An oral gavage of lysine elicited early satiation while gavages of lysine, leucine, or isoleucine prolonged satiety in pigs

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Abstract
Excess dietary amino acids (AA) may negatively affect feed intake in pigs. Previous results showed that Lys, Leu, Ile, Phe, and Glu significantly increased gut peptide secretion (i.e., cholecystokinin, glucagon-like peptide 1). However, the link between dietary AA and gut peptide secretion with changes in feeding behavior patterns has not been demonstrated to date in pigs. The aim of the present study was to determine the effect of Lys, Leu, Ile, Phe, and Glu on feed intake and meal patterns in young pigs. Twelve male pigs (Landrace × Large White, body weight = 16.10 ± 2.69 kg) were administered an oral gavage of water (control) or Lys, Leu, Ile, Phe, Glu, or glucose (positive control) at 3 mmol.kg⁻¹ following an overnight fasting. The experiment consisted in measuring individual feed disappearance and changes in meal pattern (including latency to first meal, first meal duration, intermeal interval, second meal duration, and number of meals) based on video footage. Compared to the control group, Lys significantly (P ≤ 0.01) reduced feed intake during the first 30 min and up to 2.5 h post-gavage, including a reduction (P ≤ 0.05) in the first meal duration. Similarly, Leu and Ile also significantly decreased feed intake up to 3 h post-gavage on a cumulative count. However, the strongest (P ≤ 0.01) impacts on feed intake by the two branched chained AA were observed after the first- or second-hour post-gavage for Leu or Ile, respectively. In addition, Leu or Ile did not affect the first meal duration (P ≥ 0.05). Leu significantly increased (P ≤ 0.01) the intermeal interval while decreasing (P ≤ 0.05) the number of meals during the initial 2 h following the gavage when compared with the control group. In contrast, the oral gavages of Phe or Glu had no significant impact (P > 0.05) on the feeding behavior parameters measured relative to the control pigs. In turn, glucose had a short-lived effect on appetite by reducing (P < 0.05) feed intake for 30 min after the first-hour post-gavage. In conclusion, the impact of an oral gavage of Lys on feeding behavior is compatible with a stimulation of early satiation and an increased duration of satiety. The main impact of the oral gavages of Leu and Ile was an increase in the duration of satiety. The gastrointestinal mechanisms associated with non-bound dietary AA sensing and the impact on voluntary feed intake warrant further investigations.

Lay Summary
A better understanding of the impact of individual dietary amino acids on feeding behavior in pigs can help improve current feed formulation practices. Lys, Leu, Ile, Phe, or Glu were selected based on the impact on gut peptide secretion from a previous study, to assess the effect on feed intake and meal pattern using an oral gavage model (3 mmol.kg⁻¹) in young pigs. The oral gavage of Lys resulted in early satiation as indicated by the reduction of the first meal duration and the feed intake within the first 30 min post-gavage. In addition, the Lys group showed reduced feed intake up to 3 h post-gavage, interpreted as an extended duration of the post first meal satiety compared to the control. The latter was also observed for the branched chained amino acids (BCAA) Leu and Ile. The Leu gavage resulted in an increased intermeal interval together with a reduction on the number of meals while Ile, in turn, reduced feed intake particularly during the third hour post-gavage. No significant effects of the Phe or Glu gavages on feeding behaviors were observed. Overall, these results suggest that dietary Lys, Leu, or Ile had significant anorexigenic effects. Lys increased both satiation and satiety while the BCAA Leu and Ile, mainly increased post-meal satiety in pigs.

Key words: amino acid, feed intake, meal pattern, pig, satiation, satiety

Abbreviations: AA, amino acid; BCAA, branched-chain amino acid; CCK, cholecystokinin; CNS, central nervous system; EAA, essential amino acids; GLP-1, glucagon-like peptide 1

Introduction
The lack of appetite leading to a transient low feed intake observed in post-weaned pigs remains one of the main welfare and production challenges of the pork industry (Collins et al., 2017). The early post-weaning practiced under commercial rearing conditions is associated with severe social/emotional disruption in piglets. In addition, the sudden transition to solid feed intake together with the immaturity of the digestive system may lead to high amounts of undigested matter reaching the hindgut and to the onset of diarrhea (Heo
Nutritionists formulate diets based on highly palatable and digestible energy and protein sources supplemented with limiting amino acids (AA) to enhance feed intake and meet the nutritional requirements of the young pig (van Dijk et al., 2001; Vente-Spreewenbergen et al., 2004; Dong and Pluske, 2007). However, these ameliorating practices are often insufficient to prevent a drop in feed intake and growth stagnation immediately after weaning (Bark et al., 1986; Brooks and Tsoniannis, 2003).

The use of non-protein bound AA to balance low crude protein diets has the potential to become an efficient tool to modulate appetite in pigs. Changes on feeding behavior corresponding with dietary AA are commonly associated with modifications in meal patterns such as meal duration, meal size, intermeal interval, and the number of meals (Gloaguen et al., 2013). In addition, alterations in meal patterns have been closely linked with the release of anorexigenic gut peptides, such as cholecystokinin (CCK) and glucagon-like peptide 1 (GLP-1) (Overduin et al., 2014; Williams et al., 2016). In growing pigs, the consumption of different dietary levels of Lys may influence the release of CCK (Yin et al., 2017). In addition, Leu, Ile, Phe, and Glu significantly stimulated the release of gut peptides in pigs using an ex-vivo model, suggesting that these AA may play a pivotal role on appetite control (Müller et al., 2022). Furthermore, changes on meal/consumption patterns have been described following the administration of Lys, Leu, and Ile unbalanced meals and Glu supplements (Montgomery et al., 1978; Gloaguen et al., 2013; Guzmán-Pino et al., 2019; Müller et al., 2021). However, the individual influence of these AA on feeding behavior and the physiological mechanisms behind these processes remain relatively unexplored. In particular, the short- and long-term impacts of dietary non-bound AA supplements on piglet appetite and feeding patterns are largely unknown. The aim of the present study was to study the effect of Lys, Leu, Ile, Phe, and Glu on feed intake and meal pattern in young pigs. It was hypothesized that Lys, Leu, Ile, Phe, and Glu would reduce feed intake and stimulate satiation and/or satiety by reducing the first meal duration and/or increasing the intermeal interval between the first and second meal post-gavage, respectively.

Materials and Methods

Animal ethics

All experimental procedures involving live pigs were performed under veterinary supervision and approved by The University of Queensland Animal Ethics Committee (Animal Ethics Certificate: CNFS/568/16).

Animals, housing, and diet

A total of 12 male pigs (Landrace × Large White; weighing 16.10 ± 2.69 kg each) were individually housed in slatted floor pens (1.7 m × 1.2 m) and the ambient temperature was maintained at 23–24 °C during the entire experiment at the Herston Medical Research Centre of The University of Queensland (Herston Campus, Queensland, Australia). Pigs were under 12 h of light (programmed from 7.00 h to 19.00 h), and light intensity was controlled and maintained between 40 and 60 lux. Pigs had ad libitum access to feed and water throughout the experiment, unless otherwise stated. A diet was formulated with high crude protein (25%) content to cover all limiting essential amino acid (EAA) requirements recommended by the NRC (2012) without the need of AA supplementation (Table 1). At the end of the experiment, all animals were euthanized with Lethabarb (162.5 mg/kg; Milperra, New South Wales, Australia) administered intravenously.

Oral gavage procedure

Animals were fasted overnight (13 h) before receiving an oral gavage with one of seven treatments (water, Lys, Ile, Leu, Glu, Phe, or glucose) at a dose of 3 mmol.kg⁻¹ (between 7.8 and 9.9 g total based on molecular weight). The dose selected adhered to the physiological relevance principle based on estimated daily intakes (Roura and Navarro, 2018; Müller et al., 2021). Pigs were moved to a separate room, and light anesthesia with isoflurane (1% to 3%) was applied using mask ventilation before the procedure. After 4 to 5 min of isoflurane administration, the anesthetic mask was displaced to still cover the nose but freeing the mouth. The pig was then placed on a table with the dorsal side facing upwards, and the head tilted up. A gavage (60 mL total volume) was administered by using a 60 mL syringe and a 25 cm long plastic extension tube with soft edges. After the gavage, pigs were provided with oxygen through the anesthetic mask for an additional 2 to 3 min to facilitate the recovery. Pigs were immediately returned to their pens for the subsequent video monitoring of feed intake and meal pattern parameters when exposed to a common high crude protein diet. All pigs showed signs of full recovery from the anesthetic (behaving and walking normally) within the first 5 min post-gavage. The process was repeated on 7 d, allowing 1 d of rest between tests (the full procedure lasted 14 d). All the pigs were administered all the treatments in a randomized sequential manner. No major complications occurred during the procedures.

Feed intake and meal pattern recording

Video cameras (ShenZhen Foscam Intelligent Technology Co., Ltd., Guangdong, China) were installed for video recording individual feeding behavior. Video cameras were turned on 10 min before the administration of the oral gavage and left on for the following 240 min post-gavage to record the behavioral patterns and meal structure, including the following: latency to first meal, first meal duration, intermeal interval, second meal duration and number of meals. All video images were analyzed by the same observer using the software BORIS (Behavioural Observation Research Interactive Software, version 7.4.7, Turin, Italy). Feed disappearance was measured manually by weighing food containers every 30 min for the first 4 h post-gavage and then the next morning (24 h post-gavage).

Meal criteria

Treatment effects on meal pattern were analyzed following the criteria described by Bigelow and Houpt (1998). In brief, any eating pause shorter than 10 min was counted as an inner pause within a meal, while the initiation of an eating episode following a pause higher than 10 min was annotated as a new meal.

Statistical analysis

Statistical analysis was performed using R software (RStudio, Inc., Boston, MA, USA). Data are expressed as absolute amounts or percentage of control (presented as the mean ± the standard error of the least squares mean [SEM]). Feed intake data were analyzed using a mixed model considering the fixed
Feed intake and cumulative feed intake results for all treatments are illustrated in Figures 1 and 2, respectively. Lys (P ≤ 0.01) and Leu (P < 0.05) decreased feed intake during the first 30 min post-gavage by 22% (274.17 ± 22.17 g) and 17.2% (290.83 ± 25.40 g) compared to the control pigs (351.25 ± 32.10 g), respectively. Furthermore, Lys reduced (P < 0.05) feed intake by 64.5% (22.92 ± 7.92 g) between 0.5 and 1 h post-gavage in comparison to the control group (64.58 ± 4.71 g). Lys and Leu significantly (P ≤ 0.05) reduced the cumulative feed intake up to 3 h post-gavage by 17.9% (488.75 ± 38.08 g) and 15.2% (504.58 ± 37.77 g) when compared with the control treatment (595.00 ± 57.47 g). In addition, a highly significant (P < 0.01) reduction associated with Ile was observed on cumulative feed intake between 2 h (19%, 419.17 ± 27.63 g) and 2.5 h (21.8%, 435.83 ± 29.95 g) after the gavage in comparison to the water treatment (517.08 ± 51.68 g and 557.08 ± 54.14 g for 2 h and 2.5 h, respectively). In contrast, Phe and Glu did not significantly alter feed intake or cumulative feed intake. Glucose, used as a positive control on short-term effects on feeding intake, reduced (P < 0.05) feed consumption by 82.6% (11.25 ± 3.75 g) vs. the water treatment (64.57 ± 22.45 g) during 30 min following the first hour post-gavage. No effects on cumulative feed intake were observed at the 24 h post-gavage time point for any of the AA tested or glucose.

Latency to first meal, first meal duration, second meal duration, intermeal interval, and the number of meals (during the first 2 h post-treatment) is illustrated in Figure 3. The first meal duration (shown as time spent on feeder) was significantly (P ≤ 0.05) reduced in Lys-treated pigs by 18.1% (21.92 ± 1.89 min) when compared with the control group (26.76 ± 1.37 min). In addition, Lys-treated pigs tended (P ≤ 0.1) to increase the intermeal interval by 1.9-fold (51.31 ± 8.95 min) compared to control animals (25.73 ± 3.90 min). Furthermore, Leu showed a significant impact (P ≤ 0.05) increasing the intermeal interval by 2.5-fold (66.59 ± 11.21 min) and decreasing (P ≤ 0.05) the number of meals by 28.1% in the first 2 h post-gavage. None of the other treatments tested (Ile, Glu, Phe, and glucose) had a significant impact on meal pattern.

**Discussion**

This study illustrates the individual impact of five orally gavaged AA (Lys, Leu, Ile, Glu, and Phe) and glucose on feed intake and meal patterns in pigs. To our understanding, this may be the first study to investigate the effect of orally gavaged AA on feeding behavior in young pigs. It was hypothesized that all the five AA tested would reduce feed

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1 Premix composition (ad-fed basis): vitamin A, 10,000 IU/kg; vitamin D3, 1,800 IU/kg; vitamin E, 100 mg/kg; vitamin K3, 5 mg/kg; vitamin B1, 5 mg/kg; vitamin B2, 6 mg/kg; niacin, 30 mg/kg; pantothenic acid, 30 mg/kg; pyridoxine, 4 mg/kg; biotin, 0.3 mg/kg; folic acid, 2.5 mg/kg; vitamin B12, 0.04 mg/kg; iron, 100 mg/kg, iodine, 0.7 mg/kg; manganese, 45 mg/kg; selenium, 0.3 mg/kg; zinc, 120 mg/kg; cobalt, 0.3 mg/kg; copper, 10 mg/kg.

2 Based on laboratory proximal and AA analysis.

3 Calculated values for each single amino acid refer to “Total” amounts.
intake while altering the meal pattern in pigs. The results were supportive of the hypothesis regarding Lys, Ile, and Leu but not Glu and Phe.

Lys was the most consistent of the AA tested in reducing feed intake, impacting feeding behavior in the short (within a meal) and long (between meals) terms. The anorexigenic effect of Lys has previously been described in pigs (Edmonds and Baker, 1987). In a recent commercially relevant study performed by our group, dietary Lys in excess above 20% over the nutritional requirement significantly reduced feed intake and average daily gain in post-weaning pigs (unpublished data). The fact that Lys could alter feed intake shortly after the gavage (within the first 30 min post-gavage) is an indicator of early satiation (events leading to the termination of an ongoing meal) in pigs. The secretion of anorexigenic hormones from enteroendocrine cells has been shown to contribute to the onset of satiation, causing a reduction in meal size and duration (de Graaf et al., 2004). Lys failed to stimulate Figure 1. Feed intake in young pigs after an oral gavage with water or 3 mmol.kg\(^{-1}\) of Lys (A), Phe (B), Leu (C), Ile (D), Glu (E), or glucose (F). Data are expressed as the mean ± SEM (\(n = 12\)). The statistical significance when comparing individual treatments to the control are represented by asterisks: ** = \(P \leq 0.01\), * = \(P \leq 0.05\).
CCK or GLP-1 in duodenum or ileum using an ex vivo model in pigs, respectively (Müller et al., 2022). However, increases in dietary Lys levels have been associated with enhanced CCK gene expression levels in more distal intestinal segments, such as jejunum and ileum (Yin et al., 2017). Long-term satiety signals involving the central nervous system (CNS) (through postprandial increase in plasma AA levels), insulin or leptin secretion, could explain the Lys extended anorexigenic effects in pigs (up to 3 h post-gavage) (Ren et al., 2007; Jordi et al., 2013; Yin et al., 2017).

Alterations in meal patterns including the reduction of the first meal duration were identified for Lys-treated pigs. Lys has been shown to delay gastric emptying (Lepionka et al., 1997; Maljaars et al., 2007; Jordi et al., 2013; Baruffol et al., 2014). Thus, the onset of early satiation in pigs observed in the present study is compatible with an increased gastric distension and fullness ratings. The alterations in meal pattern identified for both Leu- and Lys-treated pigs involved an increase of the intermeal interval indicating that Lys does not only affect satiation but also prolong satiety (state of fullness that follows an eating episode). Feeding pattern traits showed potential in improving feed efficiency and production (Santiago et al., 2021). Feed consumption rate (g/m) and amount of feed consumed per meal were found negatively correlated with feed efficiency and lean deposition (Andretta et al., 2016). Thus, the impact of excess dietary AA may have profound implications on production efficiency.

Figure 2. Cumulative feed intake in young pigs after an oral gavage with water or 3 mmol.kg⁻¹ of Lys (A), Phe (B), Leu (C), Ile (D), Glu (E), or glucose (F). Data are expressed as the mean + SEM (n = 12). The statistical significance when comparing individual treatments to the control are represented by asterisks: *** = P ≤ 0.001, ** = P ≤ 0.01, * = P ≤ 0.05.
Ile and Leu, resulted in lower feed intake after the oral gavage which was more pronounced around 2 h after treatment, suggesting a stronger effect on satiety rather than satiation. High dietary levels of Leu and Ile showed a strong anorexigenic effect potentially mediated by CCK and GLP-1 in pigs (Millet et al., 2015; Kwon et al., 2019; Tian et al., 2019a; Müller et al., 2022). The activation of long-term satiety signals such as leptin and insulin have also been described associated to dietary BCAA in pigs (Lynch et al., 2006; Zhang et al., 2019). Gut hormones have been involved in satiety resulting in an increase in the intermeal interval, which may explain the decreased feed intake in the Leu and Ile-gavaged pigs (Overduin et al., 2014; Williams et al., 2016). In addition, the satiating effect of Leu and Ile may also be related to post-absorptive signals (Cuber et al., 1989; Deacon et al., 1996). For example, the detection of plasma BCAA unbalances by the CNS resulted in anorectic behaviors in pigs and other species (Cota et al., 2006; Wessels et al., 2016; Kwon et al., 2019; Tian et al., 2019b).

Figure 3. Meal pattern analysis including the latency to first meal (LFM), first meal duration (FMD), intermeal interval (IMI), second meal duration (SMD) and number of meals (NM) in young pigs during the first 2 h after an oral gavage with water (control), or 3 mmol.kg⁻¹ solutions of Lys (A), Phe (B), Leu (C), Ile (D), Glu (E), or glucose (F). Data are expressed as percentage of the control group (dashed line) (n = 12). The statistical significance when comparing individual treatments to the control are represented by asterisks: ** = P ≤ 0.01, * = P ≤ 0.05.

Phe and Glu did not trigger satiation and/or satiety in pigs. These results are inconsistent with previous reports where Phe increased CCK release from duodenum, and Glu GLP-1 secretion from ileum (Feng et al., 2019; Müller et al., 2022). The nature of the ex vivo model used in the current research may have been a constraint, thus potentially explaining the contrasting results. The ex vivo model
consists of an excised intestinal tissue voided of the neural and hormonal networks (thus, feedback mechanisms) which would be active in a live tissue and may influence gut hormone secretion, and meal pattern (Cummins and Overduin, 2007; Furness et al., 2013). In addition, there is a high catabolism of Glu in the small intestine (enterocytes). This may result in low concentrations of Glu reaching the most distal segments of the gastrointestinal tract (GIT) where most of GLP-1 is secreted and blood (reducing a potential impact on the CNS) (Reeds et al., 1996). The lack of an anorexigenic effect in Glu-treated pigs is of particular interest considering that dietary supplementations of the AA have been linked with improved gut health and dietary preferences in post-weaned pigs (Guzmán-Pino et al., 2019; Chen et al., 2021). Thus, the mechanisms underlying the effect of Glu on appetite modulation merits further investigation.

On a practical comment, it may be worth to note the relevance of these results in terms of current feed formulation practices where Lys is consistently an essential dietary ingredient often included in excess of the requirement. These marginally excess amounts may account for live weight variations within the herd (Presto Åkerfeldt et al., 2019). In addition, this study corroborates previous findings indicating a negative impact of excess dietary Leu (common in corn-based diets) on feed intake in pigs (Wessels et al., 2016; Kwon et al., 2019). Thus, the dietary over supplementation of EAA seems to be detrimental for the growth performance and appetite of young pigs.

The effect of the oral gavage was limited to 4 h post-gavage, indicating that no significant effects on the 24 h cumulative feed intake were observed. This is compatible with the time required to return to baseline homeostasis in the post-prandial stages in pigs (Pluschke et al., 2018). Further investigation on the pre- and post-absorptive mechanisms involved in these effects may help better understand the appetite-modulatory role of each individual AA. Finally, it is important to mention that the responses to some of the AA highlighted in this study may be influenced by the complexity of complete feeds due to potential interactions with other nutrients within the GIT.

**Conclusions**

Acute oral doses of Lys, Leu, and Ile reduced feed intake in young pigs. Whereas Lys altered meal pattern by reducing the first meal duration followed by an increase in the intermeal interval; Leu increased the intermeal interval and reduced the first meal duration followed by an increase in the intermeal interval; Ile increased the intermeal interval and reduced the meal pattern. These behavioral responses indicate that Lys stimulates satiation and satiety while BCAA promotes mainly satiety. Dietary excesses for some of the most limiting EAA should be narrowed in feed formulations as to prevent a significant overconsumption that could lead to reduce appetite and performance, particularly during the post-weaning period.

**Acknowledgments**

This study was supported by The University of Queensland and Australian Pork Limited as part of the project APL 2016/053. The authors acknowledge the statistical counseling provided by Mr. Allan Lisle.

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**Author Contributions**

M.M.: conceptualization, investigation, data curation, formal analysis, writing—original draft. C.X.: investigation, writing—review and editing. M.N.: investigation, writing—review and editing. N.E.-M.: investigation, writing—review and editing. A.T.: conceptualization, writing—review and editing. R.B.: conceptualization, writing—review and editing. E.R.: conceptualization, writing—review and editing, supervision, project administration, funding acquisition, and resources.

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**Conflict of Interest Statement**

The authors declare there is no conflict of interest.

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