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Nanotechnology in Appetite Regulation: Targeting Hypothalamic Pathways and Gut-Brain Axis in Obesity

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ABSTRACT

Obesity is increasingly understood as a brain-centric disorder in which hypothalamic circuits and the gut–brain axis fail to correctly integrate peripheral signals of energy status. Hypercaloric diets and adipose expansion drive leptin and insulin resistance, neuroinflammation and altered gut hormone signaling, leading to persistent hyperphagia and reduced energy expenditure. Existing anti-obesity drugs, including GLP-1 receptor agonists, modulate some of these pathways but are limited by systemic side effects, variable brain penetration and receptor desensitization. Nanotechnology offers new opportunities to deliver appetite-regulating agents directly and selectively to central and peripheral nodes of energy homeostasis. This review examines the neurobiology of hypothalamic appetite control and gut–brain communication, then outlines nanocarrier strategies for crossing the blood–brain barrier or using nose-to-brain and gut-to-brain routes. We discuss nano-enabled delivery of hormones, peptides and small molecules that modulate leptin, melanocortin, GLP-1 and inflammatory pathways, including approaches that rescue hypothalamic leptin signaling and dampen diet-induced neuroinflammation. Finally, we consider theranostic systems, safety and ethical issues, and prospects for integrating nanotechnology into precision appetite-targeted obesity therapy.

Keywords: Nanotechnology; Appetite regulation; Hypothalamus; Gut–brain axis; Obesity

INTRODUCTION

Although obesity manifests as excess adiposity, its roots lie largely in the brain. Converging genetic, clinical and experimental data show that hypothalamic circuits are essential for defending body weight and that their disruption, whether through rare monogenic defects or more common diet-induced changes, predisposes to obesity[1–3]. The arcuate, paraventricular, ventromedial, dorsomedial and lateral hypothalamic nuclei integrate signals from adipose tissue, gut, pancreas and other organs, then orchestrate behavior (feeding, activity) and autonomic outflow. Under physiological conditions, adipocyte-derived leptin and pancreatic insulin inform the hypothalamus about long-term energy stores, while gut-derived hormones such as GLP-1, PYY, CCK and ghrelin convey information about recent nutrient intake[4, 5]. These hormonal cues converge on two main arcuate neuron populations: anorexigenic POMC/CART neurons and orexigenic NPY/AgRP neurons. The balance of their outputs, relayed through melanocortin and other downstream pathways, determines appetite, energy expenditure and neuroendocrine tone[6, 7].

Chronic caloric excess, high-fat diets and systemic inflammation disturb this finely tuned network. In early obesity, leptin levels rise in proportion to fat mass, but hypothalamic neurons become resistant to leptin's anorexigenic and thermogenic effects[7–9]. Mechanisms include impaired leptin transport across the blood–brain barrier (BBB), receptor downregulation, SOCS3 and PTP1B-mediated negative feedback and intracellular ER stress. In parallel, high-fat feeding induces microglial activation, astrocytosis and production of inflammatory cytokines within hypothalamic nuclei, a state of neuroinflammation that further impairs leptin and insulin signaling and remodels synaptic inputs[8].

The gut–brain axis adds another dimension. Nutrient sensing in the intestine triggers secretion of GLP-1, GIP, PYY and other hormones that act on vagal afferents and brainstem and hypothalamic targets to reduce appetite and slow gastric emptying. GLP-1 receptor agonists, now cornerstone therapies for obesity and diabetes, exploit these pathways but at supraphysiologic levels and via systemic injection. Gut microbial metabolites and low-grade endotoxemia also modulate brain function, contributing to neuroinflammation and altered reward

circuits[10]. Despite powerful new drugs, several limitations remain. Many agents act broadly, with off-target effects in cardiovascular, gastrointestinal and other systems. Large peptide hormones require parenteral injection and may not efficiently reach specific brain nuclei[8]. Chronic exposure risks receptor desensitization, and individual responses vary depending on genetics, gut microbiota and the extent of established neuroinflammation. Moreover, current therapies rarely distinguish between patients whose obesity is driven predominantly by hypothalamic damage, profound leptin resistance, disrupted gut–brain signaling or peripheral metabolic defects[11]. Nanotechnology offers conceptual solutions to each of these challenges. At the most basic level, nanocarriers can protect labile peptides, proteins or small molecules from degradation, extend their half-life and improve pharmacokinetics. More importantly, nanoscale delivery systems can be engineered for spatial and cellular selectivity. For central appetite regulation, this includes strategies to cross the BBB using surface ligands that engage endogenous transport systems, or to bypass the BBB entirely using intranasal nose-to-brain routes that exploit the olfactory and trigeminal pathways[12–14].

Recent work demonstrates that intranasal delivery of appetite-modulating agents, including oxytocin and experimental proteins, can reach hypothalamic regions and influence body weight in humans and animals with hypothalamic obesity. Nanostructured formulations have the potential to further enhance this targeting, lowering required doses and reducing systemic spillover[15]. For peripheral modulation of the gut–brain axis, oral nanoformulations can target intestinal L-cells, K-cells, vagal afferent terminals and even specific microbiota niches, enriching or locally releasing hormones and neuromodulators that influence appetite circuits[15].

Nanotechnology also enables new therapeutic strategies against central leptin resistance and neuroinflammation. DNA-based tetrahedral nanoparticles carrying celastrol, for instance, have been used as "nano-patrollers" that rescue leptin sensitivity in the hypothalamus while simultaneously acting on adipose tissue in obese mice, producing sustained weight loss with improved metabolic parameters. Other CNS-penetrant nanomedicines are being developed to block inflammatory pathways such as NLRP3 inflammasome signaling, which is strongly implicated in diet-induced hypothalamic injury and dysregulated appetite[16–18]. Beyond straightforward drug delivery, nanodevices can incorporate imaging contrast agents or responsive optical and magnetic elements, supporting theranostic concepts in which appetite-regulating interventions are monitored in real time. Integration with wearable technologies and digital health platforms could eventually allow feedback-controlled dosing based on short-term changes in energy intake, gut hormone profiles or inflammatory markers[19–21].

In summary, obesity emerges from the interplay between peripheral metabolic organs, gut microbiota and central appetite circuits. Traditional systemic pharmacology struggles to fully address this multi-organ, spatially complex problem[2, 3, 11]. Nanotechnology, by virtue of its capacity for tissue-specific delivery, BBB navigation and multi-payload integration, provides a versatile toolkit to more precisely modulate hypothalamic pathways and the gut–brain axis. The following sections examine the underlying neurobiology, the design of central and peripheral nanocarriers, and how these platforms are being used to reshape appetite regulation in preclinical and emerging translational studies.

2. Neurobiology of Hypothalamic Appetite Circuits in Obesity

Appetite regulation depends on a distributed network, but the arcuate nucleus (ARC) in the mediobasal hypothalamus is a primary integrative hub. Within the ARC, anorexigenic POMC/CART neurons and orexigenic NPY/AgRP neurons receive hormonal, nutrient and neural inputs and project to downstream nuclei, including the paraventricular (PVH), dorsomedial (DMH), ventromedial (VMH) and lateral hypothalamus[22]. Activation of POMC neurons leads to α-MSH release and stimulation of melanocortin receptors, particularly MC4R, in PVH and other targets, reducing food intake and increasing energy expenditure. In contrast, NPY/AgRP neurons promote feeding, in part by antagonizing melanocortin signaling[22].

Leptin and insulin act as adiposity signals. They cross the BBB via saturable transport mechanisms and bind receptors highly expressed on ARC neurons. Leptin stimulates POMC and inhibits NPY/AgRP neurons, while insulin exerts overlapping but distinct effects. Together, these signals adjust appetite and sympathetic outflow to match energy stores. In obesity, chronic hyperleptinemia and hyperinsulinemia paradoxically blunt central responses, a state termed leptin and insulin resistance. Mechanisms include impaired transport across the BBB, receptor downregulation, SOCS3 and PTP1B-mediated negative feedback, ER stress and inflammation-induced signaling defects[4, 23, 24]. Neuroinflammation plays a pivotal role in this transition. High-fat diets rapidly activate microglia and astrocytes in the ARC and other hypothalamic nuclei. These glial cells release cytokines such as TNF-α, IL-1β and IL-6, as well as reactive oxygen species, which interfere with insulin receptor and leptin receptor signaling, alter synaptic organization and may induce neuronal injury. The NLRP3 inflammasome is a key mediator of these processes, integrating metabolic and inflammatory cues[25, 26]. Other neuromodulators, including serotonin, dopamine, orexin, melanocortin, GABA and endocannabinoids, interact with these core circuits. Reward-related regions such as the ventral tegmental area and nucleus accumbens, and higher cortical areas, modulate hedonic feeding and cue-driven eating. Obesity reshapes these networks, often increasing responsiveness to palatable food cues while weakening homeostatic satiety signals[27, 28].

Finally, hypothalamic changes appear to be partially irreversible once established. Animal and human imaging studies indicate that prolonged obesity leads to structural remodeling, gliosis and altered connectivity in

hypothalamic nuclei. This has important therapeutic implications: simply restoring normal hormone levels may be insufficient if central circuits are chronically inflamed and structurally altered[29]. For nanotechnology-based interventions, the key points are the cellular diversity (neurons, astrocytes, microglia), regional specificity (ARC, PVH, VMH, DMH, LH) and the importance of leptin, melanocortin, insulin and GLP-1 pathways. Nanocarriers aiming to modulate appetite must either reach these nuclei directly or act on upstream gut–brain signaling to rebalance their inputs[30].

3. Nanotechnology for Central Delivery: Crossing or Bypassing the Blood–Brain Barrier

The BBB is both a physiologic safeguard and a major obstacle for appetite-targeted therapies. It restricts passage of large and hydrophilic molecules, including most peptide hormones. Nanotechnology provides several avenues to enhance central delivery while preserving some degree of selectivity[31]. One strategy is to functionalize nanoparticles with ligands that engage BBB transport systems. Transferrin receptor, insulin receptor and low-density lipoprotein receptor–related proteins are commonly exploited. Nanocarriers decorated with appropriate antibodies or peptides can undergo receptor-mediated transcytosis, ferrying encapsulated cargo such as leptin analogues, melanocortin agonists or anti-inflammatory drugs into the brain. Particle size, surface charge and hydrophilicity must be optimized to avoid rapid clearance by the mononuclear phagocyte system while maintaining efficient transcytosis[31, 32].

Intranasal nose-to-brain delivery offers a complementary or alternative route that bypasses the BBB. Drugs administered intranasally can travel along olfactory and trigeminal nerve pathways to reach the olfactory bulb, hypothalamus and other brain regions[33]. Nanostructured formulations such as mucoadhesive polymeric nanoparticles, nanoemulsions and lipid-based systems prolong residence in the nasal cavity, facilitate endocytosis into olfactory epithelial cells and enhance axonal transport. Recent work uses engineered commensal bacteria as living nanocarriers to deliver appetite-regulating molecules through the olfactory mucosa, achieving robust central exposure with reduced dosing frequency in obese mice[33]. Clinical translation of nose-to-brain approaches is already underway for hypothalamic obesity using intranasal oxytocin and other peptides, demonstrating both feasibility and safety in early trials. Nanotechnology can refine these interventions by stabilizing peptides, controlling release kinetics and adding targeting moieties that favor uptake into specific neural circuits[33].

A third route involves temporary or localized BBB disruption using focused ultrasound, hyperosmotic agents or inflammatory mediators, in conjunction with systemically administered nanoparticles. While potentially powerful, such approaches carry higher risk and are currently more suited to oncology than chronic obesity therapy[34]. Regardless of route, central nanomedicines must balance efficacy and safety. They should deliver sufficient concentrations of appetite-modulating agents to relevant nuclei without causing widespread brain exposure that could disturb other functions. Long-term accumulation of nanomaterials in neural tissue, glial activation and off-target effects on cognition, mood or autonomic control are key concerns. These considerations favor biodegradable carriers, minimalistic compositions and rigorous preclinical neurotoxicity evaluations before human use[35].

4. Nanotechnology Targeting the Gut–Brain Axis in Appetite Control

The gut–brain axis offers more accessible targets than the CNS itself and is already exploited by GLP-1 receptor agonists and bariatric surgery. Nanotechnology can enhance and diversify these interventions by acting at the level of gut hormones, sensory nerves and microbiota. Enteroendocrine L-cells, K-cells and I-cells secrete GLP-1, GIP, PYY and CCK in response to nutrients[36]. Nanocarriers administered orally can be designed to release modulators in the small intestine, either stimulating these cells directly or delivering exogenous hormone analogues. For example, encapsulating GLP-1 mimetics or co-agonists in lipid or polymeric nanoparticles can protect them from gastric degradation, promote uptake across the mucosa or favor interaction with local receptors, potentially allowing lower systemic doses. pH-responsive coatings and enzyme-sensitive matrices can direct release to specific segments, while mucoadhesive surfaces increase contact time[36].

Vagal afferents represent another key node. Their terminals in the lamina propria respond to gut hormones, nutrients and inflammatory mediators, conveying satiety and discomfort signals to the brainstem and hypothalamus[37]. Nanoformulations targeting these nerve endings, for instance, by presenting ligands for GPRs or ion channels expressed on vagal fibers, could fine-tune the intensity and timing of satiety signals without large systemic hormonal surges[37]. The gut microbiota also influences appetite by producing metabolites such as short-chain fatty acids, bile acid derivatives and indoles, which affect enteroendocrine cells and neural circuits. Nanoparticles can modulate this ecosystem by delivering prebiotics, probiotics, narrow-spectrum antibiotics or phage cocktails to specific intestinal niches[38–40]. Changes in microbial composition and metabolite profiles can, in turn, alter GLP-1 secretion, barrier integrity and low-grade inflammation that feeds back to hypothalamic circuits.

Finally, organ-on-chip models of the gut–brain axis are emerging as platforms to test nanomedicines. Microfluidic systems incorporating intestinal epithelium, enteric neurons and brain-derived cells allow controlled evaluation of how nanoformulated agents affect hormone release and neural responses, bridging the gap between reductionist cell studies and complex animal models[41]. In contrast to direct central delivery, gut-targeted nanotechnology tends to operate within established physiological routes, potentially improving

safety and regulatory acceptance[41]. However, inter-individual variability in microbiota composition, gut permeability and hormone sensitivity means that responses to such interventions are likely heterogeneous, underscoring the need for adaptive, biomarker-guided strategies.

5. Nano-Enabled Modulation of Leptin Resistance and Hypothalamic Neuroinflammation

Leptin resistance and neuroinflammation sit at the heart of many obesity phenotypes and are particularly attractive targets for nanomedicine[4, 23]. Early enthusiasm for leptin as an obesity drug waned when most obese patients proved resistant to exogenous hormone, but understanding of underlying mechanisms has grown, including the roles of impaired transport, receptor downregulation and inflammatory signaling. Nanotechnology enables several new strategies. One approach uses nanocarriers to enhance the central delivery of leptin or leptin sensitizers. Metal and polymeric nanocomposites have been proposed to deliver leptin across the BBB or intranasally, improving receptor engagement in hypothalamic nuclei while reducing peripheral exposure that might promote sympathetic or cardiovascular side effects[42]. Another focuses on delivering small molecules that restore leptin signaling pathways. Celastrol, a plant-derived compound identified as a leptin sensitizer, has been packaged into DNA tetrahedral nanostructures that circulate systemically and preferentially act in leptin-resistant tissues, including the hypothalamus and adipose depots. In diet-induced obese mice, this "nano-patroller" design normalizes leptin responsiveness, reduces food intake and enhances thermogenesis more effectively than free celastrol[42].

Targeting neuroinflammation is equally important. Obesity-related activation of microglia and astrocytes, and upregulation of the NLRP3 inflammasome, underpin many aspects of hypothalamic dysfunction[43]. CNS-penetrant inhibitors of NLRP3 and related pathways are being developed, and nanocarriers offer a means to concentrate these drugs within inflammatory hotspots while sparing the rest of the brain. A CNS-penetrant NLRP3 inhibitor (TN-783) has shown durable weight loss and metabolic improvements in obese mice, and nanotechnology could further refine its delivery profile to maximize benefit and minimize off-target effects[43]. In addition to small molecules, nanoparticles can carry nucleic acid therapies such as siRNAs or antisense oligonucleotides targeting SOCS3, PTP1B or other negative regulators of leptin and insulin signaling[44]. Lipid nanoparticles similar to those used in mRNA vaccines can deliver these cargos to hypothalamic neurons or glia if appropriately targeted. Conceptually, partial and region-specific knockdown of inhibitory pathways could restore hormone sensitivity without the risks inherent in systemic gene editing[44].

A key challenge is to avoid overshooting. Overactivation of leptin or melanocortin pathways could lead to cachexia-like states, reproductive dysfunction or hypertension. Thus, smart nanocarriers that respond to local inflammatory or metabolic cues, releasing their payload only under conditions of leptin resistance, offer an appealing but technically demanding direction[45]. Together, these nano-enabled approaches aim not merely to swamp a resistant system with more hormone but to repair underlying signaling defects and inflammatory damage, potentially yielding more durable and physiologically harmonious appetite control.

6. Theranostics, Personalization and Integration with Existing Anti-Obesity Therapies

Nanotechnology is particularly well suited to theranostic concepts, in which diagnostic and therapeutic functions are combined. In the context of appetite regulation, theranostic nanoparticles might carry both an appetite-modulating drug and an imaging agent, enabling real-time tracking of delivery to hypothalamic nuclei or gut segments[19, 46]. MRI contrast agents, PET tracers or near-infrared fluorophores can be embedded within nanocarriers, allowing non-invasive visualization of biodistribution and, in some designs, indirect readouts of target engagement. Such systems are valuable in early-phase trials to confirm central or gut targeting and to refine dosing. They also support personalization by identifying patients who achieve adequate brain or gut exposure versus those who do not, informing therapy selection or formulation adjustments. For example, patients with compromised nasal mucosa might respond poorly to nose-to-brain nanoformulations and be better served by gut-targeted or systemic strategies[47].

Integration with existing therapies is another important theme. GLP-1 receptor agonists, dual and triple incretin agonists and emerging amylin and GIP/GLP-1 co-agonists are highly effective but expensive and sometimes poorly tolerated. Nanocarriers could, in principle, deliver lower doses more efficiently to central or gut targets, reducing cost and side effects[48]. Alternatively, nanoformulated small molecules or peptides that modulate complementary pathways, such as leptin sensitivity or neuroinflammation, could be added to incretin therapy to enhance weight loss or preserve efficacy over time[48]. Personalization extends beyond drug choice to timing and intensity. Continuous or frequent monitoring of appetite-related biomarkers, energy intake patterns and physical activity via wearable devices can be integrated with nanomedicine dosing, creating closed-loop systems[49]. For instance, an oral nanoformulation that boosts GLP-1 or PYY release might be scheduled around meals that historically trigger overeating, as identified by sensor-derived patterns. Organ-on-chip and patient-derived cell models of the gut–brain axis can also be used to test individual responses to candidate nanoformulations before clinical use[49]. However, the complexity of such integrated systems raises practical and regulatory questions. Data privacy, algorithmic transparency and equitable access to the necessary digital infrastructure must be addressed. Moreover, clinicians will need clear guidance on interpreting theranostic signals and on adjusting multi-component regimens in response. In this landscape, nanotechnology is less a

standalone solution and more an enabling layer that can refine, extend and personalize the effects of current and future anti-obesity drugs along hypothalamic and gut–brain pathways.

7. Safety, Ethics and Future Directions in Nanotechnology-Based Appetite Modulation

As with any central nervous system–active or long-term therapy, safety is paramount for nanotechnology-based appetite interventions. Biodegradability and biocompatibility of nanocarrier materials are critical[50]. Lipid-based and polymeric carriers that degrade into endogenous or easily excreted components are generally preferred over inorganic materials that may accumulate in the brain or peripheral organs[51, 52]. Chronic exposure demands careful assessment of neurotoxicity, glial activation, interference with synaptic function and potential effects on cognition, mood and sleep.

Off-target appetite suppression or activation is another concern. Overly aggressive modulation of hypothalamic circuits could produce excessive weight loss, malnutrition, reproductive dysfunction or dysautonomia[53]. Conversely, partial targeting or compensatory mechanisms might blunt efficacy, exposing patients to nanomaterial risks without substantial benefit. Achieving a controllable, reversible shift in appetite set-points rather than rigid suppression is a key design goal. Ethical considerations extend to autonomy and consent. Technologies that directly modulate brain circuits involved in motivation and reward challenge traditional boundaries of medical intervention. Patients must clearly understand what aspects of their eating behavior and hedonic responses might change, and safeguards should prevent coercive use, for example in institutional settings[53].

Regulatory frameworks for nanomedicine, CNS drugs and advanced biologics increasingly overlap. Appetite-targeted nanotherapies will need to satisfy requirements for device-like characterization and drug-like efficacy and safety demonstrations[54]. Long-term follow-up, including neurocognitive assessments, will likely be required. International harmonization of guidelines will help developers navigate complex approval pathways.

Future research directions include the development of ultra-precise targeting ligands for specific hypothalamic neuron subtypes, such as newly identified leptin-responsive PNOC/NPY cells, which appear to exert strong control over feeding behavior and weight. Advances in single-cell omics and connectomics will continue to reveal candidate nodes for intervention. On the gut side, improved understanding of GLP-1 and related peptides' central and peripheral actions, including unexpected roles of brainstem GLP-1 neurons, will inform where and how nanocarriers should deliver these signals.

There is also growing interest in combining nanotechnology with emerging modalities such as gene editing, RNA therapeutics and engineered microbes for nose-to-brain delivery. These approaches promise durable alterations in appetite circuits but raise even higher safety and ethical bars.

Ultimately, nanotechnology in appetite regulation should be pursued as part of a broader strategy that includes lifestyle, environmental and policy interventions addressing obesogenic environments. Central and gut–brain nanomedicines may be most appropriately deployed in individuals with severe or refractory obesity, monogenic or hypothalamic forms of the disease or high risk of complications, where benefits clearly outweigh risks.

CONCLUSION

Nanotechnology is opening a new frontier in appetite-targeted obesity therapy by enabling more precise engagement of hypothalamic circuits and the gut–brain axis. Nanocarriers can enhance delivery of hormones, peptides and small molecules across or around the blood–brain barrier, rescue leptin signaling, dampen hypothalamic neuroinflammation and modulate gut hormone and microbiota pathways that feed into central appetite control. Early preclinical studies, including celastrol-loaded DNA nanostructures and nose-to-brain nanoformulations, demonstrate that such strategies can produce stronger and more durable weight and metabolic benefits than conventional formulations. Translating these advances into safe, affordable and ethically acceptable therapies will require rigorous neurotoxicity testing, careful patient selection, transparent communication and integration with existing pharmacologic and lifestyle approaches. If these challenges are met, nanotechnology-based modulation of hypothalamic pathways and the gut–brain axis may become an important component of precision, brain-centric obesity management.

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