Hepatic denervation does not affect plasma vasopressin response to intragastric hypertonic saline in conscious rats

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Carlson, Scott H., and J. Michael Wyss. Hepatic denervation does not affect plasma vasopressin response to intragastric hypertonic saline in conscious rats. Am. J. Physiol. 277 (Endocrinol. Metab. 40): E161–E167, 1999.—Peripheral osmoreceptors monitor dietary NaCl and modify central nervous system and renal sympathetic nervous system activity accordingly. Experimental evidence suggests that these responses are dependent on the hepatic nerves. Peripheral osmoreceptors also modify arginine vasopressin (AVP) secretion. However, although hepatic denervation reportedly blunts activation of both supraoptic and paraventricular hypothalamic neurons after intraportal NaCl infusion, the role of the hepatic nerves in the AVP release has not been directly examined. The present study tests the hypothesis that the hepatic nerves modify AVP release in response to intragastric NaCl infusion. Wistar-Kyoto rats (WKY) received either hepatic denervation or a sham operation. Intragastric NaCl infusion significantly elevated plasma AVP in both sham-operated WKY and hepatic-denervated WKY, and the responses were not different between these groups. Second, previous studies suggest that both AVP secretion and baroreflexes are blunted in spontaneously hypertensive rats (SHR), deficits that contribute to the observed hypertension in SHR. We hypothesized that SHR also have a blunted peripheral osmoreceptor reflex and that this contributes to NaCl-sensitive hypertension. In contrast to our prediction, in SHR intragastric NaCl infusion induced an increase in plasma AVP that was similar to that in the WKY groups. Thus, although hepatic osmoreceptors are important for chronic regulation of arterial pressure, renal sympathetic nervous system activity, and the activity of hypothalamic neurons, they do not appear to influence plasma AVP concentration in response to intragastric NaCl.

Peripheral osmoreceptors; arginine vasopressin; atrial natriuretic peptide; spontaneously hypertensive rats

The brain contains osmosensitive cells that respond to changes in plasma and cerebrospinal osmolality and modify central nervous system (CNS) activity accordingly. However, a number of studies suggest that osmoreceptors also exist in the periphery. Peripheral osmoreceptors were first demonstrated by Haberich in 1968 (15), and subsequently a number of studies have examined their role in homeostasis after sodium ingestion. These experiments have shown that peripheral osmoreceptors reflexively inhibit renal sympathetic nerve activity (16, 31–33), resulting in an enhanced natriuresis and diuresis (13, 31, 32, 39). Other studies suggest that peripheral osmoreceptors modify gastrointestinal sodium absorption (34, 35, 41), salt appetite (11), and water intake (23, 25). Thus the peripheral osmoreceptor response is multifaceted, serving to maintain sodium and water homeostasis after dietary NaCl intake.

Several lines of evidence suggest that peripheral osmoreceptors also modulate arginine vasopressin (AVP) release from the posterior pituitary into the circulation, a function traditionally attributed to either central osmoreceptor activation or a decrease in baroreceptor activity. Support for peripheral osmoreceptor control of AVP release includes the observation that intragastric (4, 6, 8, 9) and intraportal (3) hypertonic saline infusions significantly increase plasma AVP concentration without an increase in plasma osmolality. This indicates the absence of central osmoreceptor activation. Furthermore, the increase in circulating AVP is independent of any change in blood volume, indicating that baroreceptor feedback is not responsible for the AVP response. Despite this evidence supporting peripheral osmoreceptor control of AVP release, a number of studies have challenged the theory (43, 45), and the hypothesis remains controversial.

Several studies suggest that peripheral osmoreceptors are located within the liver and/or the portal region and project to the CNS via the hepatic nerves, which are a combination of sympathetic and parasympathetic sensory fibers that provide the primary innervation for the liver (26). Consistent with this suggestion are studies demonstrating that intraportal NaCl activates hepatic nerve fibers (1), leading to changes in electrical activity in the CNS (22, 24). Furthermore, the ability of peripheral osmoreceptors to modify renal sympathetic nervous system activity (17, 31, 33) and sodium absorption (34) is abolished by transection of the hepatic nerves. However, the role of the hepatic nerves in modifying AVP release has not been directly examined. Morita et al. (36) reported that intraportal hypertonic NaCl infusion significantly elevated Fos protein immunoreactivity in both the supraoptic (SON) and paraventricular (PVN) hypothalamic nuclei, possibly correlated with increased AVP secretion. These Fos responses were significantly reduced when the hepatic nerves were transected, leading to the conclusion that the hepatic nerves are involved in peripheral control of AVP release. However, plasma AVP was not directly measured in this study (36). A similar Fos expression pattern has been reported within the SON and PVN in response to intragastric hypertonic saline, and the Fos response was largely abolished by subdiaphragmatic vagotomy (6). Whereas this suggested that vagal osmoreceptive afferents modulate AVP release, analysis of plasma AVP indicated that lesioning the vagus did not alter the AVP response to intragastric NaCl and sug-

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suggests that Fos expression in these neurons is not associated with AVP release (6). Thus it is possible that the plasma AVP response was also unaffected by hepatic denervation in the study of Morita et al. (36).

Aside from possible modification of AVP release, it is unknown whether peripheral osmoreceptors regulate other circulating natriuretic hormones associated with sodium and water homeostasis. Atrial natriuretic peptide (ANP) serves an important role in sodium and water homeostasis. Although ANP release into the circulation is primarily attributed to stretch of the atrial myocytes in response to vascular volume expansion, experimental evidence suggests that its release is also regulated by the autonomic nervous system (14, 18). Although there are no data that directly link NaCl ingestion to ANP release, we were interested in examining the relationship for two reasons. First, given the fact that peripheral osmoreceptor activity alters renal sympathetic nerve activity, it is possible that the osmoreceptors could also modify circulating ANP levels. Second, spontaneously hypertensive rats (SHR) display elevated sympathetic nervous system activity, diminished baroreflex sensitivity, and elevated plasma NaCl (19, 38, 42). They also display blunted increases in circulating ANP in response to increased vascular volume, and exogenous administration of ANP blunts salt sensitivity in this strain (19, 38, 42). Furthermore, AVP release is disturbed in SHR (29) and has been associated with hypertension and salt sensitivity (47). These observations suggest that in response to excess NaCl ingestion, peripheral osmoreceptor control of AVP and ANP may be impaired in SHR, thereby contributing to salt-sensitive hypertension.

The present study tests the hypothesis that hepatic denervation inhibits the normal increase in plasma AVP that is induced by an intragastric NaCl infusion. Second, the experiments examine whether peripheral hepatic osmoreceptors modify circulating levels of ANP in response to NaCl ingestion. Finally, it tests the hypothesis that acute AVP and ANP responses to intragastric hypertonic saline infusion are blunted in the SHR.

MATERIALS AND METHODS

Nine-week-old male Wistar-Kyoto rats (WKY) and SHR (Harlan Sprague Dawley, Indianapolis, IN) were used in all experiments. Rats were housed in individual cages in a sound-attenuated room at constant humidity (60 ± 5%), temperature (24 ± 1°C), and light cycle (0600–1800) and were allowed ad libitum access to rat chow (Teklad, Madison, WI) and tap water. All studies were conducted in accordance with institutional and National Institutes of Health guidelines.

Surgical procedures. Rats were anesthetized with Nembutal (50 mg/kg body weight) and chronically instrumented with an indwelling Silastic arterial catheter, which was advanced into the abdominal aorta via the left femoral artery. The hepatic nerves were transected as described previously (7). Briefly, the portal vein, hepatic artery, and bile duct were isolated through a midline abdominal incision, and the segments immediately adjacent to the liver were stripped of all surrounding tissue so that no visible strands of tissue connecting the vessels to the liver remained. A 10% phenol-ethanol solution was then topically applied to the vessels. The sham surgery was identical, with the exception that no tissue was cleared around the vessels, nor was the 10% phenol-ethanol solution applied. The stomach was then retracted, and a Silastic catheter was implanted in the greater curvature. All catheters were tunneled subcutaneously to the midscapular region where they were exteriorized and secured with dental acrylic. On recovery from anesthesia, rats were returned to their home cages and were allowed a recovery period of ≥3 days before experimentation. The arterial catheters were flushed daily with heparinized saline (1,000 U/ml) and the gastric catheters were flushed daily with 1.0 ml of 0.9% NaCl.

Experimental protocol. Sham-denervated WKY (n = 6) and SHR (n = 5) and hepatic-denervated WKY (n = 7) were studied in their home cages in an isolated room, and food and water were removed at the start of the experiment. Mean arterial pressure (MAP) and heart rate (HR) were measured throughout the experiment by connecting the arterial catheter to a pressure transducer connected to a personal computer for continuous monitoring (Biopac, Santa Barbara, CA). A preinfusion blood sample (1.2 ml) was drawn into a chilled microcentrifuge tube containing EDTA (1.5 mg) for measurement of plasma AVP and was immediately replaced by an equal volume of blood from a conscious, chronically catheterized donor rat. After an equilibration period of ≥30 min, rats received a 5-min intragastric infusion (0.57 ml/min) of hypertonic (550 mosmol/l) saline. Ten minutes after the intragastric infusion, a second blood sample (1.2 ml) was drawn and replaced with an equal volume of donor blood. A 10-min postinfusion sampling period was chosen so as to maximize any potential changes in plasma ANP. We have previously measured the AVP response at several time points (0, 2, 5, and 10 min postinfusion; (Ref. 4 and unpublished observations)) and found the AVP response to be similar at all time points. The following day the experiment was repeated, and blood samples were collected into chilled microcentrifuge tubes containing EDTA (1.5 mg) and aprotinin (1 trypsin-inhibitor unit) for measurement of circulating ANP levels. In some of the rats the order of collection was reversed.

Analysis of blood samples. Blood samples were centrifuged at 4°C, and the plasma was saved for subsequent analysis of AVP and ANP concentrations. AVP was quantitated by radioimmunoassay at the Core Assay Laboratory in the Department of Physiology at the Medical College of Wisconsin (12). ANP was quantitated by radioimmunoassay using a commercially available RIA kit (Phoenix Pharmaceuticals, Mountain View, CA).

Verification of denervation. After completion of the experiments, rats were deeply anesthetized with urethan, and a section of liver was removed, immediately frozen in liquid nitrogen, and stored at −80°C. The tissue was later extracted for measurement of tissue norepinephrine levels, as described elsewhere (7). Briefly, tissue was homogenized in a 0.1 M HClO4-EDTA solution and centrifuged, and a portion of the supernatant was extracted using acid-washed aluminum oxide in 1.5 M Tris-0.1 M phosphate buffer. The samples were then analyzed for norepinephrine using high-performance liquid chromatography with electrochemical detection (HPLC-EC; Waters, Milford, MA), and the values were adjusted for recovery using 3,4-dihydrobenzylamine as an internal standard. The sensitivity of this analytic protocol is ~20 pg/ml. Individual rats were included in the present study only if their hepatic norepinephrine concentration was reduced to ≥90% of sham-operated levels.

Statistical analysis. Between-group differences in HR, AVP, ANP, and MAP response were tested using analysis of variance followed by post hoc Newman-Keuls analysis to identify
the underlying within-group and between-group contributions to significant main effects or interactions. In all cases, a value of \( P < 0.05 \) was considered statistically significant. Results are expressed as means ± SE.

**RESULTS**

In sham-operated WKY, plasma AVP concentration significantly increased in response to the intragastric hypertonic saline infusion (1.7 ± 0.6 to 3.3 ± 0.7 pg/ml; \( P < 0.05 \); Fig. 1). A similar increase in plasma AVP concentration was observed in the hepatic-denervated WKY (1.8 ± 0.3 to 4.6 ± 0.8 pg/ml; \( P < 0.05 \); Fig. 1). In SHR, plasma AVP levels also significantly increased in response to the intragastric stimulus (1.1 ± 0.7 to 2.8 ± 1.0 pg/ml; \( P < 0.05 \); Fig. 1). In contrast to our predictions, the increase in plasma AVP concentration after the intragastric NaCl infusion tended to be greater in both the denervated WKY (1.6-fold increase) and SHR (1.5-fold increase) than in the sham-operated WKY (0.9-fold increase), but this increase did not reach statistical significance.

Changes in circulating ANP levels after the intragastric hypertonic saline infusion are illustrated in Fig. 2. Plasma ANP concentration did not significantly change in response to the intragastric stimulus in either sham-operated WKY (515.5 ± 30.8 to 521.7 ± 30.2 pg/ml) or hepatic-denervated WKY (511.2 ± 33.5 to 480.8 ± 66.0 pg/ml). Circulating ANP levels also did not respond to the NaCl stimulus in SHR (318.7 ± 30.6 to 261.5 ± 29.4 pg/ml), but basal plasma ANP concentration was significantly lower in the SHR than in either WKY group (\( P < 0.05 \)).

Basal MAP was significantly elevated in hepatic-denervated WKY compared with the sham-operated WKY (119 ± 1.5 vs. 89 ± 1.3 mmHg, respectively; \( P < 0.05 \); Fig. 3). Basal MAP in the SHR group was significantly higher than in either WKY group (139 ± 3.2; \( P < 0.05 \); Fig. 3). MAP did not change in response to the intragastric infusion in any of the groups. Basal HR was similar in all groups and did not significantly change in response to the intragastric infusion (data not shown).

Compared with sham operation, hepatic denervation did not significantly alter body weight (data not shown). Hepatic denervation significantly decreased liver norepinephrine concentration by >90% from sham levels in all denervated animals (401.1 ± 104.8 vs. 37.3 ± 7.8 pg/ml; \( P < 0.05 \)).

**DISCUSSION**

Previous reports suggest that peripheral osmoreceptors modify plasma AVP concentration after intragastric NaCl (4, 6, 8, 9) and that these osmoreceptors lie...
within the liver, making it likely that the afferent projections travel via the hepatic nerves. This is consistent with a number of studies demonstrating that the hepatic nerves are integral for peripheral osmoreceptor control of both sympathetic nerve activity (31, 32, 33) and sodium absorption (34) in response to dietary NaCl. Although the hepatic nerves are also crucial in peripheral osmoreceptor activation of the SON and PVN (36), the role of the hepatic nerves in modifying AVP release has not been directly examined. This study examined the hypothesis that hepatic denervation abolishes the AVP response to intragastric hypertonic saline infusion. The results demonstrate that the plasma AVP response to intragastric NaCl is similar in hepatic-denervated WKY and sham-operated WKY, indicating that the hepatic nerves do not appear to regulate circulating AVP.

The inability of peripheral denervation to block the AVP response to intraportal/intragastric saline has challenged the hypothesis that peripheral osmoreceptors control AVP release. Baertschi et al., using splanchnic denervation (8) as well as central electrolytic (20) and chemical lesions (21), were able to achieve only a 60% reduction in the AVP response to intragastric hypertonic saline infusion. Likewise, Carlson and Osborne (6) demonstrated that the AVP response to an intragastric NaCl infusion was unaffected by either subdiaphragmatic vagotomy or splanchnic denervation alone. The only study that has reportedly blocked the AVP response to intraportal hypertonic saline was published by Chwalbinska-Moneta (10); in this study, sectioning the hepatic branch of the vagus nerve completely blocked the response of plasma AVP activity in dogs. However, numerous studies by Ramsay et al. (40) and Thrasher and colleagues (43–45) have found no evidence of peripheral osmoreceptor control of AVP in dogs. Thus, combined with the inability of total subdia-

phragmatic denervation to alter the AVP response to intragastric hypertonic saline in rats (6), the results of the study by Chwalbinska-Moneta (10) remain questionable.

Although studies have demonstrated that neither splanchnic nor vagal afferents alone appear to regulate AVP release, they have left open the possibility that AVP release is regulated by a combination of peripheral osmoreceptor projections that travel through both splanchnic and vagal nerves. The hepatic nerves appeared to be an ideal candidate for such a role, because they contain both vagal and splanchnic afferents. Furthermore, their involvement in modulating AVP release would be consistent with the observations of Morita et al. (36), who used Fos immunocytochemistry to demonstrate that hepatic denervation significantly reduces SON and PVN neuronal activity in response to intraportal NaCl and thereby attributed a role for the hepatic nerves in peripherally regulating AVP release. The results of this study indicate that the hepatic nerves do not modulate AVP release, a finding that seems to conflict with the work by Morita et al. However, it is important to note that SON and PVN Fos expression relates to general neuronal activity and does not necessarily correlate with AVP release. Carlson et al. (4) had previously characterized the AVP and Fos responses to intragastric hypertonic saline and had associated Fos expression in the SON and PVN with AVP secretion. However, in a subsequent study (6) it was demonstrated that whereas vagotomy significantly reduced SON and PVN Fos expression in response to intragastric NaCl, the increase in circulating AVP was unaffected. It was concluded that the majority of Fos expression in the hypothalamic nuclei in response to dietary NaCl is related to peripheral regulation of functions other than AVP release. In support of this is a recent report demonstrating that lesions of the area postrema significantly reduce Fos expression in the PVN in response to intragastric hypertonic saline (5), and this change in PVN neuronal activity likely correlates with peripheral modification of renal sympathetic nerve activity (37). In summary, the results of the present study suggest that much of the Fos expression in the study of Morita et al. (36) must also be attributed to activation of hypothalamic neuronal pathways related to the control of other associated functions.

Several other mechanisms could underlie the AVP response to intragastric NaCl. First, it is possible that activation of central osmoreceptors underlies this response, which would agree with the interpretations of Ramsey et al. (40) and Thrasher and colleagues (43–45). Although plasma osmolality was not measured in this study, in previous studies the identical stimulus produced no measurable change in systemic osmolality (4, 6, 9). Nonetheless, it is possible that absorption of the hypertonic saline into the vascular compartment produces an increase in systemic plasma osmolality that was not detectable. The vapor pressure osmometer used in the previous experiments (4, 6) reliably detects changes in plasma osmolality of <1% (i.e., <3 mosmol/kg). AVP release is triggered by an increase of 1–2% (3–6 mosmol/kg) in systemic osmolality. However, the intragastric stimulus employed in these studies produces a measurable 1.7% increase in the portal venous osmolality (4), and it is expected that, after dilution within the liver and on entry into the systemic circulation (i.e., entry into the vena cava and passage through the pulmonary circulation), this change in osmolality would be significantly smaller (see Ref. 6). It is therefore doubtful that such a small increase in plasma osmolality would be capable of stimulating AVP release via central osmoreceptor activation.

Another possible explanation for the inability of hepatic denervation to block the AVP response to intragastric sodium is that transection of the hepatic nerves leaves some of the hepatic afferents intact, as evidenced by inability of denervation to completely eliminate liver norepinephrine (NE) levels. However, to accurately measure tissue NE levels, it is necessary to avoid the rapid degradation of NE that would occur on deprivation of oxygen. Consequently, the livers are removed from deeply anesthetized unperfused rats, and they contain a large amount of blood. Therefore, it is likely that the residual NE content in the denervated livers is attributable to plasma NE. Likewise, all
studies utilizing hepatic denervation report residual NE content, despite the ability of hepatic denervation to completely abolish the measured parameters (28, 30, 32). Another possibility is that some of the peripheral osmoreceptor projections may travel via alternate nerves. The liver also receives innervation via the phrenic nerve, although the afferent composition of this nerve is questionable (26).

Studies by Arsenijevic and Baertschi (2) and Vallet and Baertschi (46) indicate that peripheral osmoreceptors are strategically located around the mesentery. Thus, in addition to hepatic osmoreceptors, vagal and splanchnic osmoreceptor afferents from other gastrointestinal regions may modify circulating AVP levels. However, Baertschi and Vallet (3) reported that delivery of hypertonic saline selectively to the liver modifies AVP release. Intraportal hypertonic saline infusion also modifies hypothalamic neuronal activity (36), and others have shown that the hepatic nerves enable peripheral osmoreceptors to modify sympathetic nerve activity (31–33) and sodium absorption (34). Therefore, it would be expected that if peripheral osmoreceptors modify AVP release, then hepatic denervation should affect the AVP response to an intragastric NaCl infusion.

Other mechanisms may account for the lack of hepatic nerve influence on the AVP response to intragastric sodium infusion. Peripheral osmoreceptors may modify AVP release via nonneural inputs, such as through the release of gastrointestinal hormones (e.g., cholecystokinin) or ouabain-like substances (27), which could activate the hypothalamic nuclei involved in AVP secretion. Furthermore, these pathways may fully compensate for the absence of hepatic afferent input to the CNS, thereby leaving the AVP response unchanged. However, we are unaware of any hard data supporting this. It is also possible that transient changes in blood volume occur as water is drawn from the vascular compartment into the lumen of the small intestine to create isosmotic conditions. This would decrease baroreceptor inhibition of AVP release. However, previous studies have indicated that no such volume shift occurs (4, 6). Likewise, any alteration of cardiopulmonary baroreflex feedback would affect HR and MAP, but no such changes were observed.

The failure of hepatic denervation to alter the AVP response at 10 min after the intragastric NaCl infusion does not completely rule out a role for the hepatic nerves in the AVP response to a NaCl challenge. Several lines of evidence suggest that the AVP response to a NaCl challenge has a very rapid onset and quickly reaches a plateau that is sustained for several minutes. Although we have previously measured plasma AVP at 0, 2, and 5 min after NaCl infusion and found increases similar to those of the present study (Ref. 4 and unpublished observations), a complete analysis of later time points may reveal lesion-induced alterations. It is also possible that hepatic denervation indirectly affects the AVP response pattern to intragastric NaCl infusion by altering sodium absorption in gut (34, 35, 41) or kidney (31, 32). Furthermore, this and previous studies have used a narrow range of hyperosmotic challenges (500–600 mosmol/l), and it is possible that the hepatic nerves play a more prominent role after more aggressive challenges.

We also examined whether peripheral osmoreceptors modify the release of another hormone involved in sodium and water homeostasis, i.e., ANP. Whereas the secretion of ANP traditionally has been primarily attributed to stretch of the atrial myocytes in response to vascular volume expansion, recent evidence suggests that the release of ANP is also under neural regulation (14, 18). This led us to the hypothesis that peripheral osmoreceptors modify ANP responses to NaCl ingestion. The results demonstrate that plasma ANP levels do not respond to the acute intragastric NaCl infusion in either the sham-operated or hepatic-denervated WKY.

Several studies demonstrate that SHR display blunted peripheral baroreflexes (42), SHR also do not increase plasma ANP concentration in response to vascular volume loads, and treatment with exogenous ANP abolishes the salt-sensitive hypertension observed in SHR (19, 38). This has led to the hypothesis that ANP dysregulation contributes to salt sensitivity in SHR (19, 38). Furthermore, a known disturbance in AVP release may also contribute to hypertension and salt sensitivity in SHR (29, 47). We theorized that peripheral osmoreceptor control of AVP and ANP is diminished in SHR, thereby accounting for some of the observed hypertension. Our results do not support this hypothesis. SHR and WKY display similar increases in AVP in response to the intragastric NaCl, and, like WKY, SHR do not display an ANP response to this stimulus. However, it is still possible that peripheral osmoreceptor control of sympathetic nerve activity is disrupted in SHR, thereby accounting for some of the observed hypertension and salt sensitivity. We have previously demonstrated in WKY that disruption of the peripheral osmoreceptors results in a chronic elevation in arterial pressure (7). Likewise, others have reported that, in WKY, hepatic denervation disrupts long-term sodium homeostasis (30).

Although hepatic denervation did not affect the AVP response to the intragastric hypertonic saline infusion, it significantly elevated baseline arterial pressure by ~30 mmHg in WKY. This finding confirms our previous report (7). In that study, using telemetric recording methods, we observed that arterial pressure was significantly elevated in WKY on either a normal (0.6%) or high (8%) NaCl diet. These results suggest that, although peripheral osmoreceptors do not mediate AVP release, they do contribute to the chronic regulation of arterial pressure, perhaps by modifying sodium and water balance (7, 30).

In summary, the present study fails to support the hypothesis that hepatic osmoreceptors regulate the circulating AVP response to intragastric NaCl in rats. Second, this study demonstrates that SHR have a normal AVP response to intragastric NaCl loads. Third, the results indicate that hepatic osmoreceptors do not modify plasma ANP concentration in response to acute
NaCl ingestion. However, the observation that hepatic denervation chronically elevates MAP in WKY indicates that peripheral osmoreceptors contribute to long-term control of arterial pressure. Furthermore, it has been demonstrated that splanchnic denervation (6), total subdiaphragmatic vagotomy (6), and hepatic denervation (36) disrupt the response of both hypothalamic and brain stem nuclei to acute gastric NaCl loads. It is likely that peripheral osmoreceptors modulate functions other than AVP release, including sympathetic nerve activity (11, 23, 25), and gastrointestinal sodium absorption (34, 35, 41) through these CNS pathways.

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