

Glucocorticoid regulation of amino acid and polyamine metabolism in the small intestine

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Abstract Several factors (including diets, changes in intestinal flora, and hormones) regulate postnatal intestinal growth and development. Based on the early studies involving modification of the adrenal gland, pituitary gland or hypothalamus, exogenous glucocorticoids and glucocorticoid receptor antagonists are now used to study glucocorticoid-mediated metabolism of amino acids in the small intestine. Findings from these studies indicate that physiological levels of glucocorticoids stimulate the catabolism of glutamine and proline for the synthesis of citrulline and arginine in enterocytes during weaning. In addition, increases in circulating levels of glucocorticoids enhance expression of arginase, proline oxidase and ornithine decarboxylase, as well as polyamine synthesis from arginine and proline in enterocytes. These actions of the hormones promote intestinal maturation and may have therapeutic effects on intestinal disease (e.g., necrotizing enterocolitis). Molecular aspects, species-specific effects, and developmental responsiveness to glucocorticoids should be taken into consideration in designing both experimental and clinical studies.

Keywords Intestine · Glucocorticoid · Regulation · Development · Weaning

Abbreviations

ASL Argininosuccinate lyase
ASS Argininosuccinate synthase

P5C Pyrroline-5-carboxylate
P5CS Pyrroline-5-carboxylate synthase

Introduction

Several factors play an important role in the ontogeny of intestinal digestive enzymes in mammals. These factors include diets, changes in intestinal flora, and hormones. The developmental changes of intestinal digestive enzymes associated with postnatal growth are well documented (Henning 1981). For example, pig intestinal activities of sucrase and maltase increases while lactase activity decreases during the second week of postnatal development (James et al. 1987); these changes in enzyme activity help prepare the piglet for a transition from a milk-based to a grain-based diet. The diet-induced changes in digestive enzyme profile likely results from alterations in actual dietary components (Ferraris 2001). This may help explain the proximal–distal gradient exhibited in many digestive enzymes due to a differential exposure of these intestinal segments to dietary substances (Espinoza et al. 1975, 1976; Greene et al. 1975).

There is also evidence that intestinal flora may play an important role in regulating the development of intestinal digestive enzymes (Batt et al. 1996). Administration of a probiotic to pigs immediately prior to weaning results in dramatic increases in sucrase activity in the small intestine while the administration of antibiotics prior to weaning results in a delayed decrease in lactase activity in response to weaning (Collington et al. 1990). This suggests that manipulation of bacterial populations in the small intestine will lead to changes in the activities of intestinal digestive enzymes.

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Hormonal effects on the development of intestinal digestive enzymes are well established (Chapple et al. 1989). Normal development of the small intestine, for example, is impeded or delayed by adrenalectomy or thyroidectomy (Koldovsky et al. 1964, 1975). Furthermore, administration of hormones to developing animals has been shown to increase the activity of carbohydrate-metabolizing enzymes (Koldovsky et al. 1964) and decrease the activity of milk-utilizing enzymes (James et al. 1987) in the small intestine. Given the recognized importance of amino acids to proper functioning of the small intestine (Rider et al. 2007; Wang et al. 2008a, c; Wu 1998) and whole-body homeostasis (Flynn and Wu 1996), this review will focus on the effects of glucocorticoids on amino acid and polyamine metabolism in the gut.

Early studies of glucocorticoids on intestinal development and metabolism

Initial studies concerning glucocorticoids and the small intestine

Early studies on the effect of glucocorticoids on intestinal development typically involved removal of the respective endocrine gland or modification of the pituitary gland or hypothalamus. Adrenalectomy, for instance, was associated with a delayed increase in intestinal sucrase, maltase and invertase activity and a delayed decrease in intestinal β -galactosidase activity in the weaned rat (Koldovsky et al. 1964, 1975). Additionally, hypophysectomy resulted in a delay of normal elevations of sucrase and maltase activity (Castillo et al. 1991). These studies were important toward gaining better understanding of the effects of glucocorticoids on intestinal development but they did not clearly demonstrate a direct effect of the hormones, because factors such as nonglucocorticoid adrenal secretions or pituitary-dependent factors could not be ruled out.

Effects of glucocorticoid administration on nutrient metabolism

More direct evidence for a role of glucocorticoids in inducing intestinal development came from several studies that reported a stimulatory effect of glucocorticoid administration on carbohydrate metabolism in developing animals. For example, administration of corticosterone to adrenalectomized rats increased the activity of invertase (Koldovsky et al. 1964). In addition, cortisol treatment decreased lactase activity (James et al. 1987) while increasing activities of maltase and aminopeptidase in the small intestine of weanling pigs (Chapple et al. 1989; Sangild 1995). Furthermore, glucocorticoid administration

reduced the transcription of cholecystokinin in the small intestine (Ratineau et al. 1996) and enhanced the uptake of glutamine by the canine small intestine (Souba et al. 1985).

Effects of glucocorticoids on intestinal amino acid metabolism

Weaning

Weaning is characterized by a marked change from a high fat to a high carbohydrate diet (Henning 1981). This change in the diet results in marked alterations in enzyme profiles and selective metabolism in the small intestine. Wu and colleagues discovered an induction of pyrroline-5-carboxylate synthase (P5CS) and arginase in enterocytes of 29-day-old pigs that were weaned at 21 days of age (Wu et al. 1994a; Wu 1995). The enhanced expression of these two enzymes results in the production of large amounts of citrulline from glutamine (Wu et al. 1994a; Wu and Knabe 1995), as well as the synthesis of urea from ammonia (Wu 1995), in enterocytes of post-weaning pigs. Furthermore, the weaning-associated changes in intestinal metabolism of glutamine and arginine are independent of a change in age or diet (Dugan et al. 1995). Because weaning is associated with an increase in plasma concentrations of cortisol in mammals (Henning 1981), it was suggested (Wu et al. 1994a) and subsequently demonstrated (Flynn and Wu 1997a, b; Flynn et al. 1999) that glucocorticoids play an important role in regulating the metabolism of arginine and glutamine in enterocytes. For example, administration of cortisol to 21-day-old suckling pigs (killed at day 29 of age) augmented the activities of argininosuccinate lyase (ASL) and arginase, as well as the production of CO₂, ornithine and proline from arginine in the cells (Flynn and Wu 1997a). Intestinal P5CS activity and the formation of citrulline from glutamine were also enhanced in cortisol-treated pigs compared to control pigs (Flynn and Wu 1997b). The P5CS induction is of physiological importance because it promotes the synthesis of citrulline and arginine (an essential amino acid for young pigs; Wu et al. 2004) from glutamine and glutamate in the small intestine. Effects of cortisol on metabolite production and the aforementioned enzyme induction were completely blocked by administration of RU486, a glucocorticoid receptor antagonist (Flynn and Wu 1997a). Interestingly, neither cortisol nor RU486 administration affected ASL activity in enterocytes (Flynn and Wu 1997a, b), indicating that glucocorticoids stimulate the intestinal synthesis of citrulline which can be subsequently released into the circulation. In support of this notion, the release of citrulline by the small intestine is enhanced in post-weaning pigs (Wu et al. 1994b).

Availability of glucocorticoid receptor antagonists (e.g., RU486) has been very helpful in determining whether a developmental increase in enzyme activity is mediated by glucocorticoids. We studied the effect of RU486 on arginine and glutamine metabolism in weanling and age-matched suckling pigs (Flynn and Wu 1997b). We found that RU486 administration to weanling pigs diminished, but did not completely abolish, the increase in arginase activity or the production of ornithine from arginine. RU486 administration had no effect on argininosuccinate synthase (ASS) activity, yet totally blocked the weaning-associated increase in P5CS and ASL activities (Wu et al. 2000c). The enhanced production of CO₂, citrulline and ornithine from glutamine in response to weaning was also prevented by RU486 treatment. At the molecular level, RU486 administration had no effect on ASS mRNA levels, but did suppress the weaning-associated rise in arginase and ASL mRNA levels. An additional study (Flynn et al. 1999) demonstrated that the intestinal expression of type-II arginase, but not type-I arginase, was increased in response to weaning or glucocorticoids. This finding has important implications for better understanding of the regulation of arginine metabolism because type-II arginase is a mitochondrial enzyme and type-I arginase is present only in the cytoplasm (Davis and Wu 1998; Wu et al. 2000c). The cortisol induction of type-II arginase in the small intestine of post-weaning pigs may play a major role in tissue remodeling, because proline (a major amino acid for the synthesis of extracellular matrix protein (Krane 2008) and a metabolically versatile nutrient (Phang et al. 2008)) is produced from arginine in enterocytes of weaned pigs via the type-II arginase pathway (Wu 1996; Wu et al. 1997). The induction of P5CS and arginase in enterocytes of post-weaning pigs provides a biochemical basis for the synthesis of proline from glutamine and arginine (Wu 1995; Wu et al. 2000c). This result explains why proline is an essential amino acid for suckling, but not weaned, pigs (Ball et al. 1986; Tan et al. 2008b).

On the basis of current knowledge of glucocorticoid biochemistry (Weigel 1996), a mechanism for cortisol induction of arginine and glutamine metabolism in enterocytes of post-weaning pigs can be proposed. We propose that elevating concentrations of plasma cortisol increases arginase activity and glutamine metabolism in the small intestine through the glucocorticoid receptor (Flynn and Wu 1997a, b; Flynn et al. 1999). Weaning stress increases plasma concentrations of glucocorticoids (Henning 1981). These hormones bind nuclear receptors (Weigel 1996), therefore promoting transcription of the arginase, ASL and P5CS genes. In addition, diet and thyroid hormones likely play a role in mediating the increase in ASS activity and may contribute to approximately 20% of the weaning-associated increase in intestinal arginase

activity (Flynn and Wu 1997a, b). The exact mechanism associated with an increase in ASS activity in response to weaning remains to be determined.

Perinatal

Weaning is not the only time when cortisol production is increased in mammals. It has also been established that glucocorticoid production is elevated at the time of birth (Silver and Fowden 1989; Wu et al. 2004). Studies on the effects of prenatal glucocorticoids on postnatal development of carbohydrate metabolism have been conducted (Sangild 1995; Solomon et al. 2001). However, similar studies on amino acid metabolism are lacking. The closest research involving amino acid metabolism in the newborn determined the effects of glucocorticoids on mixed function oxidases in the small intestine of rabbits (Tredger and Chhabra 1980).

Effects of glucocorticoids on intestinal polyamine metabolism

Milk has relatively high concentrations of polyamines (Dorhout et al. 1996), products of arginine catabolism (Wu and Morris 1998). This finding has led scientists to explore the role that polyamines play in intestinal development. Several studies have demonstrated the importance of polyamines in regulating epithelial cell growth and differentiation as well as remodeling in the small intestine (Johnson 1988; Sugita et al. 2007). The role of polyamines in mRNA stability and intestinal growth has been recognized (Wang 2007). To this effect, polyamine administration to weanling rats and piglets increases the maturation of the small intestine and the activities of digestive enzymes (Grèco et al. 2001; Wang et al. 2008a). Expression of ornithine decarboxylase, a key enzyme in polyamine synthesis, is also enhanced in response to weaning in rats and pigs (Lin et al. 1998; Wu et al. 2000c) or glucocorticoid administration (Wang and Johnson 1990; Wu et al. 2000b). Indeed, administration of RU486 to weaned pigs has revealed that cortisol increases the synthesis of polyamines from arginine, proline and ornithine in enterocytes (Wu et al. 2000b). It is noteworthy that the work of Wu and co-workers has shown that arginine is not a major precursor of polyamines in enterocytes of suckling mammals due to the lack of arginase activity (Wu et al. 1996). Importantly, Wu (1997) discovered that enterocytes of both preweaning and post-weaning pigs have a high activity of proline oxidase, which oxidizes proline to P5C. The proline-derived P5C is utilized efficiently for the synthesis of ornithine and polyamines (Wu et al. 2000a, 2008a).

Considerations when using glucocorticoids in intestinal studies

Molecular aspects

Glucocorticoids mediate most of their molecular effects via an interaction between a translocated nuclear receptor and a hormone response element in cellular DNA (Weigel 1996). Binding of glucocorticoids to the receptor is responsible for mediating this interaction, which affects cellular homeostasis. For example, glucocorticoid treatment can cause the preferential expression of certain subunits of an individual protein (Henning et al. 1999). This can change many aspects of protein function, including allosteric regulation, ligand binding, and enzyme kinetics. A thymidine analog study involving glucocorticoids has provided an interesting insight into the role that glucocorticoids play in intestinal maturation (Nanthakumar and Henning 1995). This study examined the effect of bromodeoxyuridine on glucocorticoid induction of brush border enzymes. There were differential effects on individual enzymes; some were affected by bromodeoxyuridine while others were not (Nanthakumar and Henning 1995). The authors suggested that changes in intestinal metabolism brought about by glucocorticoids are due to cellular cooperation between different cell types in the small intestine.

Recently, it has been suggested that glucocorticoid receptor dephosphorylation plays a vital role in regulating nuclear translocation and expression of glucocorticoid receptor in the small intestine (Takabe et al. 2008). Several studies also show that a lack of response to exogenous glucocorticoids during maturation of the small intestine is primarily due to a lack of glucocorticoid receptor expression in the anatomical location or developmental stage being studied. The intestinal NHE3 sodium/proton exchange protein response to glucocorticoids, for example, is *both* age and anatomically sensitive (Kiela et al. 2000). Additionally, certain inflammatory cytokines have been shown to increase expression of the β form of the glucocorticoid receptor (Orii et al. 2002). This form of the glucocorticoid receptor is known to be an inactive transcription factor and would thus limit the effectiveness of glucocorticoid treatment. Because glucocorticoids do mediate physiological effects independent of the glucocorticoid receptor, it is important to distinguish these effects from glucocorticoid receptor-mediated effects.

Species-specific effects

Any developmental study involving glucocorticoids and the small intestine must take into account the species of animal that is being studied. The mink exhibits a rather late

responsiveness to glucocorticoids compared to other species and mink exhibit a decreased metabolic clearance of cortisol that is contrasted with a decreased adrenal responsiveness to ACTH (Elnif and Sangild 1996; Sangild and Elnif 1996). Additionally, the same parameter, when studied across species, can exhibit differential effects. Expression of the Vitamin D receptor in the small intestine, for example, is increased in rats but decreased in mice in response to cortisol administration (Hirst and Feldman 1982). One must also consider the major circulatory glucocorticoid and response to synthetic glucocorticoids in the species being studied.

Developmental responsiveness

As noted above, the lack of responsiveness to glucocorticoids can be developmentally specific. Cross-breeding studies in mice lacking a functional glucocorticoid receptor suggest that responsiveness to glucocorticoids in rodents depends greatly upon age (Gartner et al. 2003). For instance, transcriptional activation of trehalase expression in the small intestine by glucocorticoids is possible in neonatal mice, but fetal administration of glucocorticoids fails to elicit a response (Solomon et al. 2001). In the same study, it was also determined that there was no difference in the observed response to glucocorticoids between 1 and 2 weeks of age. These differential responses are likely due to altered expression of the glucocorticoid receptor as well as the prevalence of a critical mass of responsive cell types in the small intestine. Another important factor to consider is the presence of glucocorticoid-binding proteins in the blood. These proteins could limit the availability of glucocorticoids to targeted cells. Corticosteroid-binding globulin, for instance, exhibits a sharp increase in expression during the first 3 weeks of birth in the rat (Henning 1978).

Physiological and medical implications

Several intestinal diseases can benefit from moderation of glucocorticoid biochemistry. The intestinal pathology of endotoxemia, for example, may be due to the decline in glucocorticoid receptors (Fan et al. 1994). Glucocorticoids have also been implicated in the treatment of such diseases as encapsulating peritoneal sclerosis (Imai et al. 2002) and ulcerative colitis (Kornbluth and Sachar 1997).

Several studies have demonstrated that the increase in plasma glucocorticoids in association with weaning is mirrored in response to the birth process, suggesting that glucocorticoids may play an important role in the development of newborn tissues. Changes in intestinal function are still a major factor for high mortality and morbidity in

mammalian neonates, including pigs (Wu et al. 2006, 2008b). This area of study is important to increasing the survival rate of premature infants. Premature infants are prone to an intestinal condition termed necrotizing enterocolitis. This disease is thought to occur as a result of an immature small intestine. Interestingly, the prevention and treatment of necrotizing enterocolitis using glucocorticoids is very much dependent upon the age of the premature infant (Crowley et al. 1990). Glucocorticoids play an important role in maturation of the small intestine in weanling mammals (Wang 2007; Wu et al. 2000b); therefore, these hormones may help in the treatment of diseases (e.g., necrotizing enterocolitis) that are associated with a poorly developed small intestine in premature infants (Bauer et al. 1984; Nanthakumar et al. 2005; Patole 2007).

The exact mechanisms associated with these medical observations are poorly understood but it can be appreciated that the general effect of glucocorticoids on amino acid and polyamine metabolism may play a crucial role (Wu et al. 2000a, b, c). An increase in the production of proline and ornithine from arginine would provide substrates necessary for the production of cellular matrix proteins (collagen) and polyamines (Davis and Wu 1998). These amino acids and their functional metabolites are important for intestinal growth, development, integrity, and immunity (Han et al. 2008; Li et al. 2007), as well as multi-organ functions (Wu et al. 2008c). As mentioned previously, studies of the relationship between glucocorticoids and intestinal amino acid metabolism in the very young neonate or preterm infant are lacking. What is clear, however, is the fact that arginine supplementation does improve intestinal function (Rhoads et al. 2008) and provide protective benefits to early-weaned piglets (Han et al. 2008; Tan et al. 2008a).

Future directions

While glucocorticoids clearly play an important role in regulating amino acid metabolism in the developing intestine, the underlying mechanisms remain largely unknown. Understanding the mode of actions of these hormones will be an important area of biomedical research. One interesting study demonstrated that treatment of neonatal pigs with dexamethasone inhibited intestinal growth (Burrin et al. 1999). In contrast, administration of a physiological dose of cortisol to 21-day-old piglets enhanced the growth of the small intestine (Wu et al. 2000a). Clearly, it is important to determine whether glucocorticoids regulate protein degradation via multiple pathways (e.g., ubiquitin-dependent proteolysis; Kahana 2007) and protein synthesis via mTOR signaling (Deng et al. 2008; Liao et al.

2008) in the small intestine. Additionally, studies are needed to elucidate the complex effects of glucocorticoids on intestinal amino acid metabolism using biochemical techniques, molecular biology, and bioinformatics (He et al. 2008; Hu et al. 2008a, b; Li et al. 2008b; Ou et al. 2007; Wang et al. 2008b, c). Finally, little is known about the role of glucocorticoids in intestinal and whole-body homeostasis of amino acids in mammals, birds, or fish (Aragao et al. 2008; Li et al. 2008a; Wu et al. 2008c), and these studies can be conducted using tracer methodologies (Suryawan et al. 2008). Collectively, this work will greatly advance our knowledge about the physiology and therapeutic uses of glucocorticoids in medicine.

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