Biological Psychiatry

Review

Maternal Metabolic Programming of the Developing Central Nervous System: Unified Pathways to Metabolic and Psychiatric Disorders

Rachel N. Lippert and Jens C. Brüning

ABSTRACT

The perinatal period presents a critical time in offspring development where environmental insults can have damaging impacts on the future health of the offspring. This can lead to sustained alterations in offspring development, metabolism, and predisposition to both metabolic and psychiatric diseases. The central nervous system is one of the most sensitive targets in response to maternal obesity and/or type 2 diabetes mellitus. While many of the effects of obesity on brain function in adults are known, we are only now beginning to understand the multitude of changes that occur in the brain during development on exposure to maternal overnutrition. Specifically, given recent links between maternal metabolic state and onset of neurodevelopmental diseases, the specific changes that are occurring in the offspring are even more relevant for the study of disease onset. It is therefore critical to understand the developmental effects of maternal obesity and/or type 2 diabetes mellitus and further to define the underlying cellular and molecular changes in the fetal brain. This review focuses on the current advancements in the study of maternal programming of brain development with particular emphasis on brain connectivity, specific regional effects, newly studied peripheral contributors, and key windows of interventions where maternal bodyweight and food intake may drive the most detrimental effects on the brain and associated metabolic and behavioral consequences.

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Barker and colleagues postulated the fetal programming hypothesis in a series of seminal papers focusing on maternal environmental effects on fetal development and resulting in the foundation of the field of developmental origins of health and disease (1–5). These influential theories provided a basis for the study of perinatal influences on disease development, and subsequent studies have targeted the discovery of changes to individual organ systems in response to both maternal under- and overnutrition. One organ system with a recent surge in understanding of the perinatal changes with the most robust effects on development is the central nervous system (CNS).

The CNS is a dynamic assembly of neurons and non-neuronal cells capable of mediating extremely complex processes with very distinct and tractable developmental stages (6). Within the CNS, distinct subregions have been defined by the overall function such as the maintenance of energy homeostasis by the hypothalamus (7), the formation of memory by the hippocampus (8), and the drive for reward by the midbrain (9). In humans, maternal programming through maternal obesity and/or type 2 diabetes mellitus (T2DM) has been linked with metabolic dysfunction in offspring (10,11). In the field of energy homeostasis, it is more and more apparent that a variety of interactions with additional brain networks have the potential to drive obesity and contribute to metabolic dysfunction (12). Alarmingly, reported data also link maternal metabolic state with increased risks of neurodevelopmental disorders ranging from attention-deficit/hyperactivity disorder and autism, to memory and cognitive impairments, schizophrenia, and eating disorders (13–17), underscoring the detrimental effects of unhealthy nutrition in development on all aspects of brain function. The crucial homeostatic balance of signaling, excitability, and connectivity of the brain is extensively studied in adult organisms. More recently, the field of maternal programming has uncovered direct molecular effects of maternal obesity/T2DM in generating long-lasting changes in the CNS of offspring in rodent and nonhuman primate models, which support correlative findings in humans related to metabolic and behavioral changes.

With the drastic increase in rates of gestational weight gain above recommended levels (18–20), maternal overweight or obesity (21), and the high incidence of gestational diabetes (22), it is absolutely critical that we understand how the metabolic profile of the mother directly alters fetal brain development. Below, we describe some of the ongoing pursuits of the programming field with regard to maternal metabolic influences on offspring, and where current research is driving forward understanding of neuronal connectivity and timing of exposure to an adverse maternal metabolic environment. As many of these studies have been performed in animal models, it is important to note the species-specific

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developmental timing of key events in brain development. Correlations in the developmental timeline of the human and mouse models are summarized in Figure 1. Beginning with neurulation (23,24), followed by neurogenesis (23,25,26), neuronal migration (27–29), programmed cell death (30,31), and neuronal polarization (32), these events all occur predominantly in the embryonic developmental stages in rodents and are within the first 2 trimesters in human brain development. Postnatally in rodents and in the late second trimester in humans begin the processes of axonogenesis and dendrite outgrowth (27,32–37), exponential rates of synaptogenesis (38–42), cellular subtype refinement (43), myelination (44–50), and gliogenesis (51–56), which continue in the late third trimester onward in humans and after weaning in rodents. Focusing on molecular and cellular-level changes, we shed light on the common effects of maternal overnutrition in multiple brain regions. This provides insight to the emerging correlations in humans between not only maternal overnutrition and offspring metabolic function but also risk for development of a wide range of neurodevelopmental disorders or neuropsychiatric diseases.

ESTABLISHMENT OF NEURAL CIRCUITS

While in the womb, the developing fetus is subjected to circulating maternal factors. At the macroscopic level, these changes prime the entire fetus and influence the overall developmental processes. When studying the effects of maternal obesity and/or T2DM, this discussion has typically involved the hypothalamus because the hypothalamus is the central node of homeostatic regulation [reviewed in (57)]. While hypothalamic function is critical to overall maintenance of energy homeostasis in the adult animal, a number of other brain regions as well as global effects have also been attributed to programming caused by maternal obesity and/or T2DM. Our first focus was to understand the cellular changes that may be relevant to multiple regions of the brain, which occur because of the early developmental nutritional environment, and how those changes affect not only the hypothalamus but other CNS sites as well.

Neurogenesis

A key influence of obesity and hyperglycemia on the brain involves changes in neurogenesis, namely the generation and migration of neurons into functional circuits (Figures 1 and 2). It is known that high-fat diet (HFD) consumption and consequent obesity interfere with proper neurogenesis in regions such as the hippocampus and hypothalamus (58,59). A number of groups have correlated maternal obesity with alterations in fetal and perinatal hypothalamic neurogenesis (58). Lotfi *et al.* (60) demonstrated that maternal hyperinsulinemia is sufficient to cause hippocampal neuron death in offspring as displayed by decreased neuronal density in hippocampal subregions. Recently, Dearden *et al.* (61) were able to demonstrate specific hypothalamic effects on the proliferative capacity of neurons. In this study, maternal overnutrition in mice resulted in decreased expression of proliferative gene markers *Bub1b*, *Ki67*, and *Pcna*, coupled with reduced proliferation of neural progenitor cells. Furthermore, Kim *et al.* (62) identified increased proliferation in astrocytes, suggesting overall changes in proliferative capacity in different cellular populations of the CNS. In addition to the changes in generation and proliferation of cells, Poon *et al.* (63) also show a decreased migratory ability of neurons, specifically hypothalamic neurons, in response to increasing concentrations of the potent chemokine, CCL2. Overall, alterations in neurogenesis and proper cell migration are associated with maternal HFD intake.

Neuronal Excitability

While neuron formation shows some region-specific alterations in animals with maternal metabolic alterations, an

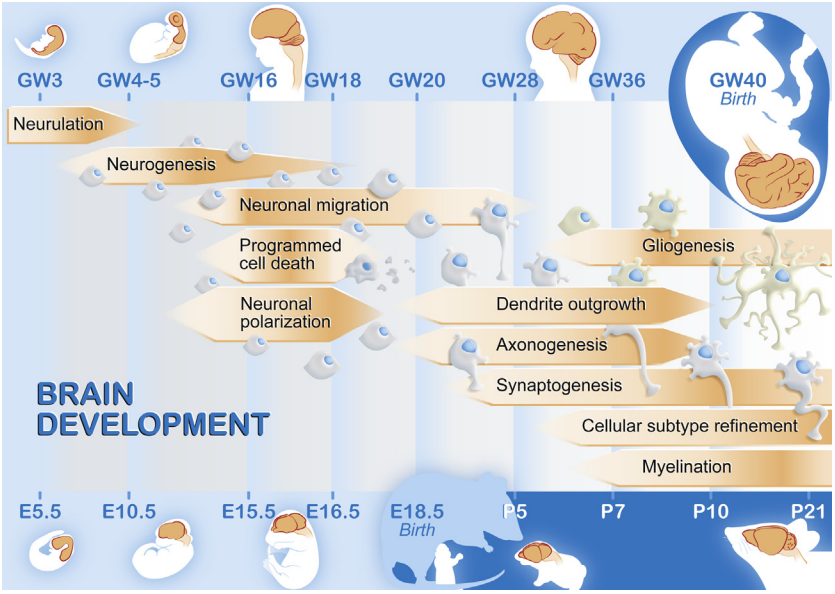

Figure 1. Timeline comparison of human and mouse brain development. Across development, key events occur around specific gestational weeks in humans that correlate with embryonic or postnatal days of development in mouse models. After neurulation is complete, neurogenesis, neuron migration, polarization and programmed cell death define the collective cells of the brain. These events all take place in the first and second trimesters of human development and correlate to the embryonic phase in mice. Postnatal development in mice and late second- and third-trimester development in humans gives rise to axon formation and dendritic refinement, a dramatic increase in synapses and the onset of refinement of cell types, formation of glial cell populations, and myelination of neurons. While each period can vary slightly between brain regions studied, understanding the hallmarks of brain development can help us to refine which periods or events may be most affected by nutritional modulation of the maternal diet. E, embryonic day; GW, gestational week; P, postnatal day.

additional aspect of maternal programming has more recently been shown to affect overall excitability of neuronal populations (Figure 2). Chandna *et al.* (64) have revealed hippocampal neuron hyperexcitability, marked by a rise in action potential and mediated by leaky K^+ channels, with exposure to maternal type 2 diabetes mellitus using a midgestational streptozotocin treatment paradigm. However, the mechanism by which maternal hyperglycemia directly alters leaky K^+ channel expression was not investigated. With regard to other neuronal systems, recent work by our group has shown direct effects on the dopamine system with lactational exposure to maternal overnutrition in mice. Specifically, midbrain dopamine neurons reduce their hallmark pace-making behavior, and targeted medium spiny neurons in regions of the striatum show reduced membrane potential and increased neuronal firing rates in response to increasing stimulation (65). This is possibly associated with changes to dopamine metabolism in target regions (66–69) and likely linked to offspring locomotor, reward, and attention phenotypes.

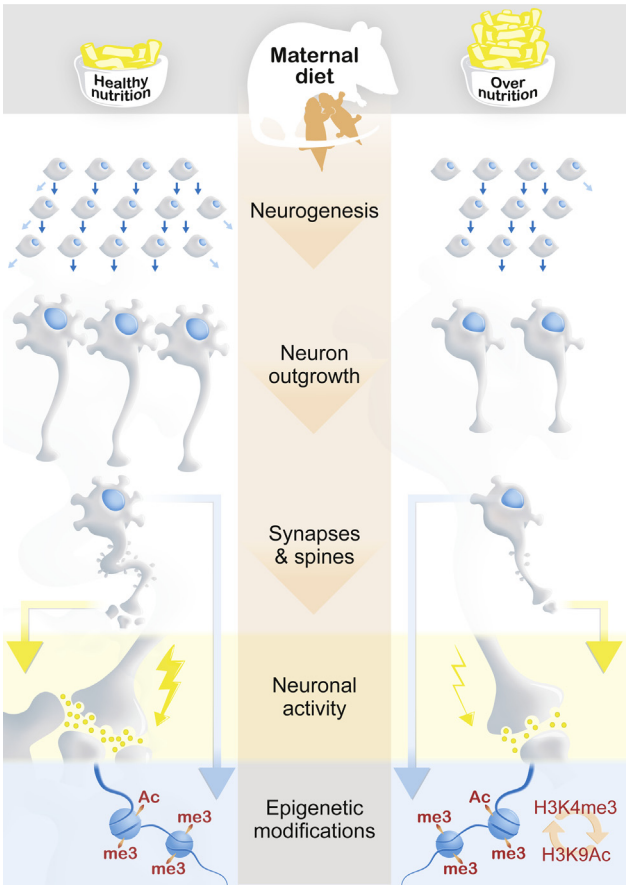

Figure 2. Molecular and cellular effects of maternal overnutrition. Effects of maternal overnutrition manifest at various levels throughout the central nervous system. Key targets include neurogenesis, neuronal outgrowth, synapse formation and spine density, neuronal activity, and chromatin modifications. The multiple molecular and cellular effects of maternal overnutrition present numerous points of overlap between metabolic systems and generalized neuronal function, which may signify common pathways for metabolic and psychiatric disorders.

Within the hippocampal area, multiple independent groups show decreases in long-term potentiation owing to maternal overnutrition, reported to also be transmitted through multiple generations (70,71). The potential for such changes to be permanently carried to future generations even without the exposure to maternal overnutrition begins to paint a grim view of the future if we do not act now to increase public awareness of the consequences of poor nutrition during development.

Neuronal Projection Development

Recent studies by our group and others have begun to focus more on the direct consequences of maternal obesity on the interconnectivity of brain regions (Figures 1 and 2). Hormonal factors involved in metabolism, and altered in maternal obesity, often function as growth factors in early brain development. These include leptin (72,73), insulin (74), insulin-like growth factor 1 (75), and ghrelin (76), among others. However, the exact timing of hormonal fluctuations as well as the effect of maternal obesity on these changes is not well defined.

Previous work by Bouret and colleagues has precisely shown the importance of leptin signaling in the development of hypothalamic projections from the medial basal hypothalamus in both a model of leptin deficiency and a model of maternal obesity (73,77,78). Our group has further described a detrimental effect of elevated insulin signaling in obese mothers on the development of intrahypothalamic connections from the arcuate nucleus to the paraventricular nucleus of the hypothalamus. Of note in this study is that the use of lactational HFD in mothers to produce the neuronal projection phenotype further supported the idea that the lactation period in mice, which is approximately equivalent to the third trimester of brain development in humans, is the most critical period for long-term consequences to brain connectivity. Specific suppression of insulin signaling via deletion of the insulin receptor on pro-opiomelanocortin neurons was sufficient to restore proper connectivity between the arcuate nucleus and the posterior paraventricular nucleus of the hypothalamus only, while other affected regions retained the decreased fiber density phenotype (79). However, despite information linking maternal diet and elevated hormone levels, such as insulin and leptin, on projection development, few studies have expanded these studies to involve any potential hormonal effects of maternal obesity on extrahypothalamic brain structures, which are known to play a role in the pathogenesis of obesity and diabetes. In an effort to further these studies, our recent work showed profound changes to the connectivity of the dopamine system on lactational exposure to maternal overnutrition (65). Another group has shown that maternal HFD during gestation specifically inhibits the development of tanycytic processes in the medial basal hypothalamus and further contributes to an alteration in the integrity of the blood-brain barrier (80). Given the recent discovery of the role of tanycytes in glucose sensing (81) and leptin signaling (82), any maternal dietary effects on this cellular compartment could have long-lasting effects on offspring metabolism. The exact mechanisms by which these neuronal projections are altered are not known, but the modulation of projections by microglia (83) could play such a role. Additional factors such as axonal guidance and retraction mechanisms are not yet sufficiently studied in developing offspring in the presence of maternal metabolic dysfunction.

Synaptogenesis and Synapse Function

One major consideration when discussing brain connectivity and overall activity must include the potential effects on synaptogenesis (Figures 1 and 2). A number of groups have shown that the induction of gestational diabetes with streptozotocin in rats led to a reduction in synaptophysin, an abundant integral synaptic vesicle protein, in the hippocampus and cerebellar cortex (84–86). However, the long-term decrease in synaptophysin expression was not analyzed in these animals to determine if the alteration in synaptophysin expression is a permanent effect of exposure to the hyperinsulinemic perinatal environment. Furthermore, Hatanaka *et al.* (87) analyzed dendritic spines and filopodia in mice born to obese mothers using two-photon microscopy of the superficial cortical region in live mice and concluded that maternal obesity leads to synaptic instability. It was specifically shown that a minimal exposure to maternal HFD only during the lactation period was sufficient to alter rates of synaptogenesis throughout adulthood to the same magnitude as exposure through the entire perinatal period (87). This suggests that development during the lactational phase is most crucial to the long-term plasticity of the brain in mice. Decreases in spine density and spine number as well as active zone and postsynaptic density size have recently been shown in hippocampal regions to persist up to three generations (70). Page and Anday (88) support these findings by showing decreased messenger RNA expression and protein levels of key synaptic players synaptophysin, SNAP25, as well as the dendritic marker MAP2 in hippocampal samples from rats exposed to maternal overnutrition. The potential influence of synaptic instability and altered synaptogenesis in other regions known to influence metabolism and behavior has yet to be thoroughly studied, but given the indication of this effect in the cortex and hippocampus, it is likely that alterations in synapse formation are found in additional brain regions.

Epigenetic Modifications

More in-depth analysis of epigenetic modifications in studies of maternal overnutrition models has provided data regarding modulation of gene expression. Methylation of key target genes has shown effects within the dopamine system (89,90), the melanocortin system (91–93), and the hippocampus (94). These changes in methylation may be attributed to a specific upregulation in the DNA methyltransferases *Dnmt1, Dnmt3a*, and *Dnmt3b* (94). While many studies focus on specific brain regions affected, the likelihood is high that multiple regions, or perhaps even the whole brain, is subjected to these types of epigenetic modifications (Figure 2). Recent studies have shared promising data that methyl donor supplementation may combat these negative effects, but this still needs to be further investigated (95). Further specific epigenetic modifications have been associated with histone modifications, resulting in gene expression changes. Glendining *et al.* (96) have shown a significant decrease in the histone methylation mark, H3K9me3, in female mice and a significant increase in the histone acetylation mark, H3K9Ac, in male mice when assessing the regions surrounding the oxytocin receptor transcription start site. This increase in H3K9Ac in male animals was also shown in the context of the cannabinoid receptor 1, with no change in the gene expression of associated histone deacetylases (97). These studies contradict findings from Liu *et al.* (98) that nuclear levels of the histone deacetylase, HDAC4, were actually increased in HFD-exposed animals and could be normalized with treatment with the HDAC4-specific inhibitor Mc1568. Furthermore, in a study by Fusco *et al.* (71), in assessment of the *Bdnf* promoter region and generally in the whole hippocampus, significant decreases in H3K9Ac and H3K4me3 were noted and correlated with overall decreases in BDNF (brain-derived neurotrophic factor) protein levels. Alarmingly, this change persisted for more than three generations of offspring, with HFD exposure occurring only in the first generation demonstrating the persistence of these genetic modifications through multiple generations. As can be seen by the status of histone marks and expression or activity of DNA methyltransferases and histone deacetylases, the effect of maternal overnutrition can have opposite effects depending on brain regions and genes of interest, highlighting the complexity of changes due to this early developmental insult.

MODULATION OF CNS-CONTROLLED BEHAVIOR

Emerging Themes

A number of single topics have surfaced in recent years pairing maternal overnutrition with other pertinent molecular or functional changes. For example, in the field of circadian regulation, Cleal *et al.* (99) have shown that maternal overnutrition consisting of HFD exposure prior to and throughout pregnancy and lactation causes significant changes to the hypothalamic metabolic clock. Alterations in the circadian rhythm of clock genes *Clock, Bmal1*, *Per2*, and *Cry2* were noted, and this was linked to changes to hypothalamic *Pomc* and *Npy* gene diurnal rhythms in male mice (99). Park *et al.* (100) studied the role of endoplasmic reticulum stress in the detrimental outgrowth of hypothalamic neurons and endoplasmic reticulum stress markers and were able to reduce or completely abolish a subset of these negative effects with neonatal tauroursodeoxycholic acid treatment. In an effort to determine beneficial postnatal interventions, researchers show that environmental enrichment may reverse some of the negative side effects of maternal nutrition (98), suggesting potential for therapeutic interventions.

Microbiome

The microbiome has recently emerged as a critical modulator of CNS processes in animals and humans [reviewed in (101)]. Indeed, it has been shown that in adult humans (102) and mice (103), obesity is associated with a change in the internal bacterial milieu of the gastrointestinal tract. This interaction is becoming more relevant in studies of maternal programming (104) because a rapid remodeling of the maternal microbiome occurs throughout normal pregnancy (105). In addition, the maternal microbiome in obese women is altered, and specifically, excessive weight gain in pregnancy can further change the microbiome (106). Whole-brain effects of the maternal obese microbiome are noted by assessing overall behavior of animals born to obese mothers (107) [for a review, see (108)]. Recently, it was reported that reconstituting the microbiome of offspring born from obese mothers is sufficient to reverse

known social deficits in these animals (109). A specific subspecies of bacteria, *Lactobacillus reuteri*, increases sociability in both offspring born to obese mothers and in germ-free mice. In addition, Paul *et al.* (110) determined that consumption of a prebiotic could help to curb the detrimental metabolic effects of maternal obesity on offspring metabolic health. However, despite the correction of alterations in offspring due to the maternal microbiome, no studies to date have determined the effects of altering the obese maternal microbiome on brain-specific circuit formation and signaling of key metabolic hormones.

Timing of Exposure

Recent human studies have linked gestational weight gain (GWG) with cognitive performance and propensity to develop obesity in humans. Diesel *et al.* (10) determined that women with prepregnancy body mass index $\geq$ 25 kg/m^2 but normal GWG show no correlation with an increased relative risk (RR) of obesity at both 10 and 16 years of age in their children. Interestingly, in both lean ($\leq$25 kg/m^2) and overweight mothers, GWG with a *z* score above 1 was sufficient to increase the RR for obesity only at age 16 by >20%. Most interestingly, lean mothers with the highest GWG had offspring with the highest RR for obesity at both 10 and 16 years of age (adjusted RR, 2.32 and 2.40, respectively), even higher than overweight mothers with the same GWG (10,111). In assessing for comorbidities as a result of maternal programming, others have shown an increased risk for attention-deficit/hyperactivity disorder as well as decreased cognitive development in offspring from lean and obese women with a large GWG (16,17,112). Furthermore, in mouse models, it is becoming increasingly apparent that HFD exposure during the period of lactation (which is equivalent to the third trimester in humans) (Figure 1) is sufficient to drive much of the abnormal developmental phenotypes that are present (113). Lactational HFD exposure represents one of the few methods by which we can mimic GWG in mice because mice exposed to a control diet or HFD have similar rates of body weight increase throughout pregnancy; however, if HFD is only provided during lactation, the animals continue to gain weight, whereas control diet animals rebound back to nonpregnant control animal levels (R.N. Lippert, Ph.D., *et al*., unpublished observation, November 2014). Our work in the hypothalamic alterations in pro-opiomelanocortin and agouti-related protein projection development as well as dopamine neuronal development demonstrates that HFD during the lactation period is sufficient to suppress innervation in a number of target regions and that this is maintained throughout adulthood (65,79). Furthermore, in the aforementioned studies on gut microbiota from normal-diet animals, normalizing aspects of social behavior in offspring was only possible if the exposure occurred directly at weaning. Delaying this exposure until 8 weeks of age was not sufficient to restore social behavior (109). Again, demonstrating the critical period of lactation and the immediate postlactational window of brain development. It is crucial to identify the time course of GWG in humans to determine if the relative weight gain solely during the third trimester of pregnancy leads to the increased risk for development of obesity and other comorbidities.

WHAT LIES AHEAD

Open Questions

Many open questions remain regarding the effects of maternal overnutrition on the offspring. While we have highlighted here a number of unique changes that occur at the cellular and circuit levels, the primary mechanisms for these changes still remain largely unclear. One open question is the progression of the cellular changes: is there an effect of maternal overnutrition on the developing brain that acts as an entry point for developmental disruption? Highlighting the progression of development outlined in Figure 1, understanding how overnutrition can alter developmental trajectories within each stage would be relevant to determine if specific time windows of development are, in fact, more vulnerable to overnutrition-related changes. For example, are the potential effects of diet on neuronal migration more or less detrimental than those on axonal outgrowth? Could initial metabolic cues that are known to influence hypothalamic development, such as leptin (73), result in connectivity changes of these neurons to their interacting downstream neuronal partners? Thus, the changes in the growth and connections of the primary metabolic circuits originating in the hypothalamus might be to blame for the developmental changes to the dopaminergic circuits, for example, caused by dampened interactions between these two developing brain regions. Does the influx of circulating hormones and other factors act across multiple brain regions with each neuronal circuit being individually affected? Furthermore, are the noted transgenerational effects entirely caused by epigenetic mechanisms? Could the changes to metabolic circuits within the hypothalamus alter circulating metabolic factors (e.g., insulin, leptin) in the offspring such that as those offspring become parents, these factors are sufficiently elevated to result in ongoing neurodevelopmental effects in later offspring? One of the main open questions that remains to be tested is if these effects are treatable or even completely reversible. Given the permanent changes to neuronal connectivity that we and others have uncovered, it could be argued that the neurocircuit effects are permanent, but to date, restoration of neuronal connectivity by dietary or exercise intervention in the offspring is not entirely clear.

Approaches for Studying Maternal Nutritional Effects on Offspring

As our understanding of the role of maternal overnutrition on brain development progresses, utilizing recent technological advancements can further uncover the long-term effects on more dynamic processes within the brain. Specifically, how can maternal overnutrition affect not only neuronal connectivity in a static sense, but also the adaptations of neuronal circuits across the life span? Furthermore, the complex interaction of maternal overnutrition and other environmental factors encountered in adulthood (stress, nutrition, etc.) need to be more thoroughly understood to determine the role of early developmental overnutrition in priming the brain for later disease vulnerability. Exciting new work on the unique dynamics

of metabolic circuit dynamics using calcium imaging techniques in adult mouse models (114–116) warrants understanding these neurocircuit dynamics in the context of previous overnutritional exposure. However, given the broad changes at the neuronal level noted above, assessment of these neurocircuit dynamics would be relevant also in behavioral conditions relating to neuropsychiatric disease to understand if previous nutritional exposures can alter adult brain function in disease contexts.

CONCLUSIONS

Overall, the field of maternal programming, through obesity and/or T2DM, continues to uncover the many alterations to the CNS on various perinatal exposure periods. Effects of maternal overnutrition in key windows of development are increasingly apparent, with our group and others showing that the lactational period is critical in aspects of hypothalamic and dopaminergic development. Specific research focusing on neurogenesis, synaptogenesis, and whole-brain effects continues to display how maternal programming heavily influences brain development at a number of molecular and cellular levels (Figure 1). Through the use of animal models of maternal overnutrition, a broader understanding of the molecular changes resulting in adverse behavioral outcomes can be elucidated. As shown here, maternal obesity is linked to various cellular-level changes that affect the formation and function of neurons. Many studies center on specific subregions, but it is increasingly relevant to understand the global effects on the whole brain. Furthermore, while the effects in neonates, postweaning animals, and young adult animals are known, it is still unclear what the long-term effects are in animals (and humans) in response to maternal overnutrition exposure in these critical windows of development. While many effects appear to culminate in the brain specifically, it cannot be overlooked that many peripheral systems, such as the microbiome, are continuing to assert profound effects on overall behavior of animals and humans. The field must be prepared to understand how the maternal metabolic state can influence the development of the brain through secondary measures peripherally via microbiome transfer and centrally via modulation of brain circuit formation. As we continue to understand the effects of maternal obesity on offspring, we can strive to find key windows for dietary intervention, critical hormones mediating these effects, and potential therapeutic options to prevent the long-lasting negative effects of perinatal programming due to overnutrition.

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ARTICLE INFORMATION

From the German Institute of Human Nutrition Potsdam Rehbrücke (RNL), Potsdam; German Center for Diabetes Research (RNL, JCB), Neuherberg; Max Planck Institute for Metabolism Research (RNL, JCB); and Policlinic for Endocrinology, Diabetes and Preventive Medicine (JCB), University Hospital Cologne, Cologne, Germany.

Address correspondence to Jens C. Brüning, M.D., at bruening@sf.mpg.de.

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