  $\beta$ AR agonists, although chronically treated calves (Zimmerli and Blum, 1990), pigs (Yen et al., 1991), and sheep (Rikhardsson et al., 1991) do not have elevated metabolic rates. These and other secondary mechanisms have been discussed previously (Beerman, 1987; Mersmann, 1989b, 1995, 1998).

## Conclusions

Although there is considerable evidence for effects of several  $\beta$ AR agonists on adipocyte lipid metabolism, both in vitro and in vivo, in cattle, pigs, and sheep, we will not know the quantitative effect of a  $\beta$ AR agonist on lipid metabolism in a particular species until there are measurements of isotopic flux. Likewise, although there are data suggesting  $\beta$ AR subtype specificity of particular agonists or antagonists in cattle and sheep, we cannot discern the correctness of these speculations until the pharmacological properties of the cloned  $\beta$ AR subtypes from those species are measured. Examination of the properties of the cloned porcine  $\beta$ 1AR and  $\beta$ 2AR has allowed verification of the distribution of subtypes in porcine adipose tissue and has proven the unique pharmacology of the porcine  $\beta$ AR subtypes.

## Implications

The diversity of  $\beta$ -adrenergic receptors, the diversity of receptor subtype tissue distribution, and the pharmacology of receptor subtypes imply that individual  $\beta$ -adrenergic agonists would have somewhat different effects in adipocytes and adipose tissue of different species.

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