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The early origins of food preferences: targeting the critical windows of development

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Short title: Critical windows for programming food preferences

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Abbreviations

DAT, dopamine active transporter; NAc, nucleus accumbens; PW, postnatal week; TH, tyrosine hydroxylase; VTA, ventral tegmental area.

Abstract

The nutritional environment to which an individual is exposed during the perinatal period plays a crucial role in determining their future metabolic health outcomes**.** Studies in rodent models have demonstrated that excess maternal intake of high-fat and/or high-sugar 'junk foods' during pregnancy and lactation can alter the development of the central reward pathway and program an increased preference for 'junk foods' and increased susceptibility to diet-induced obesity in the offspring. More recently, there have been attempts to define the critical windows of development during which the reward pathway is most susceptible to alteration, and to determine whether it is possible to reverse these effects through nutritional interventions applied later in development. This review discusses the progress made to date in these areas, highlights the apparent importance of sex in determining these effects and considers the potential implications of the findings from rodent models in the human context.

Key Words: programming, high-fat diet, reward

Introduction

Both human and animal studies have provided compelling evidence that the nutritional environment an individual experiences before birth and/or in early infancy is a key determinant of their subsequent metabolic health outcomes. In particular, individuals who are exposed to maternal overnutrition during the perinatal period have a greater propensity towards excess food intake and weight gain in child and adult life (1-6). More recently, animal studies have demonstrated that in addition to predisposing individuals to consume more energy overall, perinatal exposure to high-fat and/or high-sugar diets also increases the preference for palatable 'junk foods' in the offspring (7, 8).

Over the past few years, studies from our group and others have provided novel insights into the biological mechanisms which underlie the developmental programming of food preferences. These studies have strongly implicated altered development of the central mesolimbic reward system in this mechanistic pathway, and demonstrated that both opioid and dopamine signalling within this reward system are persistently altered by prenatal fat/sugar exposure, both in relation to gene expression of key components of these pathways and the way in which they function. The majority of studies to date have focussed on the consequences of being exposed to high-fat and/or high-sugar diets during the entire perinatal period (i.e. before birth and during the suckling period). However, given that the development of central reward systems begins before birth and extends into the fourth week of postnatal life in the rodent (9-11), there has been growing interest in defining whether there are critical windows of reward pathway development during which exposure to a maternal junk food diet is most detrimental. In addition, there remains limited information as to whether and to what extent the effects of early life exposure to poor quality diets can be reversed by interventions applied later in development.

This review summarises our current understanding of the key periods of development during which exposure to 'junk food' diets can lead to permanent changes in the mesolimbic reward pathway and establish lifelong food preferences. We also discuss the results of studies which have examined the potential reversibility of these programming effects, and highlight the challenges inherent in extrapolating the findings from the animal studies in this area to a human context.

High-Fat/High-Sugar 'Junk Foods' and the Mesolimbic Reward System

The drive to consume highly palatable foods has a strong biological basis which goes beyond the need to satisfy hunger. The reason for this is that these foods have the ability to activate the central neural circuits involved in the regulation of motivation and reward (the mesolimbic reward system) in a manner analogous to alcohol and drugs of abuse (12, 13). Studies in both humans and animals have shown that the intake of fat and sugar produces acute increases in the synthesis and secretion of opioids and dopamine within the central reward system (14-19). The similarity between the acute effects of palatable foods and those of well-characterised drugs of abuse has led to the concept of palatable foods as a 'natural' reward.

The pleasurable sensation that is experienced after consuming drugs, alcohol and palatable foods is ultimately due to the activation of dopamine signalling (20). The intake of palatable foods stimulates the synthesis of endogenous opioids, which bind to μ-opioid receptors on inhibitory GABAergic neurons in a region of the mesolimbic reward system known as the ventral tegmental area (VTA). This blocks their inhibitory action on dopaminergic neurons in this brain region and thereby increases dopamine production (21). The terminals of these dopaminergic neurons project from the VTA to another region of the mesolimbic reward pathway, the nucleus accumbens (NAc) and dopamine release into the NAc is thereby increased. Here, it binds to dopamine receptors (D1 and D2) on the post-synaptic NAc neurons and dopamine signalling is activated (21). Opioids can also act directly through receptors in the NAc to further potentiate dopamine signalling (Figure 1).

The importance of opioid and dopamine signalling in the regulation of palatable food intake has been demonstrated by pharmacological studies in both humans and animals. In rats, microinjections of exogenous opioids or dopamine receptor agonists into either the VTA or NAc enhances the ingestion of foods which are rich in fat and sugar (14, 22, 23), whilst injections of μ-opioid receptor antagonists or dopamine receptor antagonists have the opposite effect (24-27). Similarly, administering the opioid receptor antagonist naloxone to human subjects has been shown to reduce the intake of high fat/high sugar snacks including cookies and chocolate bars without altering the intake of less palatable foods (28).

In addition to the acute effects of palatable foods on the reward circuitry, prolonged exposure to excessive amounts of fat and sugar is associated with molecular adaptations which mirror those seen in drug and alcohol addiction. Chronic overconsumption of high-fat, high-sugar diets results in reduced expression of the D2 dopamine receptor (29) and decreased dopamine content (18, 30) in the NAc. We have also recently shown that feeding rats a cafeteria diet consisting of a range of common human 'junk foods', including chocolate biscuits, sweetened breakfast cereal and extruded potato snacks, for 8 weeks resulted in reduced expression of both tyrosine hydroxylase (TH), the rate limiting enzyme in dopamine synthesis and biomarker of rate of dopamine production, and the μ-opioid receptor mRNA in the NAc (31); consistent with changes in the reward pathway observed after chronic exposure to well-characterised opioid drugs, such as morphine (32). Excess consumption of 'junk foods' also leads to behavioural changes indicative of the development of dependence. Rats provided with free access to either high-fat and/or high-sugar diets consume increasing quantities as over time, and exhibit classic withdrawal signs when the diet is removed (33, 34). As a result, overstimulation of brain reward systems through excessive consumption of palatable foods results in the development of compulsive-like consumption of high-fat, high-sugar foods.

The Development of the Reward Pathway

Rodents have been the model of choice in which to study the early life ontogeny of various brain circuits, including the mesolimbic reward system. In rodents, mesolimbic opioid and dopamine neurons can be identified as early as embryonic day 13 (11, 35). At birth, dopamine fibres in the NAc are present at a higher density than in the adult rodent (36), and the abundance of the μ-opioid receptor in this brain region also peaks in the first 4 days after birth, before declining to adult levels (37). Dopamine and opioid receptors can be detected in the mesolimbic reward system in early-mid embryonic life in the rat, but only become functional at the late embryonic or postnatal stage, suggesting that the ability of the fetus to respond to endogenous or exogenous dopamine may be limited. It is not until the third to fourth postnatal week that the opioid and dopamine systems in the rodent reach their adult configuration (9-11, 38) (Figure 2).

It is important to recognise that the developmental trajectory of these pathways is likely to be different in the altricial rodent model compared to the human. While there have been relatively few human studies in this area, largely relying on information from autopsy studies,

evidence from the limited clinical studies that have been conducted suggests that both dopamine and endogenous opioids, including β-endorphin, are expressed in the fetal striatum by 12 weeks gestation (39, 40). In contrast, the associated receptors cannot be detected until gestational week 20 (41, 42). Knowledge of this area is still somewhat limited, and further studies are required to gain a better understanding of the early life ontogeny of the reward pathway in both rodents and humans. These studies will undoubtedly assist research in identifying when during development the reward circuits are likely to be most susceptible to environmental insults.

Critical Windows of Development in the Programming of Food Preferences

There are currently limited studies which have attempted to determine the separate contributions of prenatal and early postnatal exposure to 'junk food' or high-fat diets on subsequent food preferences in the offspring, and fewer still which have looked at the effects of exposure after weaning (Figure 3). However, the results from the studies to date suggest that exposure of the fetus/neonate during different periods before birth and/or in the early postnatal period may have distinct consequences for the programming of the reward circuitry and subsequent food preferences and susceptibility to diet induced obesity in the offspring.

Exposure before birth vs during the suckling period

The relative impact of exposure to a high-fat diet before birth and during the suckling period on later food preferences has been evaluated in a number of studies using a cross-fostering paradigm, in which offspring born to mothers consuming junk food/high-fat diets are transferred to mothers fed a standard chow diet, or vice versa, within 24 hours of birth. This approach provides the opportunity to isolate the effects of exposure to the junk food diet during fetal and suckling periods without any carry over effects associated with switching the same dam from one diet to another, and is thus of considerable value in defining critical developmental windows. In one such study, Chang and colleagues demonstrated that offspring who had been exposed to a high-fat diet *in utero* exhibited an increased body weight, increased body fat mass, and increased fat preference, independent of whether they were suckled by a dam consuming a control or high-fat diet (43). This study went on to show that exposure to a high-fat diet before birth, but not during the suckling period, also resulted in significant increases in the proliferation of neuronal cells involved in regulating fat intake (eg. galanin neurons) in the hypothalamic appetite regulatory centre (43). These results led the authors to conclude that exposure to a high fat diet before birth was both necessary and

sufficient to program a preference for high fat foods and thereby predispose the offspring to diet-induced obesity (43).

The findings of Chang and colleagues have not, however, been replicated in other cross-fostering studies. In one of these studies, Gorski *et al* demonstrated that exposure to a high-fat diet during the suckling period alone was sufficient to increase the offspring's appetite for high-energy foods in adulthood. In this study, the offspring of obesity-resistant dams that were cross-fostered to obesity-prone dams fed on a high energy diet, exhibited a significantly higher energy intake when given free access to the same high energy diet between 8 and 12 weeks post-weaning (44). More recently, we also used a cross-fostering paradigm to evaluate the effect of exposure to a maternal cafeteria diet before birth and/or during the suckling period on food preferences and susceptibility to diet induced obesity in adulthood. Consistent with Gorski's findings, we found that exposure to a maternal cafeteria diet during both the fetal and suckling periods or suckling period alone, but not fetal period alone, was associated with higher intake of fat, carbohydrate and total energy when offspring were given free access to both a control and cafeteria diet at 2 months of age (45). The results of the latter two studies suggest that the suckling period, rather than the prenatal period, plays the more important role in the programming of food preferences. Importantly, these studies also raise the possibility that the effects of prenatal exposure to a cafeteria diet on subsequent food preferences/susceptibility to diet-induced-obesity in the offspring could potentially be reversed by restoring appropriate nutritional intakes during the lactation/suckling period.

The results of these cross-fostering studies need to be interpreted with caution in light of reports that switching pups to a foster mother at birth, even if she is consuming the same diet, can impact on the subsequent growth, metabolic profile and behaviour of the offspring (46). However, the apparent importance of the suckling period in determining later feeding behaviour has also been demonstrated in rodent studies in which pups remained with their natural mother throughout the experiment, but the dams were only fed the cafeteria diet during either pregnancy or lactation. In one such study, Bayol and colleagues showed that the offspring of dams fed a cafeteria diet during both pregnancy and lactation had a higher BMI and food intake after weaning than offspring of mothers who were a fed cafeteria diet during pregnancy and were switched to a control diet after delivery (7). Wright and colleagues have also undertaken a similar study, in which behavioural satiety sequence analysis was applied to specifically investigate food consumption patterns of adult offspring exposed to the cafeteria diet whilst suckling, but not before birth. They reported that offspring who had been

exposed to a cafeteria diet during the suckling period alone period exhibited an increased number of feeding bouts and spent more time feeding when provided with a cafeteria diet in adulthood, than non-exposed offspring (47). Thus, while more studies are required, the weight of the evidence to date appears to suggest that exposure to a cafeteria/high-fat diet during the suckling period has a greater impact on subsequent food preferences/feeding behaviour than exposure before birth.

Post-weaning

In the rodent model, offspring are capable of consuming solid foods and are no longer dependent on their mother for nutrition by 3 weeks of age (48). However, as discussed above, the development of the reward pathway has been shown to continue into the fourth postnatal week (10, 11). This suggests that there is the potential for environmental insults in the immediate post-weaning period to also impact on the development of this pathway. In support of this, Teegarden and colleagues demonstrated that mice offspring exposed to a high fat diet only during the fourth week of life (22-28 days of age) exhibited a significant preference for this same high fat diet as adults (49). Importantly, this increased preference for fat was associated with increases in striatal expression of Cdk5 and phosphor-DARPP-32, which are negative regulators of dopamine transmission. The authors proposed that the associated inhibition of dopamine signalling in the reward system was responsible for driving the increased consumption of fat, as a compensatory response to stimulate dopamine signalling and thereby normalise dopaminergic tone (49). The ability of exposure to a highly palatable diet only during the fourth week of life to program adult food preferences has also been demonstrated in a study in which neonatal rats fed a sugary cereal from postnatal days 22-27 were shown to exhibit an increased preference for this same food in adulthood (50).

In order to further investigate the impact of altered reward signalling in the fourth week after birth, we recently undertook a study in our laboratory to determine the effect of blocking opioid signalling in the period immediately after weaning on gene expression in the reward pathway and food preferences in adult life. We found that while administering the opioid-receptor antagonist, naloxone, for ten days after weaning resulted in altered gene expression in the mesolimbic reward pathway at the end of this period, there was no impact on adult food preferences, independent of whether the offspring had been exposed to a control or junk food diet in the fetal and suckling period *(Gugusheff et al, unpublished observations)*. While the results from studies to date suggest that there may be the potential for altering the

development of the reward pathway, and thus food preferences, in the post-weaning period in rodents further studies are required to confirm this and to determine the underlying mechanism.

Adolescence

Adolescence is a period of transition from childhood to adulthood, corresponding to the age of 12 to 18 years in humans and 28 to 56 days in rodents (51). Existing evidence suggests that the adolescent brain is highly plastic, undergoes extensive re-organisation and maturation of neuronal circuits (52), and this plasticity is thought to be one of the main reasons for the increased susceptibility of adolescents to the effects of recreational drugs and alcohol. Studies on nicotine and ethanol addiction in rodents have shown that exposure to these substances during the adolescent period, but not during adulthood, results in neuronal alterations of dopaminergic, cholinergic and glutamatergic systems throughout the brain including hippocampus, striatum and midbrain (53, 54). There are currently no studies which have studied the long-term consequences for the reward pathway/food preferences of being exposed to a high-fat diet/cafeteria 'junk food' diet only during adolescence. However, the fact that drugs of abuse and palatable foods both activate the mesolimbic reward system via similar pathways (21, 55) raises the possibility that a similar phenomenon may be observed. The plasticity of the adolescent brain also suggests that it may be possible to intervene during this period to reverse the negative effects of being exposed to junk food/high fat diets during the perinatal period. Again, however, this has yet to be tested experimentally and remains an important avenue for further research.

Potential reversibility of programmed effects

The evidence linking perinatal 'junk food' exposure to an increased preference for these foods later in life, has led to growing interest in determining whether, and to what extent, the negative effects of exposure to highly palatable diets during the fetal/suckling periods can be reversed by interventions applied later in development. In order to examine the potential reversibility of programming induced by maternal junk food feeding, we have undertaken a series of studies in which we investigated whether providing offspring exposed to a maternal cafeteria diet during the perinatal period with a standard rodent diet after weaning could ameliorate the programming of food preferences and mesolimbic reward system. These

studies demonstrated that whilst consuming the standard diet for 3 weeks post-weaning did normalise chow intake and fat deposition at 6 weeks of age, the mRNA expression of the D1 receptor in the NAc, a marker which has been associated with junk food withdrawal (56), remained higher in offspring of junk food fed dams at this time. Importantly, those offspring exposed to a junk food diet during the perinatal period consumed significantly more total energy than offspring of control dams when free access to the junk food diet was reinstated from 6 to 9 weeks of age (31). These results suggest that providing a nutritionally complete, standard rat feed, for 3 weeks after weaning was insufficient to reverse the programming of an increased preference for junk food as a consequence of perinatal exposure to the junk food diet.

In this same series of studies, we also determined whether providing offspring of junk food fed dams with a standard rodent feed for a more extended period after weaning would reverse the programming effects. These studies demonstrated that a 3-month period on the standard rat feed after weaning was sufficient to reverse the increased preference for a junk food diet in male, but not female offspring (31). The findings of this study therefore suggest that, at least in male offspring, the programming effects of maternal palatable diets on subsequent food preferences can potentially be ameliorated by eliminating the junk food stimulus from weaning to adulthood (31). The importance of prolonged chow intake post-weaning was also demonstrated in a study by Velkoska and colleagues, which focussed on offspring reared in small litters to induce early postnatal overnutrition. These authors reported that when these offspring were fed on a standard rodent feed from weaning they remained fatter and hyperleptinaemic when compared to animals from normal-sized litters in adolescence (57), but were not different in relation to body weight, body composition or plasma leptin concentrations when fed on the standard feed through to adulthood (57).

While these studies suggest that the potential exists for mitigating programming effects through extended periods of consuming a nutritionally balanced standard feed post-weaning, at least in male offspring, this is not supported by all rodent studies. Indeed, there are at least 2 studies which have reported that offspring exposed to high fat diets *in utero* exhibit an increased preference for sucrose and fat at 18-24 weeks of age, even when they have been fed on a standard rodent feed since weaning (58, 59). The differences in findings may be due to the different timing and duration of the dietary perturbation in the dams, and in the specific composition of the experimental diets (and indeed the 'control' rat feed), and there remains a

need to better understand which specific dietary components are the key drivers in the early life origins of food preferences.

Sex Differences

The majority of studies to date which have focussed on the critical windows of reward pathway development and the programming of food preferences have only considered male offspring or have failed to separate male and female animals in the analysis (7, 43, 59). Many researchers choose to focus only on male offspring to avoid any possible complications in the interpretation of results introduced by the hormonal fluctuations which accompany the estrous cycle in females (60). However, there is emerging evidence to suggest that male and female offspring respond differently to early life nutritional insults, and that it is often not appropriate to extrapolate results obtained in males to females. By way of example, studies by our group have shown that maternal palatable diet consumption during the lactation increases the preference for high fat food in juvenile male offspring, but not in females, while increasing the propensity to develop diet-induced obesity in female offspring only (45).

The sex-specific effects of early life nutritional exposures on subsequent food preferences highlight the importance of separating males and females in the analysis of these experiments. Our studies have also demonstrated that these sex differences in the response to perinatal junk food exposure also extend to the effects on the developing reward pathway. Thus, female offspring of junk food fed dams exhibit increased mRNA expression of key components of the dopamine signalling pathway, TH, the D2 dopamine receptor and the dopamine active transporter (DAT), in response to a junk food challenge in adolescence, while no changes in the expression of these genes is seen in males (31). It is clear that future studies investigating the effects of maternal diet on the food preferences of the offspring will need to consider each sex separately and explore in more detail the mechanisms behind the observed sex differences.

Extrapolation to Human Studies

It is important to note that the work done to date looking at periods of plasticity during the development of the mesolimbic reward pathway have been conducted in altricial rodent models, which undergo a considerable degree of their maturation after birth, unlike human infants where brain development is largely completed *in utero*. This difference in the timing

of brain development between rodents and humans clearly needs to be considered carefully when making any attempts to translate the findings from the rodent model into a clinical setting (61), particularly in relation to critical developmental windows. It is also clear, however, that studying the impact of maternal diet on offspring feeding behaviour in humans is complicated by a number of logistical and practical considerations. It is clearly not possible from an ethical perspective to randomise women to consume a high-fat junk food diet during pregnancy/lactation, and obtaining reliable food intake data in observational studies is notoriously difficult. In addition to this, the confounding effects of sociodemographic factors in both food intake in mother and the food choices/obesity risk of their children is difficult, if not impossible, to control for. The largest study to attempt to examine this in a human context was published by Brion and colleagues in 2010. These researchers used information on dietary intakes collected prospectively from 5717 mother-child pairs and 3009 father-child pairs from the ALSPAC birth cohort to examine the relationship between macronutrient intakes in the mother/father at different stages of the mother's pregnancy and macronutrient intakes in the child at 9-10 years of age. The study reported that there was a strong correlation between maternal fat intake during pregnancy and the child's preference for fat at 10 years of age (62), but no relationship with the father's fat intake at any time. While it is difficult to completely exclude the possibility of confounding, these are nevertheless important and interesting results which support the potential for programming of food/macronutrient preference in humans.

Other studies in humans focussed on early programming of food intake have concentrated to a greater extent on the programming of specific taste preferences. A series of elegant studies by Menella and colleagues showed that exposure to certain flavours (eg carrot, garlic) either *in utero* (63) or via the breast milk (63-65) increased the children's preference towards the same flavour after weaning. In addition, a number of studies have reported that infants who are fed on soy-based as compared to milk-based formulas, which are known to have inherently different tastes, have markedly different taste preference profiles as late as 4-5 years of age. Thus, children who had been fed the more bitter soy-based formulas preferred sour- and bitter- flavoured juices at 4-5 years of age, compared to those who were fed the sweeter-tasting milk-based formula (66). This suggests that in addition to changes in the reward circuitry in response to perinatal exposure to high-fat, high-sugar foods could also potentially program a preference towards the flavours of specific junk foods. Despite the paucity of studies conducted to date, the available data does appear to provide support for a

fetal/early life origin to child and adult food preferences in humans, but there remains a need for well-constructed clinical studies in this field of research.

Conclusion

There is now clear evidence from animal studies that exposure to excess amounts of fat and/or sugar during the perinatal and immediate post-weaning periods alters the development of the central reward pathway and programs an increased preference for palatable foods later in life. Whilst the number of studies separating the impact of nutritional excess during various developmental periods remains too small to form definitive conclusions, the weight of the evidence appears to suggest that it is exposure to these diets during the suckling period which is most detrimental in relation to these programming effects. However, given that the critical windows of development of the reward pathway are likely to differ between the rodent and the human, it becomes somewhat difficult to extrapolate this to a clinical context. Nevertheless, the studies reviewed in the current paper have highlighted the exciting possibility that the negative effects of exposure to a poor nutritional environment in early fetal life could potentially be prevented by restoring appropriate nutritional intakes either later in gestation or during the early postnatal period and indicate a need for continued research in this field.

Moreover, this review has demonstrated that there are several important knowledge gaps remaining in this field of research. First, no studies conducted thus far that have investigated the role of the adolescent period as a critical window of development for food preferences. Given studies into the effects of drugs of abuse have highlighted the susceptibility of the reward pathway to alteration during this period, it is possible that junk food diet exposure during this time could be crucial for establishing lifelong food preferences but more importantly, may also offer an opportunity for positive nutritional intervention to overcome the negative effects of exposures earlier in development. Additional investigation is also required to more clearly define sex differences in the response to perinatal junk food exposure on the reward system and to evaluate the possibility of there being different critical windows in the development of the reward and/or taste pathways in males and females. In the face of the current obesity epidemic and increased availability of energy-dense junk foods, there is a need for continued research to clearly define the critical windows of development most sensitive to nutritional manipulations. Identification of these critical windows will not only improve our understanding of the mechanisms involved in the programming of food

preferences but more importantly will provide an opportunity to design targeted interventions which will be critical to breaking the current intergenerational cycle of obesity and poor metabolic health.

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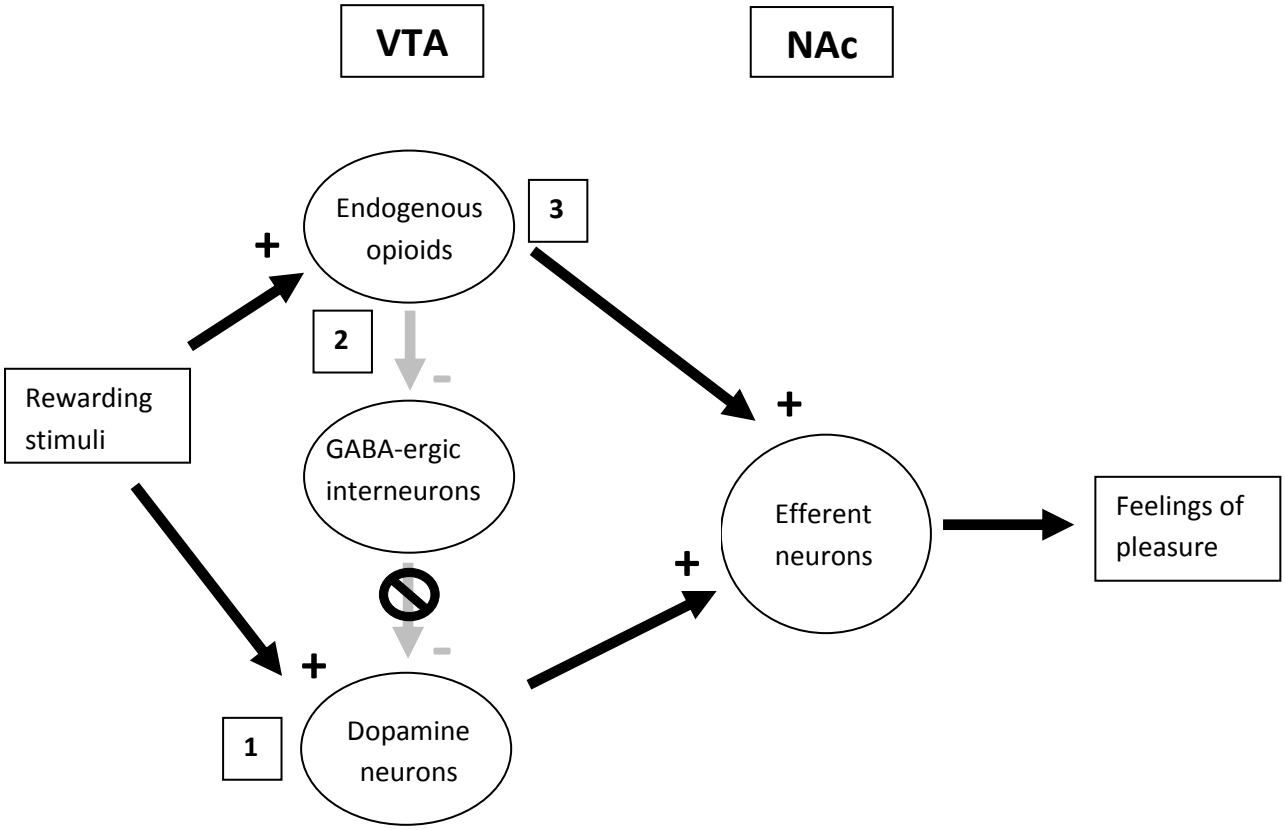
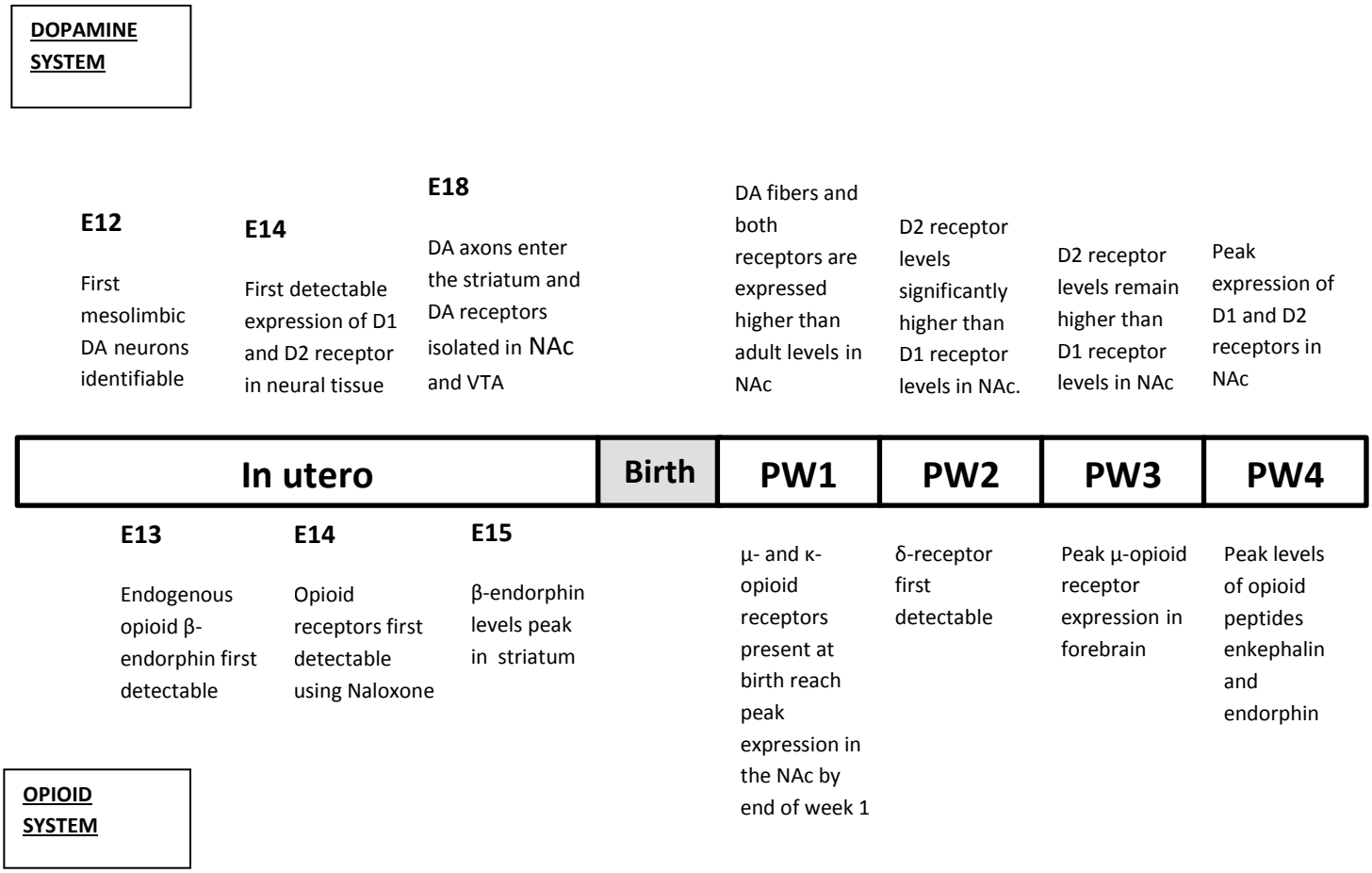
380 **Figure 1.**

381



382 **Figure 2.**

383



384 **Figure 3**

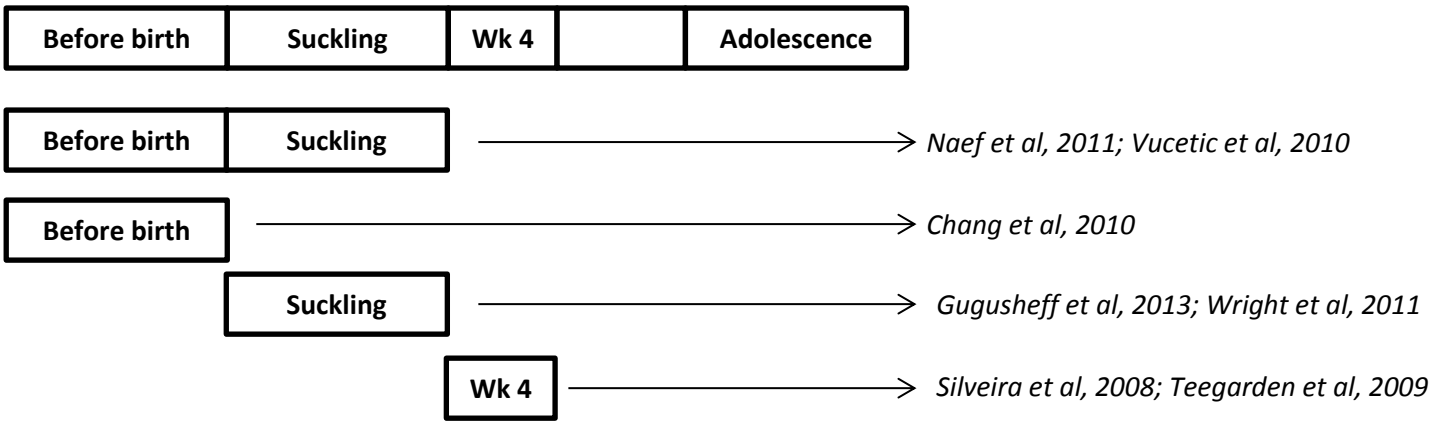

Before birth
Suckling
Wk 4
Adolescence
Before birth
Suckling
Naef et al, 2011; Vucetic et al, 2010
Before birth
Chang et al, 2010
Suckling
Gugusheff et al, 2013; Wright et al, 2011
Wk 4
Silveira et al, 2008; Teegarden et al, 2009

Figure 1. Simplified schematic of reward pathway activation 1) A rewarding stimulus such as drugs and palatable foods can stimulate the dopamine neurons at the VTA, resulting in the release of dopamine at the NAc. **2)** The rewarding stimulus can activate the release of endogenous opioids at the VTA, which inhibits GABAergic interneurons. GABA normally inhibits dopamine release. Therefore, this inhibition of GABA release disinhibits dopamine neurons resulting in increased dopamine release at the NAc. **3)** Opioids can also bind to their receptors located at the NAc. The activation of efferent target neurons at the NAc through **1), 2) and 3)** creates a pleasurable feeling associated with the rewarding stimuli. Black and grey arrows indicate neuronal activation and inhibition respectively. Neurons are represented in circles. Adapted from (67).

Figure 2. Ontogeny of dopamine and opioid systems Summary of key events in the development of the dopamine (top) and opioid (bottom) systems within the mesolimbic reward system throughout prenatal and first 4 weeks of postnatal life in the rodent. By postnatal week 4, dopamine and opioid systems are similar to that of an adult. Abbreviations: DA, dopamine; E, embryonic day; NAc, nucleus accumbens; MSN; medium spiny neuron; PW, postnatal week; VTA, ventral tegmental area. See text for references. Adapted from (68).

Figure 3. Critical windows for programming food preferences A summary of the studies which have investigated the periods of development in rodents during which high-fat/cafeteria diet exposure is able to program an increased preference for these foods in adulthood.

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