Conference: Food Intake Regulation: Neuropeptides, Circulating Factors and Genetics

Central Neuroanatomical Systems Involved in the Regulation of Food Intake in Birds and Mammals[1]

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ABSTRACT The neural regulation of food intake seems to be quite similar in birds and mammals. The ventromedial hypothalamic syndrome produced by lesions within the mediobasal hypothalamus of both birds and mammals is composed of several independent physiological and behavioral changes. Other neural sites known to be important in mammals for regulating food intake need to be examined in birds including the paraventricular nucleus, nucleus tractus solitarius and parabrachial nucleus. Members of the opioid and pancreatic polypeptide families are effective in stimulating food intake in avian species. Both prolactin and growth hormone are also efficacious in stimulating food intake. In contrast, cholecystokinin inhibits food intake when administered intracerebroventricularly. The autonomic and endocrine hypothesis developed to explain obesity in mammals appears to be quite applicable to genetic strains of commercial birds selected for meat production. Specifically the commercial broiler appears to display an imbalance of the autonomic nervous system. The parasympathetic nervous system dominates as a consequence of intense genetic selection for growth rate. J. Nutr. 124: 1355S–1370S, 1994.

INDEXING KEY WORDS:

- *hypothalamus* • *opioid peptides*
- *neuropeptide Y* • *cholecystokinin*
- *autonomic nervous system*

The majority of information known about the neural control of food intake in vertebrates has been obtained by experiments conducted with laboratory rats. Therefore for the purpose of this review, the recent literature completed in mammals was first summarized to highlight the main hypotheses that have been presented to explain the neural regulation of feeding. The neurotransmitters and neuromodulators found in the brain that alter food intake as well as major neural pathways thought to influence feeding behavior were then reviewed. The avian literature was reviewed to ascertain neural structures and neuromodulators shown to alter food intake. Finally a general hypothesis is presented based largely on mammalian data that may be of use for designing future experiments with avian species in an attempt to further the understanding of central nervous system regulation of feeding in birds.

HYPOTHESES PROPOSED TO EXPLAIN THE REGULATION OF FOOD INTAKE

Theories introduced to explain the neural regulation of food intake can be categorized into one of two groups based upon *1)* identification of the anatomical structures in the brain that can alter food intake when manipulated, and *2)* changes in a nutrient, metabolite or ion. **Table 1** is a summary of hypotheses based on the latter category. Emphasis in this review, however, will be on theories that identified a structure or structures within the central nervous system.

Dual center hypothesis. An early and long-lived hypothesis explaining the neural regulation of food intake, the dual center hypothesis, was introduced by Stellar (1954) shortly after the classic experiments of Anand and Brobeck (1951). Based on electrolytic lesions made within the diencephalon of the rat, the study showed that bilateral lesions of the ventromedial hypothalamic area resulted in hyperphagia and obesity (Hetherington and Ranson 1940) and bilateral lesions of the lateral hypothalamic area effected aphagia and body weight loss (Anand and

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TABLE 1

Traditional hypotheses of food intake regulation based on changes in a specific nutrient, metabolite, ion, neuromodulator or metabolic state

Hypothesis	Source
Glucostatic	Mayer 1953
Thermostatic	Brobeck 1948
Lipostatic	Kennedy 1953
Aminostatic	Rogers and Leung 1973
Ionostatic	Myers et al. 1972
Peptidergic	Morley 1980

Brobeck 1951). The ventromedial hypothalamus, termed a 'satiety' center, contained a set of neurons that projected to and inhibited a lateral hypothalamic area, the 'feeding' center.

Criticisms, however, arose concerning the model, particularly in addressing the exact anatomical locus mediating ventromedial hypothalamic obesity. For example, using hypothalamic knife cuts, the ventromedial hypothalamic nucleus could be spared, and rats were still obese (Gold 1973). Fiber tracts that needed to be severed to effect hyperphagia appeared to involve a longitudinal neural pathway, not a direct fiber projection between the ventromedial hypothalamic nucleus and lateral hypothalamic area (Gold 1973, Sclafani and Grossman 1969). More importantly, ventromedial hypothalamically lesioned rats still became obese when food restricted to prevent hyperphagia (Brooks and Lambert 1946, Han et al. 1965). Further research resulted in the location of additional neural sites that also had profound influence on the control of food intake (see Other Neuroanatomical Structures Important for Altering Food Intake). Finally, the 'center' concept or compartmentalized view was challenged as inappropriate for the manner in which the brain is organized, and an 'integrative or systems' approach was suggested (Morgane 1964).

Cephalic phase hypothesis. The cephalic phase hypothesis superseded the dual-center hypothesis, taking into account data accumulated on hypothalamically lesioned rats up through the mid-seventies (Powley 1977). The basis of the hypothesis was that an animal senses that it is about to eat, not unlike the Pavlovian response of an animal to the site of food. Given the above, the hypothesis states that a primary consequence of ventromedial hypothalamus lesions is an exaggeration of the cephalic reflexes of digestion (Powley 1977). In other words, the ventromedial hypothalamic syndrome is a series of augmented behavioral and physiological responses associated with food intake that result from mediobasal hypothalamic lesions.

The hypothesis thereby explained the magnified oropharyngeal contact of food exhibited by ventromedial hypothalamically lesioned rats (Teitelbaum 1955), finickiness (Mook and Blass 1968) and increased gastric acid secretion (Powley 1977, Ridley and Brooks 1965). It is of interest that the cephalic phase hypothesis was not intended to be restrictive; gastric and intestinal reflexes could be included for a general autonomic reflex model (Powley 1977). For example, taste information, the major exteroceptive stimulus for cephalic responses, was suggested not to be segregated from visceral inputs because both systems project anatomically to the same important brainstem nucleus, the nucleus tractus solitarius. It was also known that ventromedial hypothalamic obesity could be prevented if rats had undergone subdiaphragmatic vagotomy prior to hypothalamic lesions (Powley and Opsahl 1974).

Autonomic and endocrine hypotheses. A more global set of hypotheses was introduced shortly following the cephalic phase hypothesis. An autonomic hypothesis (Inoue and Bray 1979) and an autonomic and endocrine hypothesis (Bray and York 1979) suggested that the parasympathetic and sympathetic nervous systems need to be incorporated into a model dealing with food intake or obesity. These hypotheses proposed that reciprocal alterations occur in the parasympathetic and sympathetic nervous systems following ventromedial hypothalamus lesions so that activity of the former is increased and that of the latter is reduced. A key change following ventromedial hypothalamus lesions was hyperinsulemia (Assimacopoulos-Jeannet and Jeanrenaud 1976). If pancreatic β cells are first destroyed in rats by streptozotocin, and fetal pancreatic tissue is then transplanted beneath the renal capsule, the operated rats recover from diabetes. If the same rats are then given ventromedial hypothalamic lesions, the characteristic hyperphagia, obesity and hyperinsulemia are prevented, suggesting that beta cells need to be innervated in order to express the classical ventromedial hypothalamic syndrome (Inoue et al. 1978). Because interruption of the vagus nerve below the diaphragm prevented obesity following ventromedial hypothalamic lesions (Powley 1977), activity of the parasympathetic nervous system could be enhanced following ventromedial hypothalamic surgery accounting for the obesity.

Another testable thesis that stems from the original autonomic and endocrine theories was termed the Mona Lisa hypothesis (Bray 1991). The acronym stands for Most Obesities kNown Are Low In Sympathetic Activity. **Figure 1** is a modification of a schematic diagram from Bray (1991) showing a reduction in sympathetic activity following ventromedial hypothalamic lesions. The result is obesity.

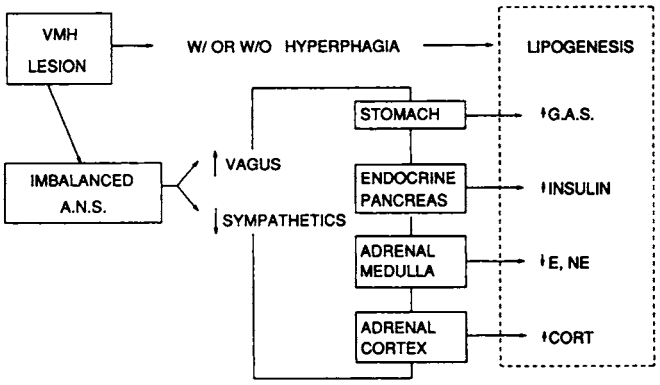

FIGURE 1 The autonomic and endocrine hypothesis. Lesions within the ventromedial hypothalamus (VMH) result in an imbalance of the autonomic nervous system (A.N.S.) with an increase and decrease in the activity of the vagus and sympathetics, respectively. Abbreviations used: CORT, corticosterone; E, epinephrine; G.A.S., gastric acid secretion; NE, norepinephrine (modified with permission from Bray 1991).

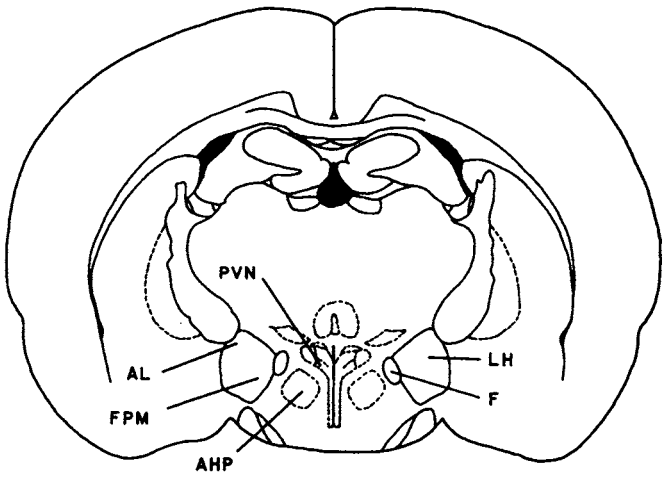

FIGURE 2 Cross-section of a rat brain taken at interaural plate 7.2 mm of Paxinos and Watson (1986) showing the location and approximate size of the paraventricular nucleus (PVN). Abbreviations used: AHP, anterior hypothalamic area, posterior; AL, ansa lenticularis; F, fornix; FPM, medial forebrain bundle; LH, lateral hypothalamic area.

OTHER NEUROANATOMICAL STRUCTURES IMPORTANT FOR ALTERING FOOD INTAKE

Paraventricular nucleus

Anatomical location and initial studies. The ventromedial hypothalamus and lateral hypothalamic area were not the only neural structures found to alter food intake when experimentally manipulated. One of the most important studied during the seventies and eighties was the paraventricular nucleus. The location of the paraventricular nucleus in the rat brain is shown in **Figure 2**. Because it is most sensitive for noradrenergic stimulation of food intake, the paraventricular nucleus is a critical neural structure (Leibowitz 1978a and 1978b). Bilateral lesions of the paraventricular nucleus also resulted in hyperphagia and obesity (Leibowitz et al. 1981). Neuroanatomical studies have shown that the nucleus comprises 8 to 10 sub-nuclei (Swanson and Kuypers 1980). More importantly, the paraventricular nucleus seems to have reciprocal connections with the median eminence and thereby a direct affect on the anterior pituitary. The magnocellular neurons of the paraventricular nucleus project directly to the posterior pituitary. The paraventricular nucleus also has a monosynaptic connection to the nucleus tractus solitarius and dorsal motor nucleus of the vagus, and, therefore, can directly affect the parasympathetic nervous system (Swanson and Sawchenko 1983). The paraventricular nucleus has also been shown to project to the periaqueductal gray, the intermediolateral column of the spinal cord and therefore the sympathetic nervous system (Luiten et al. 1987). This structure appears to be well situated and connected to affect food intake as well as serve other physiological and behavioral functions.

Regulatory vs. metabolic obesity. A classic study compared the metabolic and behavioral differences in rats that sustained bilateral lesions of the ventromedial hypothalamus vs. the paraventricular nucleus (Weingarten et al. 1985). Both groups showed hyperphagia and similar body weight gains. However, at the end of the first experiment, ventromedial hypothalamically lesioned rats were fatter. When food was freely available, ventromedial hypothalamically lesioned rats also exhibited hyperinsulemia. Further experiments showed that when food intake was restricted, the paraventricular nucleus lesioned group had the same percentage of carcass fat as controls, but the ventromedial hypothalamically lesioned group had a significantly higher percentage of fat. In addition, gastric acid secretion was elevated only in ventromedial hypothalamus lesioned rats. From these data, it was concluded that ventromedial hypothalamically lesioned rats showed metabolic obesity and paraventricular nucleus lesioned rats showed regulatory obesity (**Table 2**; Weingarten et al. 1985). In other words the primary disturbance of paraventricular nucleus lesioned rats is hyperphagia; ventromedial hypothalamically lesioned animals show metabolic changes such as hyperinsulemia, which lead secondarily to obesity with or without hyperphagia.

Ventromedial hypothalamic lesions: single versus multiple independent effects. A second fundamental interpretation made in the Weingarten et al. (1985) study was that both original food intake hypotheses

TABLE 2

Two distinct disorders occur when the ventromedial hypothalamus (VMH) or paraventricular nucleus (PVN) is bilaterally lesioned[1]

VMH lesions Metabolic obesity	PVN lesions Regulatory obesity
Great obesity	Obesity
Behavioral changes:	
Hyperphagia: sometimes	Hyperphagia: always
Affective behavior: irritable	Affective behavior: normal
When food intake is restricted:	
Obesity	Normal carcass fat
Hyperinsulemia	Normal plasma insulin
↑ Gastric acid secretion	Normal gastric acid secretion

[1]Weingarten et al. 1985.

(dual center and cephalic phase) proposed a single, primary etiological factor as responsible for the ventromedial hypothalamic syndrome, which then resulted in secondary effects. Specifically the first hypothesis championed hyperphagia as the primary etiological factor (Brobeck et al. 1943) and the second suggested an elevation of the cephalic phase of digestion (Powley 1977). An alternative interpretation is that the large lesions or knife cuts directed toward the ventromedial hypothalamus induced a series of multiple, independent disturbances, which, given the appropriate anatomical and behavioral analyses, could be dissociated from one another (**Fig. 3***A*; Weingarten et al. 1985). A similar interpretation was made with birds following ventromedial hypothalamic lesions which will be presented later (Fig. 3*B*).

Parabrachial nucleus

Anatomical location and initial studies. The parabrachial nucleus is another locus important in the control of food intake. It is located in a cross-section of brain tissue (**Fig. 4**) 0.28 mm anterior to the interaural zero reference point of the stereotaxic atlas of the rat brain (Paxinos and Watson 1986). Bilateral lesions of the dorsolateral parabrachial nucleus effected hyperphagia and obesity (Nagai et al. 1987). Of relevance is the finding that a major projection to the core of the ventromedial hypothalamus originates from the dorsolateral parabrachial region (Záborszky et al. 1984). More importantly, the ventromedial hypothalamus has been shown to have the highest cholecystokinin levels within the hypothalamus (Beinfeld and Palkovits 1981). When that projection was severed, cholecystokinin disappeared almost totally from the ventromedial hypothalamus (Záborszky et al. 1984). Removal of a peptide

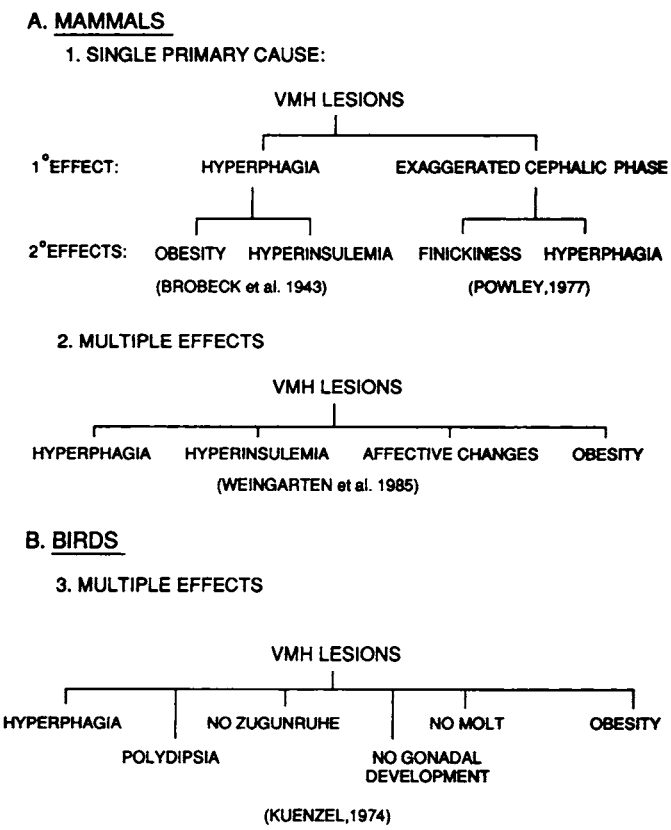

FIGURE 3 *A*) Approaches to analysis of ventromedial hypothalamic (VMH) lesions. Scheme developed by Weingarten et al. (1985) showing either one primary effect of VMH lesions in mammals or multiple independent effects. *B*) Birds and mammals appear to have multiple, independent effects from VMH lesions.

(cholecystokinin) known to inhibit food intake (**Table 3**; Gibbs and Smith 1992) could account for the hyperphagia shown by rats lesioned in the parabrachial nucleus. Hyperinsulemia was observed in bilaterally lesioned parabrachial nucleus rats after food deprivation for 2 h (Nagai et al. 1987). More data are needed to determine whether parabrachial nucleus rats will show elevated G.A.S., hyperinsulemia, and obesity when food intake is restricted to control levels in order to assess whether parabrachial nucleus rats show a regulatory or metabolic-type of obesity.

COMPOUNDS ADMINISTERED CENTRALLY—MAMMALS

Many compounds have been identified in neural tissue since the 1950s. Biochemical assays and histochemical procedures were developed and pharmacological agents synthesized to characterize better the neuroanatomical systems regulating food intake.

TABLE 3

Compounds given centrally to mammals that altered food intake

Compound	Site[1]	Food intake	Reference
Biogenic amines			
Norepinephrine	PFH	Decreased	Grossman 1962
	PVN	Increased	Leibowitz 1978a, 1978b, Goldman et al. 1985
Epinephrine	PFH	Decreased	Leibowitz & Rossakis 1979a
Dopamine	PFH	Decreased	Leibowitz & Rossakis 1979a, 1979b
Serotonin	Intra-Hypo	Decreased	Blundell 1984
(Fenfluramine)	PVN	Decreased	Leibowitz & Shor-Posner 1986
Peptides that stimulate food intake			
Opioid peptide family			
β-Endorphin	VMH	Increased	Grandison & Guidotti 1977
	ICV	Increased	McKay et al. 1981
	PVN	Increased	Leibowitz & Hor 1982
Leu-enkephalin	Intra-Hypo	Increased	Tepperman & Hirst 1983
Met-enkephalin	PVN	Increased	McLean & Hoebel 1983, Stanley et al. 1988
	DMN, LHy, Septum, Amyg	Increased	Stanley et al. 1988
Dynorphin	ICV	Increased	Morley & Levine, 1981, 1983
Pancreatic polypeptide family			
Neuropeptide Y	ICV	Increased	Clark et al. 1984, Levine & Morley 1984
	PVN	Increased	Stanley & Leibowitz 1984, Stanley et al. 1985a
	VMH, LHy	Increased	Stanley et al. 1985a
	PFH	Increased	Stanley et al. 1993
Peptide YY	PVN	Increased	Stanley et al. 1985b
Human pancreatic polypeptide	ICV	Increased	Clark et al. 1984
Other peptides			
Galanin	PVN	Increased	Kyrkouli et al. 1986, 1990
	PHN, 3rd ventricle,, Amyg, DMN[2]	Increased	Kyrkouli et al. 1990
Growth hormone releasing factor	ICV	Increased	Vaccarino et al. 1985
	MPOA	Increased	Dickson & Vaccarino 1990, Vaccarino & Hayward 1988
	PVN	No change	
	VMH	Increased	Tanaka et al. 1991
	MPOA, LHy, PVN	No change	Tanaka et al. 1991
Peptides that suppress food intake			
Cholecystokinin[3]	ICV	Decreased	Maddison 1977, Nemeroff et al. 1978, Levine & Morley 1981, Telegdy et al. 1984, Willis et al. 1984a, 1984b
	PVN	Decreased	McCaleb & Myers 1980
Bombesin	ICV (4th ventricle)	Decreased	Ladenheim & Ritter 1988b, Flynn 1989
	nTS	Decreased	deBeaurepaire & Suaudeau 1988, Johnston & Merali 1988
	PVN	Decreased	Willis et al. 1984b
	LHy	Decreased	Stuckey & Gibbs 1982
Glucagon-secretin family			
Vasoactive intestinal polypeptide	ICV	Decreased	Woods et al. 1981
Glucagon	ICV	Decreased	Inokuchi et al. 1984
Sauvagine	ICV	Decreased	Britton et al. 1984, Gosnell et al. 1983
Corticotropin releasing hormone	ICV	Decreased	Morley & Levine 1982, Britton et al. 1984, Arase et al. 1988
	PVN	Decreased	Krahn et al. 1984
	VMH, LHy, Str, GP	No change	Krahn et al. 1984
Thyrotropin releasing hormone	ICV	Decreased	Vijayan & McCann 1977, Lin et al. 1983
	VMH, LHy	Decreased	Suzuki et al. 1982
Cyclo-His-Pro[4]	ICV	Decreased	Morley et al. 1981
Amino acids			
γ-Aminobutyric acid	VMH	Increased	Kelly et al. 1977
	ICV	Decreased	Olgiati et al. 1980
Muscimol	PVN, ICV, Raphe	Increased	Kelly & Grossman 1979, Olgiati et al. 1980, Klitenick & Wirtshafter 1988

(continued)

TABLE 3 *continued*

Compounds given centrally to mammals that altered food intake

Compound	Site[1]	Food intake	Reference
Glutamate	LHy	Increased	Stanley et al. 1993
Hormones			
Insulin	VMH	Decreased	Hatfield et al. 1974
	ICV	Decreased	Woods et al. 1979, Brief & Davis 1984, Plata-Salaman & Oomura 1986
	VMN, PVN, DMN, arcuate nucleus	Decreased	McGowan et al. 1992

[1]Abbreviations used in this column: Amyg, amygdala; DMN, dorsomedial hypothalamus nucleus; GP, globus pallidus; ICV, intracerebroventricular; Intra-Hypo, intra-hypothalamic; LHy, lateral hypothalamic area; MPOA, medial preoptic area; nTS, nucleus tractus solitarius; PFH, perifornical hypothalamus; PVN, paraventricular nucleus; Str, striatum; VMH, ventromedial hypothalamus area.

[2]Higher doses of galanin were required to obtain a significant increase in food intake.

[3]An intact area postrema, nucleus tractus solitarius and vagus required for cholecystokinin suppression of food intake (Edwards et al. 1986, Smith et al. 1985, South and Ritter 1988).

[4]Cyclo-His-Pro = cyclo-histidyl-proline-diketopiperazine.

The following is a brief summary of the major neurochemical compounds that have been microinjected either within the cerebroventricular system or within specific neuroanatomical structures of the mammalian brain.

Biogenic amines. The first biogenic amine shown to have an affect upon food intake was norepinephrine. When it was injected within the lateral perifornical hypothalamus, it decreased food intake (Grossman 1962). Dopamine and epinephrine likewise depressed feeding when injected into the same neural area (Leibowitz and Rossakis 1979a and 1979b). It was determined that the catecholamine and amphetamine suppression of food intake involved β-adrenergic receptors (Leibowitz 1976). In contrast, food intake was significantly increased upon norepinephrine administration directly into the paraventricular nucleus (Leibowitz 1978a). α2-Noradrenergic receptors were shown to be involved in the response (Goldman et al. 1985). Serotonin consistently decreased food intake in mammals (Blundell 1984, Leibowitz and Shor-Posner 1986). The principle site of action of serotonin appears to be the paraventricular nucleus. Serotonin has been shown to antagonize norepinephrine-stimulated feeding, reduce the size and duration of meals, decrease the rate of feeding, but not influence latency to meal onset or frequency of meals (Leibowitz and Shor-Posner 1986; see Table 3 for summary).

Neuropeptides that stimulate food intake. A number of peptides have been shown to stimulate food intake, particularly those within the opioid and pancreatic polypeptide families. β-endorphin injected into the ventromedial hypothalamic region (Grandison and Guidotti 1977), lateral ventricle (McKay et al. 1981) or paraventricular nucleus (Leibowitz and Hor 1982) increased feeding in rats. Long-acting analogues of leucine and methionine enkephalin, [D-alanine^2-D-leucine^5]-enkephalin (Tepperman and Hirst 1983) and [D-alanine^2-methionine]-enkephalin (McLean and Hoebel 1983, Morley et al. 1982), respectively enhance food intake. Dynorphin increases food intake in rats during the light phase of the diurnal cycle (Morley and Levine 1981) and dynorphin (1-17) appears to be more effective than dynorphin (1-13; Morley and Levine 1983). Microinjections of opiates into specific neural structures has shown that the

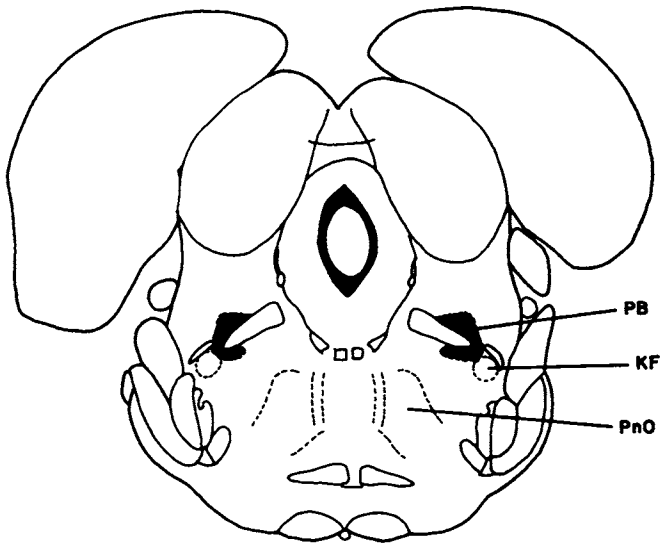

FIGURE 4 Cross-section of a rat brain taken at interaural plate 0.28 mm of Paxinos and Watson (1986) showing the location and approximate size of the parabrachial nucleus (PB). Abbreviations used: KF, Kölliker-Fuse nucleus; PnO, oral pontine reticular nucleus.

most sensitive brain loci for D-alanine^2-methionine^5-enkephalinamide induced feeding are: paraventricular nucleus, dorsomedial hypothalamic nucleus, lateral hypothalamic area, septum and amygdala (Stanley et al. 1988; Table 3).

Members of the pancreatic polypeptide family are also effective in stimulating food intake. Neuropeptide Y, peptide YY and pancreatic polypeptide are included in the family. Administration of neuropeptide Y into the cerebral ventricles (Clark et al. 1984, Levine and Morley 1984) or directly into the paraventricular nucleus (Stanley and Leibowitz 1984) effected marked hyperphagia. Chronic administration of neuropeptide Y into the paraventricular nucleus resulted in obesity (Stanley et al. 1986). The first detailed study mapping the active sites for neuropeptide Y showed that the paraventricular nucleus, ventromedial hypothalamus and lateral hypothalamic area were all equally potent for effecting hyperphagia when a volume of 300 nL (8 or 78 pmol neuropeptide Y) were injected into each site (Stanley et al. 1985). When a new injector technique was developed where only 10 nL (78 pmol neuropeptide Y) was deposited, the most sensitive site for stimulating food intake was the perifornical hypothalamus (Stanley et al. 1993). Peptide YY (Stanley et al. 1985b) and human pancreatic polypeptide (Clark et al. 1984) were found to stimulate food intake when they were injected within the paraventricular nucleus or intracerebroventricularly, respectively. No detailed studies of the most sensitive brain sites for peptide YY or human pancreatic polypeptide have been mapped because it is believed that neuropeptide Y is the only current member of the pancreatic polypeptide family that is endogenous to rat and human brains (Adrian et al. 1983, Allen et al. 1983).

Galanin, a 29 amino acid peptide isolated from porcine intestines (Tatemoto et al. 1983) is another neuropeptide that stimulates food intake when microinjected into the paraventricular nucleus (Kyrkouli et al. 1986). Further studies have shown that in addition to the paraventricular nucleus, the periventricular area, third ventricle and amygdala were other sites where galanin significantly increased food intake. The dorsomedial hypothalamic nucleus was another effective site but required a higher dose (Kyrkouli et al. 1990). Additional experiments have shown that galanin preferentially increases the ingestion of a fat diet, rather than carbohydrate or protein (Tempel and Leibowitz 1990, Tempel et al. 1988). When M40, a potent antagonist of galanin receptors was microinjected into the paraventricular nucleus, it was effective in reducing spontaneous ingestion of a fat diet (Leibowitz and Kim 1992). Mercaptoacetate, a drug that blocks fatty acid utilization, stimulates food intake. Mercaptoacetate-induced lipoprivic feeding is mediated by vagal sensory neurons which were shown to increase gene expression of galanin after injection of mercaptoacetate (Calingasan et al. 1992). A major ascending relay site from the area postrema-nucleus tractus solitarius region is to the dorsal lateral parabrachial nucleus. Electrolytic or ibotenate lesions of dorsal lateral parabrachial nucleus or central parabrachial nucleus abolished lipoprivic feeding (Koegler et al. 1992).

Growth hormone releasing factor from human pancreatic tumours or rat hypothalamus was shown to stimulate food intake in hungry rats with intracerebroventricular administration (Vaccarino et al. 1985). Further work has shown that the sensitive site for growth hormone releasing factor is within the medial preoptic area, not the paraventricular nucleus (Dickson and Vaccarino 1990, Vaccarino and Hayward 1988). In contrast, Tanaka et al. (1991) have shown that the brain locus for stimulating feeding is the ventromedial hypothalamus while no significant effect was obtained by microinjecting growth hormone releasing factor into the medial preoptic area, lateral hypothalamic area or paraventricular nucleus.

Neuropeptides that suppress food intake. The best characterized peptides that inhibit feeding in animals are cholecystokinin (cholecystokinin-8) and bombesin. Both are highly concentrated in the gastrointestinal tract of many species, and both suppress feeding when administered either centrally or peripherally. Intracerebroventricular administration of cholecystokinin has been shown to be highly effective for decreasing food intake (Levine and Morley 1981, Maddison 1977, Nemeroff et al. 1978, Telegdy et al. 1984, Willis et al. 1984a). Other work has shown that microinjections of cholecystokinin into the paraventricular nucleus suppress the noradrenergic feeding system (McCaleb and Myers 1980). Peripheral or central administration of the sulfated form of the synthetic, C-terminal, cholecystokinin-8 produced satiety, whereas the desulfated form did not (Gibbs et al. 1973, Zhang et al. 1986). The work suggested that exogenous cholecystokinin acts at the type-A cholecystokinin receptor (predominates in the periphery), rather than at the type-B receptor (most prominent in the brain). The initial peripheral site of action appears to be afferent (Smith et al. 1985), capsaicin-sensitive (South and Ritter 1988) neurons of the abdominal vagus. Vagal neurons are thought necessary for satiety caused by action of peripherally injected cholecystokinin. Ablation of the area postrema and caudal and medial nucleus tractus solitarius (site of the first, central synaptic relay of gastrointestinal vagal afferent neurons) abolished the effect of low but not high doses of cholecystokinin (Edwards et al. 1986). In contrast to the proposed mechanism of cholecystokinin's action, satiety effected by bombesin is not compromised by complete subdiaphragmatic vagotomy (Gibbs and Smith 1988). Both high thoracic spinal-visceral neural disconnection and complete vagotomy were required to

abolish the action of bombesin (Stuckey et al. 1985, Ladenheim and Ritter 1988a). Similar to cholecystokinin, fourth ventricular injection of bombesin suppressed ingestive behaviors in rats (Ladenheim and Ritter 1988b, Flynn 1989). In addition, lesions of the area postrema and nucleus tractus solitarius attenuated the inhibitory effect of peripherally administered bombesin on food intake (Ladenheim and Ritter 1989) thereby providing additional evidence for the importance of the dorsal hindbrain for housing afferents that effect satiety evoked by both peptides. Microinjection of bombesin into the nucleus tractus solitarius (deBeaurepaire and Suaudeau 1988, Johnston and Merali 1988), paraventricular nucleus (Willis et al. 1984b) and lateral hypothalamic area (Stuckey and Gibbs 1982) effected satiety.

Another group of peptides, included in the glucagon-secretin family, largely suppress food intake. Members of the family are glucagon, secretin, vasoactive intestinal polypeptide, PHI (peptide with NH_2-terminal histidine and COOH-terminal isoleucine amide), corticotropin releasing hormone, savagine, and growth hormone-releasing factor. Only the latter has been shown to increase food intake following central administration (Table 3). Intracerebroventricular injection of vasoactive intestinal polypeptide (Woods et al. 1981), glucagon (Inokuchi et al. 1984) and savagine (Britton et al. 1984, Gosnell et al. 1983) significantly reduce food intake in rats (Table 3). Considerably more feeding studies have been conducted with corticotropin releasing hormone. Although corticotropin releasing hormone is best known as the primary hypothalamic peptide for the release of pituitary adrenocorticotropic hormone (Spiess et al. 1981) and thereby is necessary for mediating stress responses in animals, other studies have suggested that it plays a role in food consumption (Morley et al. 1983). With intracerebroventricular administration, corticotropin releasing hormone reduces food intake (Arase et al. 1988, Britton et al. 1984, Morley and Levine 1982) and retains its hypophagic effects in hypophysectomized animals (Morley and Levine 1982). It is also effective in reducing food intake in obese rats (Arase et al. 1989a, 1989b). Microinjection studies have shown that corticotropin releasing hormone decreases feeding when administered to the paraventricular nucleus, but not the ventromedial hypothalamus, striatum, lateral hypothalamic area or globus pallidus (Krahn et al. 1984). When mapping studies were completed regarding the effect of corticotropin releasing hormone on stimulating sympathetic firing rate, the medial preoptic area was most effective. In contrast, no change in sympathetic firing rate was observed when corticotropin releasing hormone was injected into the anterior hypothalamic nucleus, paraventricular nucleus, ventromedial hypothalamus, dorsomedial hypothalamic nucleus, or lateral hypothalamic area (Egawa et al. 1990). Further work is needed to determine the effective brain loci that effect a decrease in food intake from microadministration of corticotropin releasing hormone.

The last peptide group covered in this review is thyrotropin releasing hormone and its related compound cyclo-histidyl-proline-diketopiperazine [cyclo-(His-Pro)]. Vijayan and McCann (1977) first showed that intracerebroventricular injection of thyrotropin releasing hormone decreased food intake. Other studies confirmed that work but significantly higher levels of thyrotropin releasing hormone were required (Lin et al. 1983); thyrotropin releasing hormone also reduced food intake in hypophysectomized animals (Morley and Levine 1980). Specific neural sites where thyrotropin releasing hormone administration reduced food intake were the ventromedial hypothalamus and lateral hypothalamic area (Suzuki et al. 1982). The first published work of the anorectic effect of cyclo-histidyl-proline-diketopiperazine was that of Morley et al. (1981). Of interest is that this compound is elevated in the hypothalamus of unfed but not fully-fed rats (Mori et al. 1983) and may play a role in macronutrient selection (Prasad et al. 1992).

Amino acids that affect food intake. Two amino acids have been shown to have significant effects on food intake, γ-aminobutyric acid (GABA) and glutamate. Bicuculline methiodide, a putative GABA antagonist, increased ingestion of sweet milk, when administered into the lateral hypothalamic area and suppressed feeding when injected into the ventromedial hypothalamus. Conversely, GABA injections into the ventromedial hypothalamus increased intake (Kelly et al. 1977). The GABA agonist muscimol effected an increase in food intake when injected into the paraventricular nucleus while bicuculline methiodide suppressed feeding (Kelly and Grossman 1979). Intracerebroventricular injections of GABA or ethanolamine-O-sulphate (GABA-transaminase inhibitor) gave different results from intracerebroventricular administration of muscimol (GABA receptor-agonist). The former decreased while the latter increased food intake (Olgiati et al. 1980). Additional studies have shown that muscimol injected into the midbrain raphe nucleus or ventral tegmental area increases food intake (Klitenick and Wirtshafter 1988). Intra-raphe injections of two excitatory amino acid antagonists, kynurenic acid and 2-amino-5-phosphonovaleric acid resulted in dose-dependent increases in food and water intake (Wirtshafter and Trifunovic 1988).

Recent work has shown that an excitatory amino acid, glutamate can stimulate food intake in rats. The primary site mediating glutamate-induced eating is the lateral hypothalamic area (Stanley et al. 1993).

Hormones given centrally (insulin). Hatfield et al. (1974) were the first to show that high doses of insulin into the ventromedial hypothalamus decreased

feeding in normal and diabetic rats. Large doses of intracerebroventricular administered insulin also reduced food intake (Brief and Davis 1984, Plata-Salaman and Oomura 1986, Woods et al. 1979). Bilateral injection of insulin antibodies into the ventromedial hypothalamus increased food intake (Strubbe and Mein 1977). McGowan et al. (1992) reported that the most sensitive sites within the ventromedial hypothalamic area that decreased food intake from small insulin injections included portions of the ventromedial hypothalamic nucleus, paraventricular nucleus, dorsomedial hypothalamic nucleus and arcuate nucleus. They also confirmed that injection of antibodies to insulin within the ventromedial hypothalamus increased food intake and body weight.

NEURAL REGULATION OF FOOD INTAKE IN BIRDS

To date, the hypotheses that have been proposed to explain the neural regulation of food intake in vertebrates have been derived from those developed for mammals. Because the majority of neural sites involved in the control of food intake in mammals are located in lower brain levels (medulla oblongata, pons and diencephalon) and the process of feeding is such a basic requirement for survival of all animals, it makes sense that the regulation of appetite in birds and mammals should share fundamental mechanisms. The main idea of this section will be that the autonomic and endocrine hypothesis proposed for regulating feeding in mammals (Bray and York 1979, Inoue and Bray 1979) is quite relevant to explain the neural control of food intake and body weight changes not only in domestic avian species but wild ones as well.

To this end neuroanatomical structures identified that alter food intake, compounds administered centrally and neural pathways associated with the autonomic nervous system in avian species will be reviewed.

AVIAN NEUROANATOMICAL STRUCTURES IMPORTANT FOR ALTERING FOOD INTAKE

Electrolytic lesions of the ventromedial hypothalamus of Leghorn chickens (Lepkovsky and Yasuda 1966, Snapir et al. 1973, Sonoda 1983) and of the ventromedial hypothalamic nucleus including the inferior hypothalamic nucleus of White-throated Sparrows (Kuenzel and Helms 1967) effected hyperphagia and obesity. Further studies showed that several functions characteristic of the annual cycles of migratory birds were disrupted by the ventromedial hypothalamic lesions including water intake, gonadal development, Zugunruhe (migratory behavior (nocturnal activity) shown by birds in cages), and molt (Kuenzel 1974, Kuenzel and Helms 1970). The most common occurrence from ventromedial hypothalamic lesions was hyperphagia, obesity, polydipsia, no gonadal development, no Zugunruhe and no molt, however a number of combinations of different effects were obtained. The overall conclusion of the study was that in birds the ventromedial hypothalamic syndrome involves the disruption of a number of physiological and behavioral events, the neural control mechanisms for each being anatomically separable (Kuenzel 1974). It is of interest that Weingarten et al. (1985) suggested that ventromedial hypothalamic lesions in rats induce a set of independent disturbances as well (Fig. 3).

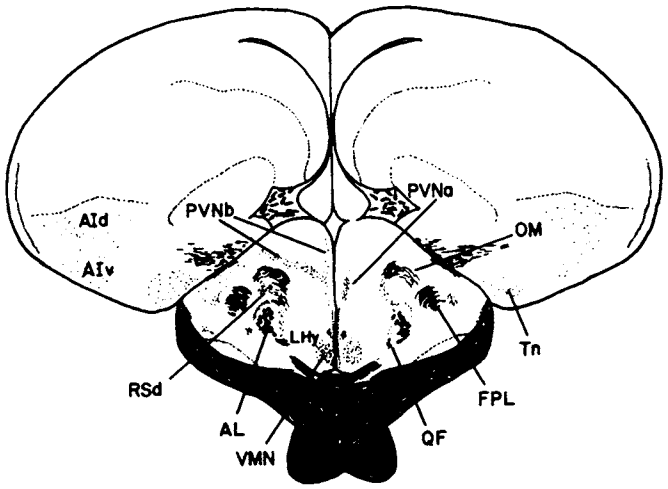

FIGURE 5 Cross-section of a chick brain taken from atlas plate A 7.4 mm of Kuenzel and Masson (1988) showing the location and approximate size of the paraventricular nucleus (PVN). The PVNa shows its size when stained with classical nissl stains. The PVNb is much larger and sweeps out toward the lateral portion of the thalamus when sections are immunostained with an antibody to arginine vasotocin. Abbreviations used: AId, v, the dorsal and ventral divisions of the archistriatum; AL, ansa lenticularis; FPL, lateral forebrain bundle; LHy, lateral hypothalamic area; OM, occipitomesencephalic tract; QF, quintofrontal tract; RSd, dorsal, superior reticular nucleus; Tn, nucleus taeniae; VMN, ventromedial hypothalamic nucleus.

No published studies were found where the paraventricular nucleus or parabrachial nucleus was lesioned in any avian species. The paraventricular nucleus is a large, hypothalamic nucleus in chicks and, similar to that in rats, can be divided into at least 10 sub-nuclei (unpublished data). When brain slices are immunostained with an antibody to arginine vasotocin (equivalent to vasopressin in mammals), the paraventricular nucleus extends from the traditional midline nucleus to the lateral borders of the thalamus (**Fig. 5**). By its size alone as well as its

important connections to the nucleus tractus solitarius and dorsal motor nucleus of the vagus (Arends et al. 1988, Berk and Finkelstein 1983), parabrachial nucleus (Wild et al. 1990) and median eminence (Kiss 1988, Korf 1984) warrants study of its effect on food intake. No studies have been completed where ventromedial hypothalamic lesions have been compared to paraventricular nucleus lesions in birds to determine whether there is a metabolic vs. a regulatory obesity. Sonoda (1983) has demonstrated that insulin levels are higher than controls in ventromedial hypothalamically lesioned chickens. Nineteen days following surgery, when food was withheld from ventromedial hypothalamically lesioned birds and controls, ventromedial hypothalamically lesioned birds had significantly elevated plasma insulin suggesting that they, like mammals, may show metabolic obesity.

Lateral hypothalamic lesions have been performed in chickens (Feldman et al. 1957), White-throated Sparrows (Kuenzel 1972), pigeons (Ziegler 1976, Ziegler and Karten 1973, Zeigler et al. 1969) and broiler chicks (Kuenzel 1982). Results were consistent in that lesions in and around the lateral hypothalamic area effected reduced food intake. A marked difference between birds and mammals, however, was that the aphagic response was not permanent. Large, bilateral lesions involving the ansa lenticularis, quintofrontal tract and lateral hypothalamic area were most effective for reducing food intake but it usually returned to preoperative levels within 1 wk (Kuenzel 1982). Similar results were obtained when stimulus-bound feeding was attempted in fowl. More than 625 sites were implanted with electrodes for electrical brain stimulation in conscious animals. No positive brain loci were identified for stimulus-bound food intake (Tweeton et al. 1973). With respect to the function of the lateral hypothalamic area, either birds are different from mammals, or the equivalent neural area has not been identified to date in avian species.

COMPOUNDS ADMINISTERED CENTRALLY IN BIRDS

The first compounds given centrally to birds were biogenic amines. In broiler-type chickens (selected for growth rate and meat production), intracerebroventricularly injected epinephrine significantly increased food intake (Denbow et al. 1981). In contrast, no significant change was noted when Leghorn chicks (strain selected for table egg production) were given epinephrine (Denbow et al. 1983). Intracerebroventricularly injected norepinephrine had an overriding narcoleptic effect on birds that masked other behaviors. When it was injected into specific brain loci at lower doses, clearer effects on food intake were obtained. Specifically, norepinephrine microinjected into the medial preoptic area, anterior medial hypothalamic nucleus, paraventricular nucleus or medial septal nucleus of broiler chicks increased food intake (Denbow and Sheppard 1993). Norepinephrine administered near the lateral septal organ [a circumventricular organ in birds (Kuenzel and Blähser 1994, Kuenzel and vanTienhoven 1982)], within the dorsal, superior reticular nucleus or lateral forebrain bundle resulted in significant reductions in feeding (Denbow and Sheppard 1993). When 6-hydroxydopamin was given intracerebroventricularly to broiler chicks, food intake was greatly reduced as was striatal, hypothalamic and brainstem norepinephrine and striatal dopamine (Kuenzel et al. 1987b). Intracerebroventricular serotonin also significantly reduced food intake in fully fed broilers, but was ineffective for causing satiety in broilers unfed for 24 h (Denbow et al. 1982; **Table 4**).

A diverse group of peptides, amino acids, and hormones has been shown to stimulate food intake. Within the opioid peptide family, β-endorphin (ostrich) was first shown in pigeons to stimulate food intake with intracerebroventricular injection (Deviche and Schepers 1984). β-Endorphin (human) likewise stimulates food intake in both broiler-type and egg-layer type chicks (McCormack and Denbow, 1988). Methionine-enkephalin stimulates food intake in broiler-type chicks (McCormack and Denbow 1989). Within the pancreatic polypeptide family, three have been shown to significantly increase food intake. Neuropeptide Y and peptide YY given intracerebroventricularly to broiler chicks had a robust effect on food intake (Kuenzel et al. 1987a). Following neuropeptide Y injections, significant increases in plasma insulin were obtained with no changes in glucagon or plasma glucose (Kuenzel and McMurtry 1988). Avian pancreatic polypeptide injected into Leghorn hens also was effective for increasing food intake (Denbow et al. 1988). As can be seen in Table 4, the only peptide applied centrally to date in birds that decreases food intake is cholecystokinin. Intracerebroventricular injection of cholecystokinin-8 reduced food intake in broilers (Denbow and Myers 1982). It would be of interest to determine whether any of the other peptides that have been effective in reducing food intake in mammals (Table 3), particularly bombesin and members of the glucagon-secretin family, likewise reduce food intake. The author only uncovered one study addressing central administration of an amino acid. Intracerebroventricular injection of muscimol, a GABA agonist, increased food intake in turkey hens (Denbow 1991).

The author was unable to find published information on central injections of insulin in birds. The lack of supporting evidence for a glucostatic control of food intake in birds could be one reason for the paucity of information. As summarized previously, there is no evidence of increased food intake in birds

TABLE 4

Compounds administered centrally that alter food intake in birds[1]

Compound	Species	Dose	Site	Food intake	Reference
		μg			
Biogenic amines					
Epinephrine	Broiler, Leghorn	33–100	ICV	Increased/no change	Denbow et al. 1981, 1983
Norepinephrine	Broiler	1.25–2.5	POA, AM, PVN, SM	Increased	Denbow and Sheppard 1993
			LSO, LFB, RSd	Decreased	
Epinephrine-norepinephrine	Turkeys	33–67	ICV	Decreased	Denbow 1983
Serotonin	Fully fed broilers	67–100	ICV	Decreased	Denbow et al. 1981
6-OH Dopamine[2]	Broilers	136–204	ICV	Decreased	Kuenzel et al. 1987b
Peptides					
Opioid peptide family					
β-Endorphin (ostrich)	Pigeon	0.2–5.2	ICV	Increased	Deviche and Schepers 1984
β-Endorphin (human)	Rock Cornish and Leghorn chicks	1.5–6.0	ICV	Increased	McCormack and Denbow 1988
Met-enkephalin	Rock Cornish chicks	1.0–8.0	ICV	Increased	McCormack and Denbow 1989
Pancreatic polypeptide family					
Neuropeptide Y	Broilers	5.0–9.0	ICV	Increased	Kuenzel and McMurtry 1988, Kuenzel et al. 1987a
Peptide YY	Broilers	1.0–5.0	ICV	Increased	Kuenzel et al. 1987a
Avian pancreatic polypeptide	SCWL hens	0.25	ICV	Increased	Denbow et al. 1988
Cholecystokinin-8	Broilers	0.1–0.15	ICV	Decreased	Denbow & Myers 1982
Amino acids					
Muscimol (γ-aminobutyric acid agonist)	Turkey hen	14.6	ICV	Increased	Denbow 1991
Hormones					
Prolactin (turkey)	Turkey hen[3]	1.6	ICV	Decreased	Denbow 1986
Prolactin (turkey)	Turkey hen[4]	0.8–3.2	ICV	No change	Denbow 1986
Prolactin (ovine)	Ring dove	1.0	ICV	Increased	Buntin 1989
Prolactin (turkey)	Ring dove	1.0	ICV	No change	Buntin and Figge 1988
Growth hormone (human)	Ring dove	1.0	ICV	Increased	Buntin and Figge 1988
Growth hormone (turkey)	Ring dove	1.0	ICV	Increased	Buntin and Figge 1988
Growth hormone (ovine)	Ring dove	1.0	ICV	Increased	Buntin and Figge 1988

[1]Abbreviations used: AM, Anterior hypothalamic nucleus; ICV, Intracerebroventricular; LFB, Lateral forebrain bundle; LSO, Lateral septal organ; POA, Preoptic area; PVN, Paraventricular nucleus; RSd, Nucleus reticularis superior, dorsal portion; SCWL, Single Comb White Leghorn; SM, Medial septal nucleus.

[2]6-OH Dopamine resulted in a decrease in striatal dopamine and norepinephrine, hypothalamic norepinephrine and brainstem norepinephrine.

[3]Photostimulated.

[4]Non-photostimulated, light:dark cycle (8 h:16 h).

following goldthioglucose or 2-deoxyglucose administration, and birds are resistant to drugs that cause diabetes, e.g., alloxan (Simon 1989). Of particular interest, however, is the increase in food intake shown in ring doves following intracerebroventricular administration of prolactin (Buntin 1989) and growth hormone (Buntin and Figge 1988). In a mapping study addressing the most sensitive brain sites for eliciting an orexigenic effect of prolactin, the ventromedial hypothalamus and medial preoptic area were found to be the most sensitive sites (Hnasko and Buntin 1993). Interestingly, the former site has also been shown to have a high density of prolactin binding sites in ring dove brains (Fechner and Buntin 1989). Because mammals have been shown to increase food intake following administration of growth hormone releasing factor into the ventromedial hypothalamus or medial preoptic area (Table 3), and vasoactive intestinal polypeptide has been shown to be a potent releaser of prolactin in birds (Opel and Proudman 1988, Sharp et al. 1989), both vasoactive intestinal polypeptide and growth hormone releasing factor would be worth investigating in birds as being two other peptides that could stimulate food intake particularly following

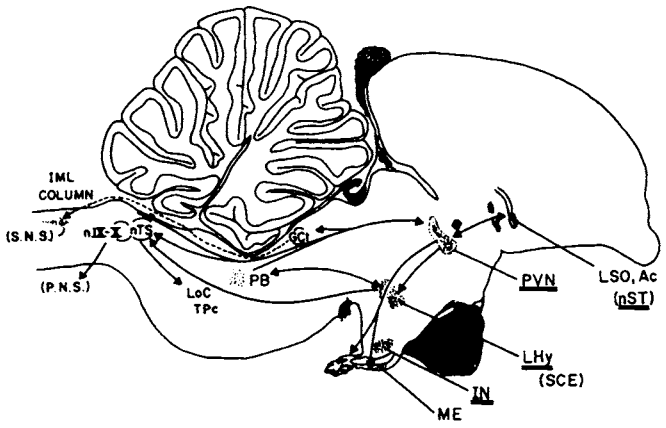

FIGURE 6 A sagittal-section of a chick brain taken from atlas plate L 0.2 mm of Kuenzel and Masson (1988) showing projections that have been documented in the avian brain that can affect the sympathetic (S.N.S.) and parasympathetic (P.N.S.) nervous systems. Abbreviations used: Ac, nucleus accumbens; GCt, central grey; IML, intermediolateral; IN, infundibular nucleus; LHy, lateral hypothalamic area; LoC, locus ceruleus; LSO, lateral septal organ; ME, median eminence; n IX-X, glossopharyngeal and dorsal motor nucleus of vagus; nST, bed nucleus stria terminalis; nTS, nucleus tractus solitarius; PB, parabrachial nucleus; PVN, paraventricular nucleus; SCE, stratum celluare externum; TPc, substantia nigra.

administration to the ventromedial hypothalamus or medial preoptic area.

NEUROANATOMICAL PATHWAYS OF IMPORTANCE IN BIRDS WITH RESPECT TO THE AUTONOMIC AND ENDOCRINE HYPOTHESIS

The most critical neuroanatomical sites in mammals for regulating food intake include the ventromedial hypothalamic area (ventromedial hypothalamic nucleus, dorsomedial hypothalamic nucleus and infundibular nucleus), lateral hypothalamic area, paraventricular nucleus, perifornical hypothalamus, nucleus tractus solitarius, and parabrachial nucleus. If the equivalent avian structures are then grouped according to known projections within the avian brain, the schematic diagram in **Figure 6** is obtained. Note that the lateral hypothalamic area projects to the nucleus tractus solitarius (Berk 1987) and the nucleus tractus solitarius projects to the dorsal motor nucleus of the vagus (noted as n.IX-X in Fig. 6; Arends et al. 1988). This structure contains the preganglionic neurons that are a major component of the parasympathetic nervous system. The mammal has a similar projection and the components have been shown to be part of the parasympathetic nervous system (Luiten et al. 1987). In contrast, the ventromedial hypothalamus projects mainly to the central grey (line not shown on Fig. 6; Berk and Butler 1981). In mammals the central grey projects to the intermediolateral column that houses preganglionic neurons serving as major components of the sympathetic nervous system. The dashed line in the diagram indicates that more neuroanatomical studies are needed to verify the projection in birds. Hence the ventromedial hypothalamic area, composed of the ventromedial hypothalamic nucleus and infundibular nucleus is part of the sympathetic nervous system (Luiten et al. 1987). The original ventromedial hypothalamus lesion studies of Hetherington and Ranson (1940) and the lateral hypothalamic area studies of Anand and Brobeck (1951) make sense from the perspective that the former attenuated sympathetic influence while the latter decreased parasympathetic tone. Therefore ventromedial hypothalamic lesions predictably resulted in obesity and lateral hypothalamic area lesions effected a loss of body weight. The paraventricular nucleus is interesting in that, in mammals (Luiten et al. 1987) and birds, it has both parasympathetic and sympathetic connections. The sympathetic component must be the dominant one in mammals as paraventricular nucleus lesions result in hyperphagia and obesity (Leibowitz et al. 1981). It would be of interest to bilaterally lesion the paraventricular nucleus in birds to determine whether hyperphagia and obesity result. The tracing study of Berk and Finkelstein (1983) shows a clear parasympathetic component as well as a suggestion of a sympathetic projection from the paraventricular nucleus in pigeons. Because the paraventricular nucleus is as complex in birds as in mammals, with at least 10 subnuclei (unpublished data) and also projects to the median eminence and posterior pituitary (Korf 1984), it is a critical nucleus to focus upon in avian brains.

The autonomic and endocrine hypothesis appears to be very applicable to some of the avian strains found in the commercial poultry industry. For many years turkeys and particularly broilers have been genetically selected for meat production. In selecting for growth rate, birds have also been inadvertently selected for appetite. Broiler breeders are a good example of birds that have a voracious appetite and a tendency to become obese. Their offspring are generally hypoactive and have a lower basal metabolic rate (Kuenzel and Kuenzel 1977) and a rapid growth rate. In other words, broilers show a dominance of the parasympathetic nervous system similar to that of ventromedial hypothalamically-lesioned rats and in some obese humans. It will be important in the future for poultry geneticists to attempt to bring back into balance the sympathetic and parasympathetic nervous systems of some commercial poultry strains.

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