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Food preferences and aversions in human health and nutrition: how can pigs help the biomedical research?

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The establishment of food preferences and aversions determines the modulation of eating behaviour and the optimization of food intake. These phenomena rely on the learning and memory abilities of the organism and depend on different psychobiological mechanisms such as associative conditionings and sociocultural influences. After summarizing the various behavioural and environmental determinants of the establishment of food preferences and aversions, this paper describes several issues encountered in human nutrition when preferences and aversions become detrimental to health: development of eating disorders and obesity, aversions and anorexia in chemotherapy-treated or elderly patients and poor palatability of medical substances and drugs. Most of the relevant biomedical research has been performed in rodent models, although this approach has severe limitations, especially in the nutritional field. Consequently, the final aim of this paper is to discuss the use of the pig model to investigate the behavioural and neurophysiological mechanisms underlying the establishment of food preferences and aversions by reviewing the literature supporting analogies at multiple levels (general physiology and anatomy, sensory sensitivity, digestive function, cognitive abilities, brain features) between pigs and humans.

Keywords: pig, conditioned learning, eating behaviour, animal model, biomedical applications

Implications

Investigation of the behavioural and neurophysiological mechanisms of the establishment of food preferences and aversions can lead to important developments in the context of human nutrition and health. Because the rodent models are not always adequate in this field, there is a need to develop alternative experimental models. Pigs have numerous similarities with humans in terms of the physiology, anatomy, sensory sensitivity, cognitive abilities and brain functions. The aim of this paper is to promote the use of pigs for biomedical research in human nutrition.

Introduction

Feeding is a complex behaviour, which can be described as 'the research and consumption of food and drink to maintain vital functions' (Bellisle, 1999) and to 'fulfil the metabolic needs of the organism' (Ferreira, 2004). Today, it is also well acknowledged that a high proportion of human food consumption in developed countries appears to be driven by pleasure (for a review, see Lowe and Butryn, 2007) and sociocultural influences. Food consumption is also involved in fundamental metabolic homeostasis regulation, as it controls the supply of energy and nutrients in the organism (Bellisle, 1999). According to Ferreira (2004), feeding behaviour implies that animals learn to consume high-energy foods and to avoid toxic foods. Establishment of food selection implies that, during its first experience with food, the organism memorizes the sensorial characteristics of the food (e.g. taste, odour, texture and visual cues) and the post-ingestive consequences of its ingestion, and associates these food characteristics with these consequences (Garcia *et al.*, 1974; Sclafani, 2001; Ferreira, 2004). This regulation of food choices requires learning and memory capacities (Bernstein, 1999; Houpt, 2000; Welzl *et al.*, 2001), which enable the animal to adapt its feeding behaviour towards a novel food. Such food selection leads to the constitution of a feeding repertoire, which is dependent on the particular feeding situation and on the needs of the organism (Bellisle, 1999). The feeding repertoire and food selection constantly evolve throughout life governed by several factors, such as genetic and environmental, and according to sensorial, physiological and psychological states (Bellisle, 2006). In numerous animal species, including humans, development of food preferences and aversions makes a major contribution towards the establishment of the feeding repertoire.

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The aim of this review is threefold. In the first part, the characteristics and development of aversions and preferences, two phenomena involved in the establishment of eating behaviour and feeding repertoire, will be described in the light of recent literature. The second part of the review will summarize the current socio-economic and medical context related to preferences and aversions in human nutrition and will aim to justify the current needs for research in this topic. The last part of the review will focus on the methods and animal models currently used to address questions in this field, and put forth some arguments in favour of the use of pigs as a preferred model for studying the development of food preferences and aversions in humans.

Characteristics and development of preferences and aversions

Food preferences and aversions: a classical conditioning

Food preference or aversion learning is a form of classical conditioning first described by Pavlov (1960). A conditioned stimulus (CS) is associated with an unconditioned stimulus (US). In the case of conditioned food preference and aversion, animals come to consume or avoid a food (CS) that produces positive or negative post-ingestive symptoms (US), respectively (Pavlov, 1960; Garcia *et al.*, 1974).

When food intake generates unpleasant gustatory perception (e.g. bitter taste) or is followed by a visceral malaise (nausea, diarrhoea, etc.), the organism learns to avoid the consumption of that food or other food that presents the same sensory characteristics (Ferreira, 2004). This is known as conditioned food aversion. This ability to learn to avoid potentially toxic foods has been demonstrated in numerous animal species, from invertebrate to humans (for a review, see Bernstein, 1999; Paradis and Cabanac, 2004). Indeed, food aversion has been described in a variety of mammals, in addition to humans (Garcia *et al.*, 1974; Bellisle, 1999; Ravasco, 2005; Bellisle, 2006) or rats (Yasoshima *et al.*, 2000; Ferreira, 2004), and in livestock species such as horses, sheep and cattle (Houpt *et al.*, 1990; Burritt and Provenza, 1996; Halaweish *et al.*, 2002; Ginane and Dumont, 2006; Pfister *et al.*, 2007), and also in birds (Skelhorn and Rowe, 2006; Halpin *et al.*, 2008; Skelhorn *et al.*, 2008) and reptile species (Terrick *et al.*, 1995; Paradis and Cabanac, 2004). Experimentally induced food aversions are frequently conducted by an intragastric or an intraperitoneal injection of lithium chloride, an emetic substance known to induce visceral malaise. As a result, animals come to avoid the food that has been paired with this treatment (Pavlov, 1960; Garcia *et al.*, 1974).

Post-ingestive consequences can also lead to the establishment of food preferences. When food intake generates positive appetitive or post-ingestive consequences (e.g. abundant supply of energy), the organism learns to preferentially consume this particular food, which is known as a conditioned food preference. Two main categories of preferential conditioning are reported: the flavour–flavour and the flavour–nutrient conditionings. The first category consists of the association between the flavour of an unfamiliar food and one that is familiar and/or already has a high hedonic value. This kind of association has been widely studied in rats (Sclafani and Ackroff, 1994; Warwick and Weingarten, 1994 and 1996) and humans (Mobini *et al.*, 2007; Brunstrom and Fletcher, 2008). In contrast, flavour–nutrient conditioning is induced by pairing the flavour of an unfamiliar food with an energy supply, thats is, positive post-ingestive consequences (Myers and Sclafani, 2006). Flavour–nutrient learning has been studied in humans (Brunstrom and Mitchell, 2007; Mobini *et al.*, 2007; Zeinstra *et al.*, 2009) and rats (Sclafani and Ackroff, 1994; Warwick and Weingarten, 1994; Lucas *et al.*, 1997; Lucas and Sclafani, 1998; Sclafani, 2001). Although they are often combined, the ingestion of highly palatable food (e.g. sweet food) is often paired with an energy (caloric) supply (Myers and Sclafani, 2006). The two types of independently operating conditioned learning have been experimentally induced, especially in rats (Ackroff *et al.*, 2001; Gilbert *et al.*, 2003; Touzani and Sclafani, 2005; Myers, 2007; Touzani and Sclafani, 2007; Touzani *et al.*, 2009a and 2009b). Flavour–flavour association was achieved by adding an appetent taste or flavour in the test solution (e.g. non-caloric sweet taste) to induce an oral-hedonic reinforcement, whereas flavour–nutrient association was achieved by pairing food ingestion (CS) with an intragastric or an intraperitoneal injection (US) of energy (e.g. glucose or fructose) to induce positive post-ingestive consequences.

Considered as forms of classical conditioning, food preference and aversion learning have certain features in common: they are extremely robust and can be acquired in a single learning trial for a novel food, that is, after only one pairing of CS to US (Garcia *et al.*, 1974; Bellisle, 2006; Myers, 2007). Significant aversions also develop to the CS despite long delays between exposure to the CS and US (Garcia *et al.*, 1966). However, one should keep in mind that, for practical purposes, preferences are often stronger to acquire than aversions and their acquisition often requires more than one association to achieve a strong and long-lasting effect, although some studies in rats showed that the acquisition of a preference can be rapid (Myers, 2007; Ackroff *et al.*, 2009).

The development of food preferences and aversions is governed by sociocultural and familial influences

Even if conditioned food preferences and aversions broadly depend on factors related to learning and memory, food selection also depends on subtle factors that are genetic, hedonic, ontogenic and sociocultural. According to Birch (1999), genetic predispositions include the ability to express 'innate' preferences, the capacity to reject novel food (neophobia) and the ability to learn preferences. The development of food choices implies that environmental factors combine with these genetic predispositions (for a review, see Wardle and Cooke, 2008) and this complex association of factors leads to the formation of 'innate' and learned preferences and aversions.

In humans and several animal species, reflex responses to taste and smell are present in the neonate before any spontaneous feeding experience (Birch, 1999), suggesting

that the development of food preferences and aversions does not depend only on learning processes. The study of facial expressions induced by taste stimulations showed that neonates prefer foods that are sweet (sugar) and reject sour or bitter food (Steiner, 1979). Moreover, preference for salt develops in human infants approximately 4 months postnatally (Beauchamp *et al.*, 1994). However, it is necessary to be cautious with the use of the term 'innate preferences'. As the foetus can perceive some sensorial stimuli even during the last weeks of pregnancy (i.e. has functional olfactory receptors or taste papillae; Mennella and Beauchamp, 1996; Bellisle, 1999; Doty and Shah, 2008), these newborn preferences are likely to have been influenced by several pre- and postnatal stimulations.

The environment and especially mother–child interactions also play an important role in shaping children's preferences (Birch, 1999). What the mother eats during pregnancy and lactation can have an impact on children's food choice, as volatile compounds of the mother's diet (e.g. vanilla, garlic, anis, alcohol) are transferred from the maternal circulatory system to the amniotic fluid (Doty and Shah, 2008) and milk (Mennella and Beauchamp, 1993 and 1996). Mennella and Beauchamp (1993) showed an effect of prior experience with garlic in mother's milk on the breast-feeding behaviour of their infants: children with mothers who had consumed garlic during pregnancy showed a weaker aversion to garlic odour compared with non-exposed children. Similarly, the mother's consumption of vanilla altered the behaviour of her infant during breast-feeding: human infants whose mothers had consumed vanilla during gestation showed greater acceptance of vanilla flavour than non-exposed infants (Mennella and Beauchamp, 1996). Similar results on the impact of mother–young interactions were found in pigs (Campbell, 1976). Langendijk *et al.* (2007) showed that pre- and postnatal exposure to flavours (garlic or anis) increases postweaning feed intake in pigs. Exposure to flavours through the sow's diet during gestation and lactation increases acceptance by piglets (Oostindjer *et al.*, 2010). Saint-Dizier *et al.* (2007) also found that the development of food preference in lambs depends on observation of the mother that provided visual and behavioural cues to eat or avoid the food.

In addition to the maternal influences, these food choices are also strongly modulated throughout life via feeding experiences in association with sociocultural influences (Bellisle, 1999 and 2006; Birch, 1999) including the family circle, the social group or the cultural environment of children. For instance, exposure to a variety of flavours in the familial environment enhances food acceptance in children (Gerrish and Mennella, 2001), whereas children who rarely have the opportunity to try new food, perhaps because of rigid control by parents of the food environment of their infant, are more likely to be neophobic in the future (Hursti and Sjödén, 1997).

Overall, these findings suggest that social environment is important and that genetic factors may play a minimal role in the phenomenon of food preferences. The association between these two factors may explain the considerable inter-individual variability between children and between adults in their food preferences (Bellisle, 2006; Wardle and Cooke, 2008). In summary, food preferences and aversions are complex phenomena and their development does not only rely on classical learning processes but also on numerous factors, genetic or socio-cultural.

Study of feeding behaviour and the current socio-economic context

Investigation on the development of feeding preferences and aversions and their inherent mechanisms (behavioural and neurobiological) may fulfil the current needs of research and development in human nutrition and health. The relevance of studying feeding behaviour for human health applications is addressed in this chapter of the review by drawing up a non-exhaustive list of possible applications. The first section will introduce the problems of appetite and feeding disorders, especially obesity, a condition that is reaching epidemic proportions in wealthy countries. In the second section, the applications in biomedical and pharmacological research will be investigated.

Obesity and eating disorders

The establishment mechanisms of food selection described above have a strong adaptive value and so does the organisms' capacity to store energy. These mechanisms present an unquestionable advantage in an environment where resources are scarce. However, with the recent development of fundamental, unprecedented increases in food availability in modern human societies (i.e. plethoric and appetent food), these same mechanisms can lead to detrimental conditions, such as obesity and eating disorders (Lowe and Butryn, 2007).

Indeed, obesity has become a worldwide phenomenon and a major health issue (Popkin and Doak, 1998; Spurlock and Gabler, 2008). In 2005, the World Health Organization stated that approximately 400 million adults were obese (Singh-Manoux *et al.*, 2009). Obesity is characterized by an unbalanced hunger/satiety ratio and by an overaccumulation of fat in adipocytes. It is a multifactorial disease that can cause or arise as a consequence of eating disorders, although the relationship between obesity and eating disorders is very complex. Obesity may result from several influences, including genetic, metabolic, nutritional, hormonal, behavioural, environmental (e.g. stress) or iatrogenic (i.e. due to medical treatment) factors (Bellisle, 1999; Stein and Colditz, 2004). Regarding environmental influences, it seems that activity changes (e.g. urbanization, structure of work, more passive leisure-time and sedentary activities) are responsible for decreased physical activity and energy consumption of excess empty calories (for a review, see Popkin and Doak, 1998). Although low levels of physical activity contribute towards increased obesity rates, the onset of an excessive and unbalanced diet is also a major contributor to overweight and obesity (Blundell and Finlayson, 2004; Lowe and Levine, 2005; Lowe and Butryn, 2007). This so-called 'western diet' is

characterized by a high proportion of palatable foods, such as high-carbohydrate and high-fat foods, that are responsible for food binges with exaggerated preferences (Yanovski, 2003). Fat consumption is considered to be pleasurable because fat increases the palatability of foods, enhancing food sensorial characteristics, such as flavour, odour and texture (Drewnowski, 1997; Yanovski, 2003; Mizushige *et al.*, 2007). The tendency to prefer high-fat and high-carbohydrate foods is enhanced by the lower cost of those diets compared with the cost of healthy diets including fruit and vegetables (Bernstein *et al.*, 2010). Low-income consumers are particularly concerned about the cost of food rather than its nutritive and health benefits and prefer low-cost foods rather than healthy foods (Hampson *et al.*, 2009). The modern food transition and the widespread availability of highly palatable and low-cost food providing an 'obesogenic environment' have stimulated food intake, leading to energy intake beyond that required to balance energy expenditure (Wardle, 2007). Thus, although socio-economical factors play a predominant role in the emergence of feeding disorders, the sensorial characteristics of foods are also likely to be involved.

Being overweight or obese has various negative consequences and can cause several chronic health diseases. The disorders that develop are associated with increased mortality and risks for coronary heart diseases, type-2 diabetes, hypertension and some types of cancer (for a review, see Sturm, 2002; Stein and Colditz, 2004). Cole *et al.* (2010) reported that overeating and consumption of high-fat/high-caloric diets increase the risk of age-related brain diseases later in life, such as Alzheimer's disease, Parkinson's disease or frontal temporal dementia. As obesity is strongly associated with clinical diseases, it also reduces health-related quality of life and increases health-care and medication costs (Sturm, 2002).

Considering the epidemic of obesity and its detrimental consequences on health, there is an urgent need for optimization of methods to prevent and treat obesity. As the sensorial characteristics of food may be involved in the development of eating disorders, such as binge eating and food addictions, a better understanding of food preferences and aversions may lead to improved methods for the prevention and treatment of obesity and eating disorders (Yanovski, 2003). Study of food preferences and aversions could thus lead to the development of new, more efficient strategies to promote the establishment of good eating habits and diversified food repertoires in children, through acceptance of novel healthy food, from a young age. The development of such preventive methods is crucial as the prevalence of nutritional pathologies and diseases such as obesity can only be reduced by means of a close association between preventive and palliative methods. Children often exhibit some spontaneous neophobic responses and/or aversions towards novel food, and especially healthy food (e.g. vegetables), which are known to have a 'low reinforcement value' (Zeinstra *et al.*, 2009). Some behavioural techniques are already being used to facilitate the acceptance of novel and healthy foods by children. For instance, mixing vegetables with other more palatable ingredients may encourage the intake of vegetables later in life (Zeinstra *et al.*, 2009). Preference for a food can also be acquired in children by regular and repeated exposure to it (Wardle and Cooke, 2008). Using food as a reward may also be an effective strategy to increase food acceptance by children, although this strategy is slightly controversial, as the reward strategy may be strongly related to the child's perception of the context (Wardle and Cooke, 2008). Therefore, it is necessary to develop our knowledge of the behavioural and neurophysiological mechanisms underlying the development of such learning. This may lead to recommendations in terms of feeding learning and diversification in children and adults.

Biomedical applications

Chemotherapy and radiotherapy. In cancer patients, chemotherapy and radiotherapy treatments often have detrimental or harmful side effects (e.g. nausea and vomiting) that may lead to the establishment of food aversions and ultimately to clinical anorexia and cachexia (Bernstein, 1978). Cancer patients under chemotherapy often show avoidance or aversion for a meal taken before the administration of treatment, because the meal is associated with therapy-induced malaise (Bernstein, 1978), which acts like a CS. Moreover, patients often complain about these symptoms before the infusion. The environmental context of drug administration (e.g. entry of the nurse or the doctor, sight of the syringe and of the infusion apparatus, hospital odours) can be associated with the symptoms and acts like a CS in itself. Thereby, after some pairings of CS) and US, some anticipatory symptoms may occur before the onset of the infusion, which clearly indicates conditioning (Stockhorst *et al.*, 1998; Stockhorst *et al.*, 2007). Holmes (1993) reported that 82% of patients under chemotherapy developed food avoidance, whereas, according to Mattes *et al.* (1987), over 50% of patients developed a food aversion after chemotherapy. Moreover, a reduction in taste sensitivity (hypogeusia), an absence of taste sensation (ageusia) or a change in taste sensitivity (dysgeusia) often occurs in patients receiving radiotherapy against cancers (Ripamonti *et al.*, 1998; Berteretche *et al.*, 2004). These taste alterations, which decrease the hedonic value of food, are another cause of nausea or vomiting in these patients (Lévy *et al.*, 2006; Bernhardson *et al.*, 2007)

The conditioned aversions to food and beverages developed after chemotherapy or radiotherapy might explain the loss of appetite and the decreased energy intake recorded in some cancer patients (Bernstein, 1978). The detrimental consequences of this malnutrition are diverse: poor prognosis, morbidity, decreased quality of life and clinical management of patients, but also anorexia (Bernstein, 1978; Andreyev *et al.*, 1998; Berteretche *et al.*, 2004). Taste changes, which are among the most common chemotherapy-associated side effects (Ravasco, 2005), are not only distressing for patients and impact on their quality of life (Epstein *et al.*, 1999 and 2002; Ohrn *et al.*, 2001), but also lead to food aversions and reduced food intake (Ravasco, 2005).

Although absent in rodents, the emetic reflex exists in several mammalian species, including humans, monkeys, dogs, cats and ferrets. As a result, the ferret has been used as an alternative model to rodents for chemotherapy-induced emesis (Andrews and Horn, 2006). Those pharmacological studies enabled the identification of efficient antiemetic agents such as serotonin type 3 receptor antagonists (anti-5HT3) or neurokinin type 1 receptor antagonists (anti-NK1) that are frequently used during chemotherapy treatments to inhibit nausea and vomiting in cancer patients (Durand *et al.*, 2009). As nausea and vomiting appear to be responsible for significant decreases of food intake in cancer patients, treatments based on these antiemetic drugs may result in an increase of food intake. However, despite modern antiemetic treatment, approximately 25% to 30% of chemotherapy patients still exhibit anticipatory nausea or vomiting immediately after re-exposure to the stimuli that usually signal the drugs' infusion (Stockhorst *et al.*, 2007). According to Schwartz *et al.* (1996), it seems that the presence of nausea following chemotherapy administration is correlated with a decrease in hedonic rating towards food but not with a decrease in consumption. Mattes *et al.* (1987) also suggest that nausea and vomiting may not be essential stimuli for the acquisition of conditioned food aversions. Antiemetic medications during chemotherapy may also be ineffective in preventing the development of aversion to foods, and thereby ineffective in increasing food intake (Schwartz *et al.*, 1996).

As a result of these issues, the study of the development of food aversions is clearly needed to develop new treatments and strategies to increase food intake in these patients. One of the interesting strategies developed as a result of the study of food aversions in humans is the 'scapegoat' technique (Broberg and Bernstein, 1987; Mattes *et al.*, 1987; Stockhorst *et al.*, 1998). This technique is based on the overshadowing principle underlying the principles of the classical conditioning technique (Pavlov, 1960). It consists of the presentation of a compound of two stimuli as a potential CS, which is paired with the US. The more salient of the stimuli is assumed to override the effects of the less salient one and the conditioned response elicited by the less salient element is weaker than if it alone had been paired with the US (Miller *et al.*, 1990; Stockhorst *et al.*, 1998). Broberg and Bernstein (1987) found that using strongly flavoured candies as scapegoats reduces food aversions during chemotherapy and, thereby, increases food consumption among paediatric patients. Furthermore, Mattes (1994) showed that patients exposed to a particular sensory stimulus demonstrate a statistically significant 30% reduction in the development of food aversion compared with the non-exposed patients.

The elderly and undernutrition. In addition to application to cancer patients under chemotherapy, the study of food aversions and preferences has other interesting biomedical applications, particularly in the hospitalized elderly. During the past century, the proportion of older individuals in developed countries has increased to a considerable extent and continues to grow rapidly. A decline in appetite is often observed in this population and is logically associated with a decreased food intake (for a review, see MacIntosh *et al.*, 2000; Beckoff *et al.*, 2001; Kagansky *et al.*, 2005; Fetissov *et al.*, 2009). This phenomenon is known as 'physiological anorexia of ageing'. Consequently, malnutrition is frequent in elderly populations, even in the developed countries, and even among the hospitalized elderly, nutritional status can be poor (MacIntosh *et al.*, 2000; Kagansky *et al.*, 2005). As for cancer patients, malnutrition is found to negatively influence the quality of life of older adults in nursing homes (Crogan and Pasvogel, 2003). Moreover, poor nutritional status has been implicated in the development and progression of chronic diseases commonly affecting the elderly and leading to complications during hospitalization, poorer clinical outcome and increased mortality (Kagansky *et al.*, 2005). Malnutrition is a predictor of long hospital stay and high mortality in geriatric and cancer patients (Chima *et al.*, 1997; Kagansky *et al.*, 2005).

St-Arnaud-McKenzie *et al.* (2004) suggest that the development of nutritional interventions to maintain hunger and reduce aversion may be necessary to ensure optimal food intake among hospitalized people (cancer patients, geriatric patients, etc.). For instance, Beckoff *et al.* (2001) showed that the use of glucose or other carbohydrate supplements in the diet can increase the total energy intake of older subjects and thus prevent weight loss in the elderly. Improving the pleasurable qualities of food, that is, taste and smell, may stimulate an increase in appetite and food intake in the elderly (MacIntosh *et al.*, 2000). As the sense of taste decreases with ageing (Bellisle, 1999; MacIntosh *et al.*, 2000), and given that taste and smell (i.e. flavour) are important features for the motivation to eat, an increased understanding of the sensorial characteristics of food that induce a deterioration in food intake in terms of quality and quantity in the elderly seems necessary. This should facilitate the development of appropriate preventive and treatment strategies to improve the health of older individuals.

Optimization of pharmaceutical medicines. The study of the perceived and preferred sensorial characteristics of food may also lead to an improved tolerance of oral medications, through enhancement of their palatability. Indeed, several medicines and active pharmaceutical ingredients may be difficult to ingest or may not very palatable due to their propensity to irritate the mouth or throat and their unpleasant taste (e.g. too bitter). This is particularly true for paediatric patients. These patients may have many of the same diseases and are often treated with the same drugs as those used to treat adults, although they are often more sensitive to gustatory cues (Mennella and Beauchamp, 2008). For instance, this is the case with oral contrast agents (Arya *et al.*, 2009) used before computed tomography examinations; especially large volumes must be ingested for investigations of intra-abdominal pathology (Weyant *et al.*, 2000). Paediatric patients' care is often disrupted because they have difficulty in tolerating the oral contrast solution, which has low palatability. Arya *et al.* (2009) have demonstrated that

oral contrast is more palatable when mixed with flavoured commercial drink mixes compared with the standard contrast mixed with water. Similarly, in their review, Mennella and Beauchamp (2008) argued that children's acceptance of many medicines may be increased by improving their palatability. For example, addition of sugars or salt substances may be effective in suppressing the bitter taste of some medications. Altogether, these results prove that a better understanding of the sensorial characteristics of food and beverages that are preferred or disliked may be very useful to improve biomedical treatments in hospital.

As reviewed above, in patients suffering from malnutrition, such as the elderly or cancer patients, stimulation of appetite by appetitive factors or by the addition of aroma to food might be a useful method to maintain weight and food intake. Further investigations are needed to identify the more pertinent food characteristics that could be manipulated to promote food intake and fight aversion in a clinical context.

The development of new strategies and innovative techniques may have a significant impact on the outcome of therapy and on the patients' quality of life. This biomedical research requires the use of animal models, depending on the experimental design and research paradigm to be investigated. It is obvious that the choice of an animal model has to be well considered, according to their biological characteristics and the research topic addressed. Most of the biomedical research is performed in rodent models, although this approach has severe limitations, especially in the nutrition field. An alternative model to rodents or non-human primates is the pig, which has several similarities to humans in terms of the digestive physiology, feeding behaviour, sensory sensitivity and brain organization and functioning. Pigs also have high cognitive capacities that allow them to integrate very complex conditioned learning, especially when this learning is coupled with socio-environmental determinants. The last part of the review focuses on the features that make the pig an ideal model to study preferences and aversions in human nutrition and health research.

The pig: a preferential animal model in human nutrition research?

Numerous studies on the development of food aversions and preferences have been carried out in rodent models (e.g. Touzani and Sclafani, 2005 and 2007; Touzani *et al.*, 2009aand 2009b) and have led to many significant and useful findings on the behavioural and neurobiological mechanisms underlying these feeding processes (for a review, see Ferreira, 2004). However, due to the huge phylogenic difference between rodents and humans, rodents are not suitable models to study such processes in humans. The considerable metabolic and physiological differences between humans and rodents have complicated the translation of research findings into applications in human biomedical and nutrition research (Table 1; Spurlock and Gabler, 2008). Moreover, due to ethical and practical reasons, some research on feeding behaviour cannot be conducted in humans or in non-human primates, especially since a recent European directive (EU Directive E4131, 2008) limits the use of non-human primates as animal models. The need for new animal models for applications in the domain of human health and nutrition emerged during the last decades (Vodicka *et al.*, 2005), with alternative and complementary models allowing the translation of science into biomedical methods for prevention and intervention, especially in the case of obesity (Spurlock and Gabler, 2008). In this context, the pig has been used extensively in human nutrition research. In addition to having a longer lifespan than mice, greater cost savings in housing under controlled conditions than for non-human primates (Vodicka *et al.*, 2005) and lesser risk of zoonoses (diseases spread by animals), pigs have several similarities with humans.

Anatomo-physiological similarities

Pigs and humans have several anatomical and physiological features in common. Pigs are monogastric omnivores, such as humans, with proportionally similar organ sizes and very comparable gastrointestinal tract anatomy, morphology and physiology (Spurlock and Gabler, 2008), despite some slight anatomical differences in their digestive systems. The total length of the gastrointestinal tract of a growing pig weighing approximately 30 to 40 kg is similar to that of an adult human. Moreover, the relative diameters of human and pig gastrointestinal tracts are very comparable. Pigs and humans also have approximately the same dietary requirements in terms of nutrients, although the quantitative requirements for each nutrient differ between the two species (Gandarillas and Bas, 2009). As a consequence of their similar digestive physiology, pigs have been extensively used as a model for assessing nutrient absorption in humans (Gandarillas and Bas, 2009).

The similarities between the two species extend to numerous other physiological functions (Vodicka *et al.*, 2005). For example, pigs and humans also have very similar cardiovascular systems (Xi *et al.*, 2004; Sahni *et al.*, 2008; Spurlock and Gabler, 2008), making pigs an excellent model for cardiovascular studies and for the development of new surgical procedures. Moreover, due to the similar size and physiological capacity of the organs, pigs may be the most suitable donors for animal-to-human xenotransplantation (Vodicka *et al.*, 2005; Sahni *et al.*, 2008). For the same reasons, pigs have also been used as a general surgical model for most organs and systems, particularly to assess the feasibility of surgical techniques or to evaluate their postoperative metabolic consequences (for a review, see Gandarillas and Bas, 2009). Another interesting factor is that pigs can develop some of the same disease as humans, such as obesity, diabetes, or cardiovascular diseases such as atherosclerosis (for a review, see Jokinen *et al.*, 1985). For instance, miniature Ossabaw pigs have a 'thrifty genotype' that confer them with a naturally increased predisposition to the development of obesity or insulin resistance in response to high-fat/high-carbohydrate diets (Dyson *et al.*, 2006; Clark *et al.*, 2011). Göttingen minipigs also have a high propensity

Table 1 *A non-exhaustive comparison of features and strains in pigs and rodents, highlighting the similarities or discrepancies of these models with humans, and their advantages and limitations for studies on human nutrition and eating disorders*

	Pigs	Rodents
General features		
Phylogeny	Close to humans	Huge difference from humans
Lifespan	Long (12 to15 years), enabling long-term studies	Short (2 to 3 years)
Availability	Numerous breeds, including conventional and miniature pigs	Some rodent models (e.g. obesity) derived from closely bred strains → homogeneous genetic data altering the translation of knowledge to humans with high genetic heterogeneity (Augustine and Rossi, 1999)
Genome	Sequenced (Archibald *et al.*, 2010)	Sequenced, easily modified by genetic engineering, but extreme cost of maintaining the offspring at a sufficient scale (Speakman *et al.*, 2008)
Housing recommendations (EU Directive 8869/10)	5- to 50-kg pig or minipig: compartment $>2\ m^2$, surface per animal of 0.20 to 0.70 m^2 in the case of group housing 50- to 100-kg pig: compartment $>3\ m^2$, surface per animal of 0.80 to 1 m^2 in the case of group housing	20- to 30-g mouse: 330 cm^2 in laboratory 200- to 600-g rat: 800 cm^2 in laboratory $>$600g-rat: 1500 cm^2
Behavioural features		
Sweet craving, phagomania	Reported both in obese pigs (Val-Laillet *et al.*, 2010c) and in humans (Yanovski, 2003)	Reported in obesity-prone compared with obesity-resistant rats (Pickering *et al.*, 2009)
Learning and cognitive abilities	Efficient learning abilities during behavioural tests (e.g. the open field or the novel object tests; Lind *et al.*, 2007; Kornum and Knudsen, 2011)	Rats less efficient compared with pigs during some cognitive tasks (e.g. progressive ratio; Ferguson *et al.*, 2009) or social recognition tests (Held *et al.*, 2005)
Anatomo-physiological features		
General anatomy	Organ sizes proportionally similar to humans	Small size of the organs with a different overall organization
(GIT)	Very comparable to humans, (e.g. similar length and diameter of the GIT of a growing pig and that of a human; Spurlock and Gabler, 2008)	Same overall organization of the GIT as in humans, but few differences (e.g. relative lengths of the small intestine; DeSesso and Jacobson, 2001). Different anatomical and functional development of the GIT (Ménard, 2004)
Digestive physiology	Similar dietary requirements, digestive physiology and nutrient absorption processes as in humans (Gandarillas and Bas, 2009)	Differences in the relative absorptive surface areas of the GIT (e.g. faster nutrient absorption in humans than in rats; DeSesso and Jacobson, 2001)
Ability to develop human diseases	Obesity (Val-Laillet *et al.*, 2010a, 2010b and 2010c; Clark *et al.*, 2011), diabetes (Bellinger *et al.*, 2006; Liu *et al.*, 2007), atherosclerosis (Xi *et al.*, 2004; Miyoshi *et al.*, 2010).	Obesity, metabolic syndrome (Li *et al.*, 2008; Aleixandre de Artiñano and Miguel Castro, 2009)
Adipokines and obesity	Same adipokines linked to obesity in pigs and in humans (e.g. adiponectin and leptin; Spurlock and Gabler, 2008)	Conflicting results compared with humans (e.g. lower adipsin rates in obese than in lean mice *v.* higher rates in obese than in lean humans, TNF-α released into the circulation in obese animals but not in obese humans; Arner, 2005)
Taste receptors	Intestinal taste receptor subunits (T1R2 + T1R3, associated with the gustatory G-protein (gustducin) involved in sweet taste recognition characterized in pigs (Moran *et al.*, 2010b) humans (Li *et al.*, 2002) and rats (Mace *et al.*, 2007)	
Sweet perception	Perception of the sweet taste of some compounds known to be sweet to humans by pigs (Hellekant and Danilova, 1996 and 1999) and rats (Frank and Blizard, 1999)	
Neurobiological features		
Brain anatomy	Gyrencephalic brain of approximately 180 g (1300 g in humans; Sauleau *et al.*, 2009)	Lissencephalic brain of approximately 10 g (Sauleau *et al.*, 2009)
Brain structures	Brain similar to that of humans in terms of structure, vascularization, anatomy, growth and development (Vodicka *et al.*, 2005; Lind *et al.*, 2007)	Many differences in the organization of some brain structures and in neuronal density compared with humans (e.g. amygdala; Pitkänen and Kemppainen, 2002)

Table 1 *Continued*

	Pigs	Rodents
Imaging techniques	Large brain that enables the identification of cortical and subcortical structures by neurosurgery or conventional imaging techniques in living animals (MRI, CT, SPECT, PET; Sauleau *et al.*, 2009)	Small brain compatible for micro-imaging techniques (micro-PET, micro-MRI, micro-CT; e.g. Tai *et al.*, 2005; Wu *et al.*, 2008), but with higher radiation exposure to obtain the same resolution as in humans → potential tissue damage (Ritman, 2007)
Neurotransmitters	Similar neurotransmitters involved in feeding behaviour (serotonin, dopamine, opioid systems), e.g. developing 5-HT system in human infants and piglets (Niblock *et al.*, 2005)	Similar neurotransmitters involved in feeding behaviour (e.g. the dopamine system related to the food reward perception; Barbano and Cador, 2007), serotonin system involved in hedonic processing during food intake (Berridge, 2000)
Brain and obesity	Deactivation of some brain structures (e.g. prefrontal cortex) in obese compared with lean subjects (Val-Laillet *et al.*, 2011), as in humans (Le *et al.*, 2006)	Deactivation of the frontal cortex and activation of the superior colliculus in obese compared with lean rats (Thanos *et al.*, 2008)
Examples of the strains currently used as models for human obesity and/or eating disorders		
Induced models of obesity		
Genetic models	Knockout models of pigs (e.g. Casu *et al.*, 2010), but not dedicated to the study of feeding behaviour or nutritional diseases	Numerous knockout models to study eating pathologies in humans (e.g. the *axl* mouse ; action on the tyrosine kinase receptor; progressive obesity without hyperphagic behaviour but with an increase of TNF-α)
Dietary models	High propensity of Göttingen minipigs (Val-Laillet *et al.*, 2010a, 2010b and 2010c) and microminipigs (Miyoshi *et al.*, 2010) to develop obesity in response to diets enriched with carbohydrates and lipids in only 15 weeks	Diet-induced obesity rodents with increase of body weight, adiposity, circulating leptin and insulin levels and decrease of insulin sensitivity. But, discrepancies in gene-expression alterations between diet-induced obese rats and obese humans (Li *et al.*, 2008)
Spontaneous models of obesity		
Genetic models	Thrifty genotype of Ossabaw minipigs with a natural predisposition to the development of obesity in response to high-fat/high-carbohydrates diets and even in absence of high-fat diets (Dyson *et al.*, 2006; Spurlock and Gabler, 2008; Clark *et al.*, 2011)	Ten spontaneous single-gene mutations leading to obesity (Augustine and Rossi, 1999; Speakman *et al.*, 2008; e.g. *ob/ob* mice; mutations in the leptin gene), *db/db* mice and Zucker (*fa/fa*) obese rats (mutations in the leptin receptor gene) → spontaneous obesity with increased weight gain and hyperphagia
Spontaneous or induced models of anorexia nervosa		
	The wasting pig syndrome, infectious disease caused by porcine circovirus 2 (Chae 2004) used as a model of anorexia nervosa with decreased appetite, great weight loss and acute motor activity (Casper *et al.*, 2008; Treasure and Owen, 1997)	'Activity-stress' or 'activity-based anorexia' model in mice and rats with restricted food intake in the presence of hunger, weight loss, excessive activity (Casper *et al.*, 2008) Anorexic (*anx/anx*) mouse, spontaneous mouse mutation with decreased food intake leading to death)
Induced models of binge eating		
	Sweet craving induced thanks to dietary model of obesity in minipigs, with exacerbated preference of obese minipigs for high-carbohydrate diets paired with high food intake (Val-Laillet *et al.*, 2010c)	Genetic models: link between high sensitivity to stress and binge eating disorders → genetic mouse model of stress sensitivity used to induce binge eating to high-fat or high-carbohydrate diets (e.g. CRFR2-deficient mice; Teegarden and Bale, 2008)

GIT = gastrointestinal tract; MRI = magnetic resonance imaging; CT = computed tomography; SPECT = single photon emission computed tomography; PET = positron emission tomography; 5-HT = the medullary serotoninergic system; TNF = tumour necrosis factor.

to develop obesity (i.e. weight gain, overeating) in only 15 weeks and in response to diets enriched in carbohydrates and lipids (e.g. Val-Laillet *et al.*, 2010a, 2010b and 2010c). Thus, conventional pigs and minipigs are often used as models of high-fat and/or high-carbohydrate diet-induced obesity (Val-Laillet *et al.*, 2010a, 2010b, 2010c and 2011, Clark *et al.*, 2011), diabetes (Bellinger *et al.*, 2006; Liu *et al.*, 2007) or atherosclerosis (Xi *et al.*, 2004).

With regard to hormonal regulation of feeding behaviour, pigs and humans share some taste receptors and hormones that are involved in appetite/satiety regulation. Pigs' intestines have numerous sugar transporters similar to those in humans (for a review, see Wood and Trayhurn, 2003), such as GLUT5, a Na^+-independent fructose transporter, or the Na^+/glucose co-transporter 1 (SGLT1) that transports glucose and galactose from the lumen of the intestine into enterocytes (Moran *et al.*, 2010b; Shirazi-Beechey *et al.*, 2011). Moran *et al.* (2010a) reported that the supplementation of the diet of weaning piglets with artificial sweeteners (i.e. Sucram, a combination of saccharin and neohesperidin dihydrochalcone) led to an enhancement of the expression of SGLT1 and of the subsequent intestinal glucose transport function by acting on the intestinal and lingual sweet taste receptor T1R2+T1R3, subunits that are associated with the gustatory G-protein gustducin (for a review, see Shirazi-Beechey *et al.*, 2011). These intestinal taste receptor subunits and their involvement in sweet taste recognition have been characterized in pigs (Moran *et al.*, 2010b), humans (Li *et al.*, 2002) and rats (Mace *et al.*, 2007; Sclafani, 2007). Food intake also induces the release of several gut hormones from the endocrine cells of the small and large intestines, such as glucagon-like peptide 1 (GLP-1) or 2 (GLP-2) or the leptin, a hormone that is particularly expressed in adipocytes and acts as a satiety signal. These hormones and their involvement in the induction of satiety and regulation of feeding behaviour have been identified both in humans (Ahima and Antwi, 2008; Steinert *et al.*, 2011) and in pigs (Schlatter *et al.*, 2007; Liu *et al.*, 2011).

Neurobiological similarities

The use of pigs in neurosciences has increased widely in the past decade due to interesting neurobiological similarities between pigs and humans (for a review, see Lind *et al.*, 2007; Sauleau *et al.*, 2009). Pigs and humans have most of their cerebral structures in common and their brains appear to be comparable in terms of structure, vascularization, anatomy, growth and development (for a review, see Vodicka *et al.*, 2005; Lind *et al.*, 2007).

In terms of gross neuroanatomy, pigs have a convoluted or a gyrencephalic cortical surface, superficially resembling the human brain (Figure 1; Hofman, 1985), whereas rodents have a small lissencephalic brain. The pig brain, which has human-like vascularization characteristics, is large enough to enable the identification of cortical and subcortical structures by neurosurgery and conventional imaging techniques in living animals (Lind *et al.*, 2007; Sauleau *et al.*, 2009). The pig's brain, being relatively large, is suitable for imaging techniques and machines used for humans, for instance, magnetic resonance imaging, computed tomography, single photon emission computed tomography (SPECT) or positron emission tomography (PET; Figure 1). Thus, pigs have been used as a model for human research in a wide range of imaging studies, such as in traumatic brain injury (Grate *et al.*, 2003), Parkinson's disease (Mikkelsen *et al.*, 1999; Cumming *et al.*, 2003) or stroke (Sakoh *et al.*, 2000; Røhl *et al.*, 2002). Anatomical brain imaging studies on pigs have allowed the identification of swine cerebral structures and the conception of stereotaxic atlases of the pig brain (e.g. Felix *et al.*, 1999; Watanabe *et al.*, 2001; Saikali *et al.*, 2010). Thanks to these atlases, numerous anatomical brain analogies between pigs and humans have been highlighted.

Despite these anatomical similarities and the huge number of neurobiological studies, few studies have focused on the characterization of structures that are specifically involved in feeding behaviour and especially in the establishment of food preferences and aversions (Figure 2; Biraben *et al.*, 2008; Val-Laillet *et al.*, 2010d). Brain structures involved in the establishment of conditioned food preference or aversion and structures of the 'brain reward system' involved in the hedonic perception of food have been widely described in the rat model (for a review, see Ferreira, 2004; Berridge, 2009). This functional brain network consists of structures such as the amygdala (Gilbert *et al.*, 2003), the insular cortex (Desgranges *et al.*, 2009; Roman *et al.*, 2009) or the parabrachial nucleus (Reilly, 1999; Reilly and Trifunovic, 2000), which are involved in the establishment of a feeding preference or aversion, depending on the sensorial stimuli involved. Literature data also report 'hedonic hotspots' distributed in different brain structures such as the nucleus accumbens (Baldo and Kelley, 2007; Barbano and Cador, 2007; Pritchett *et al.*, 2010), the ventral pallidum (Berridge, 2009) or the subthalamic nucleus (Baunez *et al.*, 2002). The ventral striatum (i.e. nucleus accumbens) is also involved in feeding behaviour (Kelley *et al.*, 2002; Will *et al.*, 2006). These hedonic hotspots play a role in the perception of the hedonic features of food intake and in the characterization of food palatability, that is, mediate pleasure associated with the gustatory signals.

In contrast, few functional studies have been carried out in pigs on the brain structures specifically involved in feeding behaviour and especially in the establishment of food preferences and aversions. In the past decades, some neurobiological studies used pigs to investigate human brain anomalies and feeding behaviour disorders (Sauleau *et al.*, 2009). The changes in the metabolism of some brain structures in obese pigs, used as a model of obese humans, were studied using a SPECT imaging technique (Val-Laillet *et al.*, 2011). This study suggests that, as in obese humans, compared with lean subjects, obese minipigs (Figure 3) had relatively less activation in specific brain structures, including the prefrontal cortex, the nucleus accumbens and the ventral tegmental area. Moreover, it has been demonstrated that chronic vagus nerve stimulation, which was originally used as a treatment for refractory epilepsy in humans, also affected food intake and weight gain in humans and obese

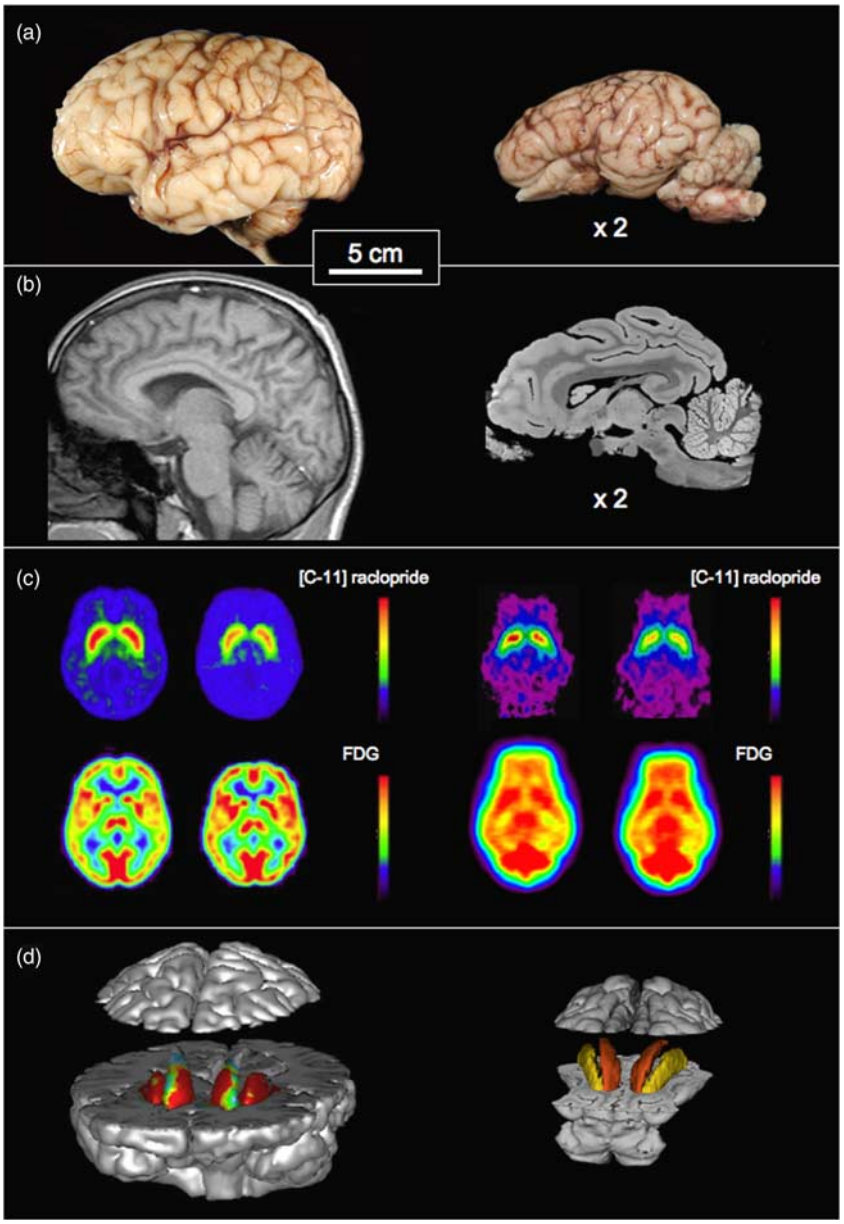

Figure 1 Comparison of human (left) and pig (right) brain images. (a) *Ex vivo* anatomical brain and (b) magnetic resonance brain images. The image of the extracted human brain was used with the permission of J. C. Fournet (University Hospital Sainte-Justine, Montreal, Canada, http://www.humpath.com). The other images are from our institution. (c) ^{11}C-Raclopride positron emission tomography (PET) and ^{18}fluorodeoxyglucose (^{18}FDG) PET brain images. PET images of humans were obtained with the permission of Gene-Jack Wang (Brookhaven National Laboratory, Upton, New York, USA) and Elsevier (Wang *et al.*, 2001), illustrating the metabolic differences between a lean and an obese patients, respectively. ^{11}C-Raclopride PET images of pigs were obtained with the permission of P. Cumming (Pet Center, Århus University Hospitals, Åarhus, Denmark; http://www.cfin.au.dk/index.php?menu=262). ^{18}FDG PET images of pigs are from our institution. (d) A three-dimensional (3D) view of the dopaminergic nuclei in both species. The human model was obtained from the website http://www.brainvisa.info/museum.html. The pig model was obtained from a stereotactic 3D atlas realized in our institution (Saikali *et al.*, 2010).

minipigs (Biraben *et al.*, 2008; Val-Laillet *et al.*, 2010c). Indeed, vagus nerve stimulation decreased weight gain, food consumption and sweet craving in adult obese minipigs (Val-Laillet *et al.*, 2010c). Numerous studies support the idea that this potential therapy against obesity would be as effective in humans as in animal models such as pigs. Interestingly, Biraben *et al.* (2008) studied the activation of cerebral structures during chronic vagus nerve stimulation using the SPECT imaging technique. They reported that chronic vagus nerve stimulation activated some cerebral structures known to be involved in feeding behaviour and the reward system (e.g. nucleus tractus solitarius and dorsal motor nucleus of the vagus, the olfactory bulb, the globus pallidus, the hippocampus and the cerebellum).

More recently, a study investigated for the first time the brain structures specifically involved in the establishment of food preferences and aversions in pigs (Gaultier *et al.*, 2011). The paradigm was based on the use of flavours positively or

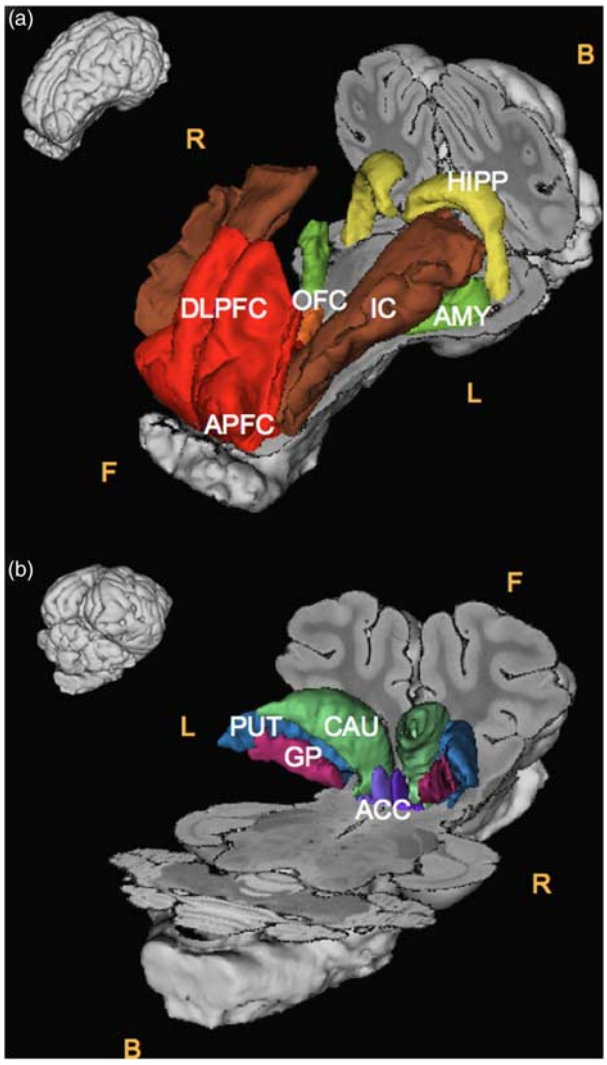

Figure 2 Localization of some brain structures involved in the establishment of food preferences and aversions, in reward expectation and/or in the characterization of food palatability. (a) Skinned front view of the pig brain with three-dimensional (3D)representations of the amygdala (AMY), the insular cortex (IC), the hippocampus (HIPP) and some structures of the frontal and prefrontal cortices, including the anterior prefrontal cortex (APFC), the dorsolateral prefrontal cortex (DLPFC) and the orbitofrontal cortex (OFC). (b) Skinned back view of the pig brain with 3D-representations of several structures of the 'brain reward system' including the nucleus accumbens (ACC), the globus pallidus (GP), the putamen (PUT) and the caudate nucleus (CAU). All these images were obtained from a stereotactic 3D atlas realized in our institution (Saikali *et al.*, 2010). In the top left corner of each part of the figure (a and b), complete 3D models of the pig brain in the same orientation as the skinned representations are shown (F = front; b = back; R = right; L = left).

negatively conditioned through the ingestion of a flavoured meal coupled with an intraduodenal injection of NaCl (sham treatment) or lithium chloride, respectively. The brain activations were then explored via SPECT during olfacto-gustatory stimulations with the conditioned flavours. The results showed contrasting brain activation patterns in response to the different flavours. Positively and negatively associated flavours notably induced different metabolic responses in the brain structures involved in food recognition, memorization and

Figure 3 The minipig is a good model for studying human diseases and pathologies in biomedical research. (a) Lean Göttingen minipig; (b) obesity induced in a Göttingen minipig after a high-fat and high-carbohydrate diet ('Western diet').

reward. These results are quite promising and could be coupled with the strong parallels highlighted in brain metabolism between pigs and humans. Such investigations represent interesting biomedical findings for the comprehension of the neurobiological mechanisms underlying the establishment of feeding behaviour in humans, with interesting opportunities for applications, notably for the treatment of eating disorders and obesity.

To extend the comparison between the brain metabolism of pigs and humans, it would be interesting to compare the neurotransmitter systems associated with the brain structures involved in feeding behaviour. It is well acknowledged today that the dopamine and opioid systems play an important role in the modulation of feeding behaviour, although they are involved in different steps of this process. These two systems, which are important for the 'reward circuit' and play a major role in food pleasure and selection, have been relatively well characterized in humans and rats (Berridge, 2000; Kelley *et al.*, 2002; Barbano and Cador, 2007; Barbano *et al.*, 2009; Wassum *et al.*, 2009) but not yet in pigs.

Literature data in rodents report that dopamine release could be related to the perception of the stimulus that predicts the reward (e.g. food reward; Barbano and Cador, 2007). The dopamine system is thus rather related to the appetitive phase of feeding behaviour, that is, the phase that precedes the consumption itself. Regarding the opioid system, it seems to

be involved in the modulation of the food hedonic perception and in the characterization of food palatability (Barbano and Cador, 2007; Barbano *et al*., 2009). To summarize, although the opioid system seems to be involved in the modulation of the perception of the hedonic features of food, dopamine plays more of a role in the anticipatory aspect of feeding. It is obvious that other neurotransmitter systems are involved in the modulation of feeding behaviour. In his review, Berridge (2000) mentioned that the serotonin system may be involved in hedonic processing during food intake, suggesting that serotonin causes a specific negative shift in palatability.

Thanks to molecular imaging techniques, the distribution of the dopamine and serotonin neurotransmitters has been well characterized in pigs' brains. In their review, Niblock *et al*. (2005) carried out a comparison between the medullary serotoninergic (5-HT) system development and the anatomy of human infants and piglets. They concluded that the developing 5-HT systems of human infants and piglets are very close, although some structural and developmental differences exist. Despite these slight differences, some serotonin receptors (e.g. $5HT_{1B}$) are very similar to those of humans (Lind *et al*., 2007). As impairments in the serotoninergic system (5-HT) are known to be involved in several brain diseases in humans (e.g. depression, schizophrenia, Alzheimer's disease), some authors developed and validated pig models for serotonin depletion. Cumming *et al*. (2007) reported that the vulnerability of serotonin transporters in pigs to 3,4-methylendioxymethamphetamine treatment and the distributions of serotonin transporters and $5HT_{1A}$ receptors in the brain of Göttingen minipigs are similar to those reported in humans. Ettrup *et al*. (2011) also investigated the distribution of 5-HT_{1A} and 5-HT_{2A} receptors in the pig brain. Their results showed that the binding of 5-HT_{1A} and 5-HT_{2A} receptors was not affected by serotonin depletion achieved by a para-chlorophenylalanine treatment, whereas this treatment increased 5-HT_4 receptor binding, especially in the nucleus accumbens. They also showed that, overall, the distributions of 5-HT_{1A} and 5-HT_{2A} receptors were concordant with those of humans. Interestingly, according to Prelusky's study (1993), serotoninergic activity is negatively correlated to food intake, given that a decrease in food intake after the administration of a toxic substance (mycotoxin : deoxynivalenol) is associated with a decrease in brain serotonin turnover. Although the dopamine system has received less attention, the distribution of mesencephalic neurons is similar in pig and human brains (Minuzzi *et al*., 2006; Lind *et al*., 2007). The availability of D_2 dopamine receptors for binding of radioligands (e.g. ^{11}C-raclopride) is influenced by competition from endogenous dopamine. In their PET study, Lind *et al*. (2005) reported some similarities in the decreased availability of ^{11}C-raclopride-binding sites for D_2 receptors in the striatum caused by amphetamine treatment between pigs and humans. In their autoradiography study using [^{3}H]raclopride and [^{3}H]SCH 23390, respectively, Minuzzi *et al*. (2006) showed that the distribution and the density of dopamine $D_{2/3}$ and D_1 receptor-binding sites of Göttingen minipigs are very similar to those of humans, with a high abundance of these receptors. The use of dopamine receptor ligands such as ^{11}C-raclopride may indeed represent an interesting tool to understand the normal and pathological molecular mechanisms underlying feeding behaviour. Some studies identified efficient radioligands and isotopes currently used to explore the dopamine transporter (DAT) because this molecular target is involved in numerous neurological diseases such as Parkinson's disease in humans. In their study, Wang *et al*. (2007) used the ^{18}F-FP-CIT, a radiotracer that binds specifically to DAT, whereas Chalon *et al*. (2006) used the ^{11}C-LBT-999 to investigate the DAT variations in baboons. Minuzzi *et al*. (2006), however, reported that several usual radioligands failed to bind to DAT in the pig brain, although they revealed the presence of DAT in rat, ferret, monkey and human brains. However, according to previous studies using a ^{11}C-raclopride paradigm, pigs possess functional DAT (Rosa-Neto *et al*., 2004). These discrepancies may be due to the aberrant binding properties of DAT in pigs compared with those in other species. Altogether, these results emphasize the limitation of using pigs for some dopamine studies. These radioligands have not yet been used to investigate the involvement of these neurotransmitters during feeding behaviour in pigs. The establishment of eating disorders in humans is strongly influenced by the perception of food sensorial characteristics and palatability, and interestingly, some studies showed that obesity and/or food addiction, for example, are associated with brain metabolic disorders including the low availability of D_2-receptors (Wang *et al*., 2001; Volkow *et al*., 2008). The existing similarities of some neurotransmitter systems involved in the perception and characterization of food in pigs and humans represent a huge opportunity to gain a better understanding of these diseases. It would be interesting to use these radioligands to quantify the involvement of neurotransmitter receptors and transporters in the acquisition of food preferences or aversions.

Behavioural similarities

Neophobic responses towards food. The knowledge generated about pig behaviour in livestock production enables to draw an interesting parallel between the pig and human feeding behaviour, for example, in the development of food preferences and aversions, or the emergence of neophobic responses towards novel food. In livestock production, pigs may face stressful periods during which their feeding activity is strongly disrupted due to unfamiliar feeding and environmental conditions (Meunier-Salaün and Picard, 1996). For instance, at weaning, piglets have to face a huge and abrupt modification of their diet associated with important changes in their physical and social environment. Weaned piglets are separated from their mother (disruption of the mother–young bond) and are classically mixed in pens with unfamiliar congeners. Their diet changes drastically, with the disappearance of the mother's milk and the supply of a concentrate diet mainly formulated with cereals. During the growth period, diets are formulated to satisfy the animal's nutrients and energy requirements and depend on the available dietary sources. When exposed to novel food during the food transition, a period of slow growth is often

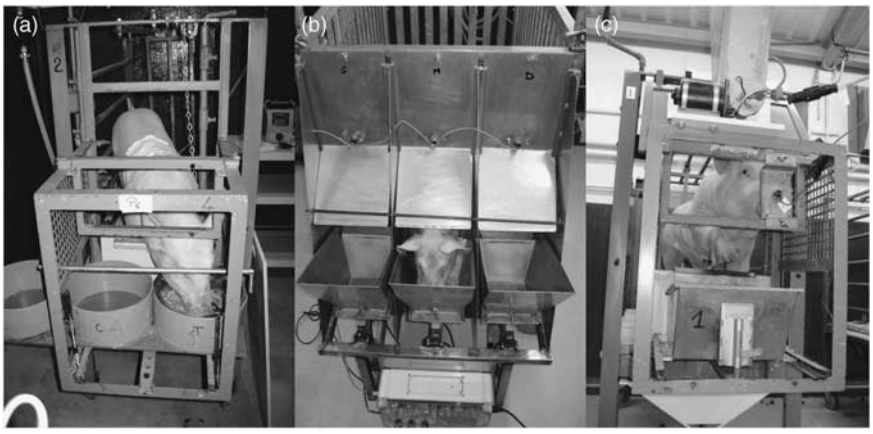

Figure 4 Examples of the experimental cages and operating devices used to investigate the feeding behaviour and motivation in pigs. From left to right: (a) simple two-choice feeding test, in which the animal has to choose between two different diets, (b) three-choice feeding test, in which the animal has to choose between three different diets held in three different troughs equipped with mechanical trap doors controlled by three different buttons accessible to the animal and (c) operant conditioning test, in which the animal has to push a button to activate the food dispenser, the number of pushes necessary to obtain a small ration of food being variable. The operating devices and testing parameters are controlled by a computer and all troughs can be connected to strain gauges, allowing for a precise calculation of the quantity consumed and the ingestion speed. All these images are from our institution. The operating devices and analysis software solutions were designed by C. H. Malbert and E. Bobillier.

reported in pigs, until such time as they accept their novel feeding and environmental conditions fully (Campbell, 1976; Dong and Pluske, 2007). Humans, and especially children, also exhibit this 'neophobic response' towards novel foods and this phenomenon is reinforced by an associated novel environment (Hursti and Sjödén, 1997). This response is caused by the fear of novelty and is responsible for transiently decreased food consumption.

The development of feeding behaviour and its environmental determinants. In addition to this neophobic response towards food, pigs and humans share some development characteristics of their feeding behaviour and especially for the acquisition of food preferences and aversions. As in humans (Mennella and Beauchamp, 1993; Beauchamp *et al*., 1994), the food choices in weaned piglets can be modulated by the mother's diet or early experience (King, 1979). Indeed, piglets weaned from sows fed with a flavoured diet and then fed with a post-weaning diet of a similar flavour ate significantly more food and grew significantly faster during the immediate post-weaning period than pigs that were not familiar with the flavour (Campbell, 1976; Langendijk *et al*., 2007; Oostindjer *et al*., 2010).

The impact of conspecifics is also an important social factor that influences food choices and intake among pigs (Forbes, 1995; Meunier-Salaün and Picard, 1996; Meunier-Salaün *et al*., 1997; Meunier-Salaün and Bergeron, 2005). In the study of Meunier-Salaün *et al*. (1997), piglets aversively conditioned towards a diet with concanavalin A (an emetic substance) added and re-exposed to the aversive diet showed diet refusals, indicating that they remembered the conditioning. However, when re-exposed to the aversive diet in the presence of a naïve congener, conditioned pigs resumed eating. This social facilitation phenomenon is also encountered in humans: observing people eating may influence children's food preferences, thanks to the tendency of children to imitate their peers' behaviour, especially in the home environment (Hursti and Sjödén, 1997; Wardle and Cooke, 2008). Moreover, food diversity allows for better food intake in humans (Gerrish and Mennella, 2001). When a choice of diets is offered to pigs during growth, pig performance (i.e. food intake, daily weight gain) is highly improved compared with a situation where pigs have no food choice (Lawlor *et al*., 2003).

Cognitive abilities during behavioural tests aiming to assess feeding behaviour. As feeding behaviour requires learning and memory capacities, the animal model chosen for studying feeding behaviour in humans must have significant cognitive capacities. Numerous studies have investigated and attested to the learning and memory abilities of pigs during behavioural tests (e.g. the open field or the novel object tests; for a review, see Lind *et al*., 2007; Kornum and Knudsen, 2011).

The numerous tests developed to assess feeding preferences are based on the hypothesis that preferred food (i.e. the most palatable food) would be consumed the most (for a review, see Meunier-Salaün and Picard, 1996; Meunier-Salaün and Bergeron, 2005). Two main types of methods emerge: choice tests and operant conditioning (Figure 4). Two methodologies exist in the feed choice tests: a one-way test in which various diets are alternatively presented, and the 'multiple-way choice test' in which two or more diets are presented simultaneously in a free-choice situation (e.g. Schöne *et al*., 2006; Guillemet *et al*., 2007; Sola-Oriol *et al*., 2009). In the free-choice situation, the result does not predict the behaviour in a practical situation in which a unique food is usually supplied, whereas the one-way test allows the analysis of feeding preference, but at the same time limits the influence of alternate food resources

available in the livestock environment, such as straw indoors or various herbaceous and invertebrate resources outdoors (Meunier-Salaün and Picard, 1996). In the case of the operant conditioning methodology, pigs must work (e.g. push a button) to obtain a resource, food (e.g. Bergeron *et al.*, 2000; Robert *et al.*, 2002), space or a social stimulus. Operant conditioned tests are used to assess the feeding motivation and feeding preferences, based on the assumption that the quantity of work provided would be higher for food and for preferred food.

From the perspective of animal production, these methods have been used extensively to understand the feeding problems (under- or overconsumption) encountered in livestock production and to improve the rate of weight gain (e.g. growth of growing pigs: Campbell, 1976; King, 1979; Lawlor *et al.*, 2003; Edge *et al.*, 2005; Schöne *et al.*, 2006; Langendijk *et al.*, 2007; Sola-Oriol *et al.*, 2009; or reproductive sows: Bergeron *et al.*, 2000; Robert *et al.*, 2002; Guillemet *et al.*, 2006 and 2007). Just like weaning pigs, reproductive sows have to cope with changes in their physical and social environment and modifications in their diet throughout their breeding cycle. Pregnant sows are subjected to a food restriction to prevent overeating and subsequent excessive weight gain. After farrowing, lactating sows receive *ad libitum* feeding and a novel food, which is adapted to the very high energy requirements of milk production (Forbes, 1995). During this transition phase, usually, the spontaneous food consumption of the animal is low, especially in primiparous sows (Forbes, 1995). Insufficient food intake generally induces lower productivity (decreased milk production and/or fertility) and decreased animal welfare (weight loss, weakened state; Dourmad *et al.*, 1994).

As high-fibre diets may have beneficial effects on sows' welfare during both gestation and lactation (Philippe *et al.*, 2008), several studies have investigated the use of such diets to regulate food consumption of reproductive sows. The use of fibrous diets is a promising method to prevent overeating in gestating sows because such diets seem to reduce hunger and maintain satiety for a longer period of time after feeding in restricted-fed sows (Meunier-Salaün *et al.* 2001; Robert *et al.*, 2002). In their study, Bergeron *et al.* (2000) also showed that a high-fibre diet efficiently increased satiety in gestating sows, but they failed to demonstrate that this diet reduced food motivation in operant tests. The discrepancy between this study and previous ones may be due to protocol differences, such as their use of relatively old sows when other studies used gilts. Providing a high-fibre diet during gestation may also be beneficial for lactating sows because it prepared the sows for an *ad libitum* food supply after farrowing and increased food consumption, especially in primiparous young sows and during the first week of lactation (Guillemet *et al.*, 2006). However, when subjected to two-way choice tests, gestating sows preferred standard gestation and lactation diets to a high-fibre diet, consistent with its lower palatability (Guillemet *et al.*, 2007 and 2010). These results showed the positive impact of a fibrous diet in improving animal welfare during pregnancy when the diet was supplied without any alternative choice, and also highlighted the necessity to ameliorate its organoleptic properties, so as to prevent its avoidance under circumstances of multiple food choices.

Even more than sows, adult humans are subjected to a plethora of physiological (e.g. pregnancy, ageing) and social changes throughout life and have to adapt their feeding behaviour according to these changes. Studying the modulation of feeding behaviour in sows may enable a better understanding of the mechanisms underlying modulations of human feeding behaviour. For instance, interesting parallels can be drawn between the effects of dietary fibre supplementation in reproductive sows and in humans. Lindström *et al.* (2006) showed that an increased fibre intake coupled with a low-fat diet induced a long-term weight reduction in overweight adult humans, suggesting that fibres may also be used to prevent overweight in humans.

Gustatory responses to food. As the flavour of food plays a major role in the establishment of preferences and aversions, a good animal model must have well-developed sensorial capacities and share some characteristics with humans in terms of taste and odour responses. Using behavioural feeding choice tests, Glaser *et al.* (2000) highlighted several similarities in gustatory responses towards some carbohydrates (mono- and oligosaccharides), polyols and natural or artificial compounds used as sweeteners in humans. Pigs showed gustatory preference for all the 15 carbohydrates (e.g. sucrose, fructose, glucose) tested over water, as for all the seven polyols (e.g. xylitol). Moreover, for 12 out of the 15 carbohydrates tested in pigs (like sucrose or fructose), detection and recognition thresholds on a molar basis were relatively close to the thresholds found in humans. In terms of natural or artificial sweeteners (e.g. sucralose, saccharin), 5 out of the 12 sweeteners tested elicited gustatory responses in pigs, but of a weaker intensity than that in humans. Tinti *et al.* (2000) carried out similar experiments to compare pigs' and humans' gustatory responses to glycine and 28 amino acids. Out of 17 amino acids, which are sweet to humans, 12 were preferred by pigs over water during two-bottle tests. Altogether, these results confirm the existence of a general positive correlation between pigs' and humans' preferences towards sweet compounds. However, Nofre *et al.* (2002) also tested gustatory responses of pigs towards 60 compounds perceived as sweet by humans using the two-bottle preference test method. According to their results, only 35 out of the 60 compounds tested elicited preference responses in pigs, among these most notably lugduname and carrelame (i.e. two of the most potent artificial sweeteners known in humans). These results emphasize that it is essential to make no hasty conclusions and to take into account the fundamental differences between pigs' and humans' preferences towards sweet compounds, especially because data refer to a different method of evaluation (Tinti *et al.*, 2000; Nofre *et al.*, 2002). In humans, evaluation of sweetness is based on a subjective assessment of the intensity of a compound's sweet taste. In pigs, sweetness

evaluation refers to solutions' palatability, which is assessed by the mean of preference tests, based on consumption rates and feeding behaviour.

Studies based on electrophysiological recordings allow better comparison between the gustatory responses of pigs and humans. Responses to taste stimulations in pigs were recorded at the level of the chorda tympani nerve (CT) and the glossopharyngeal nerve (Hellekant and Danilova, 1999). The information of taste is assessed through nerve fibres classified according to their response to salt, sour, sweet and bitter compounds (e.g. the fibres are designated as sweet if sucrose elicits the maximum responses; Hellekant and Danilova, 1996). In electrophysiological studies on pigs, recordings of the spontaneous nerve impulses after various taste stimulations (i.e. rinsing the tongue with different solutions of interest) have been used to classify the fibres' responses in terms of quality and intensity. In Hellekant and Danilova's study (1996), 13 compounds known to be sweet to humans have been tested in pigs. Out of the 13 compounds, three (sucrose, glucose and fructose) elicited responses of the CT fibres, thus demonstrating that pigs perceived the sweet taste of these compounds. Conversely, 7 out of these 13 compounds, including alitame, aspartame, super-aspartame and saccharine, did not elicit or elicited little nerve response, although these compounds are perceived as sweet-tasting by humans. Similarly, among 30 compounds tested that are sweet to humans, only glycine, xylitol, sucrose, fructose and glucose elicited nerve activity (Hellekant and Danilova, 1999). These electrophysiological data showed that it is of fundamental importance to exercise caution in assuming the cross-species identity of taste preference because some porcine gustatory responses are different from those of humans.

Conclusions

The extensive physiological similarities between the pig model and humans in the major mechanisms involved in the regulation of the feeding behaviour emphasize the research perspectives using a pig model to investigate the behavioural and neurophysiological mechanisms underlying the establishment of food preference and aversions, in relation to human nutrition issues. However, the use of pigs is not free from limitations. Owing to the high weight of adult standard pigs, imaging studies are carried on juveniles and the translation of research findings into applications in adult human biomedical research must be carried out carefully. The emergence of minipig models represents an interesting alternative to the use of standard pigs in biomedical research. Various strains of minipig promise to enable longitudinal studies and/or studies on adult stages, providing an accurate translation into human applications.

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