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Review

Role of central neurotensin in regulating feeding: Implications for the development and treatment of body weight disorders

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ABSTRACT

The peptide neurotensin (Nts) was discovered within the brain over 40 years ago and is implicated in regulating analgesia, body temperature, blood pressure, locomotor activity and feeding. Recent evidence suggests, however, that these disparate processes may be controlled via specific populations of Nts neurons and receptors. The neuronal mediators of Nts anorectic action are now beginning to be understood, and, as such, modulating specific Nts pathways might be useful in treating feeding and body weight disorders. This review considers mechanisms through which Nts normally regulates feeding and how disruptions in Nts signaling might contribute to the disordered feeding and body weight of schizophrenia, Parkinson's disease, anorexia nervosa, and obesity. Defining how Nts specifically mediates feeding vs. other aspects of physiology will inform the design of therapeutics that modify body weight without disrupting other important Nts-mediated physiology.

1. Ingestive behavior impacts health

The physiological processes that sustain life constantly tap bodily energy reserves, which must be replaced via ingestion; hence, feeding is a compulsory behavior for survival. Decades of research have proven that the brain is the master-organizer of feeding behavior, vigilantly monitoring energy status and coordinating appropriate ingestive behavior. For example, fasting-induced hunger increases the motivation to find and ingest food, while stomach fullness or increased body fat cue the cessation of feeding. However, despite recognition that these processes take place, and the fact that eating and drinking are perhaps the most commonly performed behaviors in animals and humans, the precise mechanisms by which the brain orchestrates these processes remain incompletely understood.

Defining the biology of ingestion is necessary not only to understand immediate survival but also to treat, and ultimately prevent, feeding dysregulation that endangers health and well-being. For example, intake of excess calories, along with insufficient physical activity and metabolic rate to consume them, results in increased adiposity. The rise in highly palatable, energy-dense foods, their ease of acquisition and the widespread increase in sedentary lifestyles have contributed to the worldwide rise in the overweight and obese [1]. Increased body weight, as assessed via body mass index, elevates risk of developing severe chronic conditions, including cardiovascular disease, type-2 diabetes, kidney disease, cancer and disability, and has been accountable for 4 million annual deaths [2]. Though lifestyle intervention is safe and somewhat effective in promoting weight loss, it is difficult to maintain and, as a result, has not been sufficient to counteract the overweight and obesity epidemic. Bariatric surgery is currently the most effective option to treat obesity; however, not all patients are able to undergo such procedures because of cost, complications, or restrictive guidelines [3]. In addition, the search for both safe and efficacious pharmacological therapies to treat obesity has proven difficult. For example, serotonin reuptake inhibitors were found to have serious cardiopulmonary side effects that limited their usage [3]. Cannabinoid type 1 receptor antagonists appeared to hold promise as effective weight loss medications without adverse cardiovascular-related events, but these drugs caused severe psychiatric side effects that precluded their usage [3]. This stresses the need to find efficacious pharmacological interventions with suitable safety profiles that both support weight loss and prevent debilitating chronic conditions that diminish life span.

Insufficient feeding can be equally deleterious. This is evidenced by the wide array of medical complications that arise with the self-imposed feeding restriction that defines the eating disorder anorexia nervosa (AN) [4]. This “relentless pursuit of thinness” has the highest mortality rate of any psychiatric illness [4], and there is an urgent need to find therapies that improve outcomes. AN is often accompanied by other psychiatric illness, including mood, anxiety and substance use disorders, and comorbidity is present in about 50% of all adolescents with AN [4]. Such comorbidity dictates the types of medications these patients receive. While use of antidepressants and antipsychotics can improve psychiatric symptoms, they fail to restore body weight [4]. As

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with obesity, finding efficacious pharmacotherapies for these patients has proven particularly difficult and has been limited by an incomplete understanding of how the brain regulates feeding. Thus, there is a crucial need to elucidate the neural signals that regulate feeding to direct discovery of interventions to treat eating disorders.

Neuropeptides have emerged as important regulators of body weight, with some promoting feeding (orexigenic) and others suppressing it (anorexigenic). The field has learned much about orexigenic neuropeptides. Yet, many anorexigens are comparatively less well characterized, though they may hold particular therapeutic promise for treating body weight disorders. Recently there has been increasing attention directed at how the neuropeptide neurotensin (Nts) modifies body weight. Nts signaling appears to play a pivotal, yet still poorly understood, role in intestinal fat absorption [5], but pharmacological data suggest that Nts may act centrally to suppress feeding. This review will focus on the growing understanding of how Nts signals within the brain, its contribution to regulation of energy balance and how disruption of central Nts signaling may underlie disordered feeding and body weight in disease.

2. Neurotensin (Nts) structure and expression pattern

Nts was first isolated from purified bovine hypothalamus by Carraway and Leeman. Injecting the isolated peptide intravenously into rats led to the initial characterization of Nts as a powerful hypotensive agent, an inducer of vascular permeability and a regulator of intestinal and uterine contraction [6]. These data suggested that Nts may not strictly exist as a central neuropeptide. Indeed, Nts was subsequently found within epithelial cells of the stomach and intestine [7]. Cloning of the Nts gene revealed that it contains coding sequences for both Nts and the Nts-related peptide Neuromedin N and led to the discovery that it produces a 169 amino acid precursor protein (pro-neurotensin, [pro-Nts]), which has an N-terminal signal sequence and is processed into both peptides [8]. Furthermore, two different-sized mRNA products, a 1.0 kb or 1.5 kb mRNA species, may be produced, and these mRNAs differ in their 3′ untranslated regions. Both transcripts are present in approximately equal ratios throughout the brain; however, the 1.0 kb mRNA species is 10 times more prevalent than the 1.5 kb mRNA within the intestine [8], suggesting tissue-specific regulation and perhaps differential peptide functions in the brain and periphery. Pro-Nts is subsequently cleaved by prohormone convertases to produce Neuromedin N and the Nts tridecapeptide (Glu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu-OH) [9]. Intriguingly, a truncated form of Nts (Nts 8–13) has superior Nts Receptor binding affinity compared to the full-length peptide, and this fragment is often used for in vitro studies of Nts action [9].

Nts is produced centrally and peripherally, but these pools of Nts are thought to mediate distinct actions. The abundant amount of Nts peptide found within the plasma may originate from the adrenal gland [10] and from the subset of intestinal enteroendocrine cells termed N-Cells [11]. Central vs. systemic administration of Nts produces different physiological responses. For instance, with intracisternal administration (a method of direct infusion into the subarachnoid space that allows drugs to bypass the blood-brain barrier), Nts induces antinociceptive and hypothermic effects. By contrast, intravenous (systemic) administration fails to produce either of these responses and, in fact, has been shown to result in elevated body temperature [12]. Intestinal Nts has recently been shown to be necessary for fat absorption via yet to be established mechanisms [5]. Circulating Nts levels are increased after bariatric surgery and weight loss, raising the possibility that Nts exerts some peripheral regulation of body weight [13]. Though the differential effects of central vs. peripheral Nts administration have led to the consensus that the blood-brain barrier is impermeable to Nts, new data suggests that there is some Nts transport to and from the brain [14]. This is further supported by the fact that peripheral Nts can activate brainstem structures in vagotomized mice and can induce gene

Table 1
Distribution of Nts cells in the central nervous system.

Summary of structures reported to contain Nts immunoreactivity in brains from colchicine-treated rats [16–20] and guinea pigs [21]. Results convey the relative density of Nts-labeled cell bodies or fibers. NR not reported; + few or sparse; ++ some; +++ many; ++++ very dense.

Structures reported to contain Nts	Supporting literature	Density of cell bodies	Density of fibers
Spinal cord			
Spinal cord: laminae I and II	[18]	NR	+++
Spinal cord: lamina III and IV	[18]	NR	++
Spinal cord: lamina X	[18]	+	++
Hindbrain			
Spinal trigeminal nucleus (Sp5C)	[16,18,21]	+++/+++	+++
Cuneate nucleus (Cu)	[18]	NR	++
Nucleus ambiguus (Amb)	[18]	++	+++
Pontine reticular nucleus (PnR)	[18]	NR	++++
Pontine central gray (PCG)	[18]	NR	++++
Mesencephalic Trigeminal Tract (me5)	[18]	NR	++++
Trapezoid Nucleus (Tz)	[18,21]	+++	+++
Gigantocellular reticular nucleus (Gi)	[18]	NR	++++
Paragigantocellular reticular nucleus (PGi)	[21]	+++	NR
Parvocellular reticular nucleus	[18]	NR	++
Lateral reticular nucleus (LRt)	[21]	++	NR
Ventrolateral reticular formation	[18]	+	+
Ventral reticular formation	[18]	NR	++++
Nucleus linearis	[18]	NR	++
Nucleus of the solitary tract (NST)	[16,18,21]	++/++ +	+++/+ +++
Nucleus raphe magnus (RMg)	[18,21]	++	++++
Nucleus raphe pallidus (RPA)	[21]	++	NR
Nucleus raphe obscurus (RO)	[21]	++	NR
Dorsal Cochlear nucleus (DC)	[16]	+	+
Area Postrema (AP)	[18]	+	++
Floor of the 4th Ventricle (4 V)	[16,18]	++	++
Parabrachial nuclei (PB)	[16,18,21]	++/++ +	++/++ ++
Locus coeruleus (LC)	[16,18,21]	++	++
Midbrain			
Dorsal raphe nucleus (DR)	[16,18,21]	++/++ +	++
Pontine raphe nucleus (PnR)	[18]	++	++++
Median raphe nucleus (MnR); also known as “nucleus centralis superior”	[18]	++	++
Periaqueductal gray (PAG); also known as “central gray”	[16,18,21]	++	++/++ +
Pretectal nucleus (APT)	[18]	NR	+/++
Medial pretectal area (MPT)	[18]	NR	++
Lateral lemniscus (LL)	[18]	NR	+++
Ventral tegmental area (VTA); also known as “Paranigral nucleus”	[16,18,21]	+++/+++	++
Interpeduncular fossa (IPF)	[18]	NR	++
Substantia nigra pars compacta (SNC)	[18]	NR	+++
Thalamus & nearby regions			
Periventricular nuclei of Thalamus	[18]	++	++
Medial Thalamic nuclei	[18]	NR	++
Rhomboid thalamic nucleus (Rh)	[18]	NR	+++
Reuniens thalamic nucleus (Re)	[18]	NR	+
Posteromedian Thalamic nucleus	[18]	NR	+
Parafascicular Thalamic nucleus (PF)	[21]	+++	NR
Medial geniculate (MG)	[18]	NR	+/++
Lateral Habenula (LHb)	[18]	+	NR
Hypothalamus & nearby regions			
Posterior hypothalamic nucleus	[17,19]	+	+
Dorsal hypothalamus	[18]	NR	++++

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