Oxytocin release in magnocellular nuclei: neurochemical mediators and functional significance during gestation

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Bealer SL, Armstrong WE, Crowley WR. Oxytocin release in magnocellular nuclei: neurochemical mediators and functional significance during gestation. Am J Physiol Regul Integr Comp Physiol 299: R452–R458, 2010. First published June 16, 2010; doi:10.1152/ajpregu.00217.2010.—When released from dendrites within the supraoptic (SON) and paraventricular (PVN) nuclei (intranuclear release) during suckling, oxytocin exerts autocrine and paracrine effects on oxytocin neurons that are necessary for the unique timing and episodic pattern of oxytocin release into the systemic circulation that is characteristic of lactation. Recent reports have shown that stimulation of central noradrenergic and histaminergic receptors are both necessary for intranuclear release of oxytocin in response to suckling. In addition, in vitro studies indicate that excitatory amino acids may also be critical for central oxytocin secretion, although in vivo experiments have not provided direct support for this hypothesis. In addition to a critical role in intranuclear oxytocin release during lactation, norepinephrine has also been shown to stimulate central oxytocin during gestation. Stimulation of central oxytocin receptors during gestation appears critical for normal systemic oxytocin secretion in responses to suckling during the subsequent period of lactation. Oxytocin receptor blockade during pregnancy alters normal timing of systemic oxytocin release during suckling and reduces milk delivery. Several adaptations occur in the central oxytocin system that are necessary for determining the unique response characteristic observed during parturition and gestation. Central oxytocin receptor stimulation during gestation has been implicated in pregnancy-related morphological changes in magnocellular oxytocin neurons, disinhibition of oxytocin neurons to GABA, and adaptations in membrane response characteristics of oxytocin neurons. In conclusion, intranuclear oxytocin release during gestation and lactation are critical for establishing, and then evoking the unique pattern of systemic oxytocin secretion in response to the suckling offspring necessary for adequate milk delivery. Furthermore, activation of central noradrenergic receptors appears to be critical for release of central oxytocin in both of these reproductive states.

intranuclear oxytocin; pregnancy; lactation; suckling

IN ADDITION TO ITS ROLE AS a circulating neurohormone released from the neurohypophysis, oxytocin serves as a peptidergic neurotransmitter in the brain. Neurally-released oxytocin within the central nervous system (CNS) has been implicated in regulation of reproductive, maternal, and affiliative behaviors, and is a critical component of the integrated response to stress (for reviews see Refs. 30 and 44). The CNS sites where central oxytocin mediates these actions include several structures in the hypothalamus and limbic system that receive projections from hypothalamic oxytocin neurons, and are components of regulatory networks controlling specific physiological and behavioral functions (30).

In addition to these more distal sites, oxytocin is released locally within the magnocellular nuclei of the hypothalamus, i.e. the paraventricular (PVN) and supraoptic (SON) nuclei, where oxytocin-synthesizing neurons are predominantly localized. Unlike oxytocin in other brain regions that occurs from axon terminals, oxytocin released within the PVN and SON appears to derive exclusively from dendrites and possibly somata (49). This intranuclear or dendritic oxytocin release in magnocellular nuclei, is involved in critical neuroendocrine regulation of oxytocin secretion into the systemic circulation, particularly in the reproductive states of lactation and parturition.

Since the initial demonstration of intranuclear oxytocin release by Moos and Richard in 1989 (41), a number of excellent reviews have discussed the mechanisms underlying its stimulation and physiological significance during parturition and lactation (8, 13, 30, 32, 36, 44, 50, 52). Taken together, the evidence strongly suggests that oxytocin released in PVN and SON is critical for generating the pulsatile pattern of systemic oxytocin secretion characteristic of these reproductive conditions. As reviewed previously (13, 22), oxytocin release into the systemic circulation in these states is charac-
terized by discrete pulses rather than tonic increases, as seen for example, in response to other stimuli such as stress. Moreover, it is well established that each episode of oxytocin release is preceded by a burst of firing, during which the entire oxytocin neurosecretory population appears to become activated in a highly coordinated fashion. During lactation, these milk ejection bursts are induced by the suckling stimuli of the offspring, but they also occur during parturition. Extracellular oxytocin in the magnocellular nuclei has pre- and postjunctional effects on oxytocin neurons that are essential for coordinating and synchronizing firing of the entire population of oxytocin neurons during parturition and lactation.

Neurochemical Mediators of Central Oxytocin Release During Lactation

Although systemic secretion of oxytocin can be evoked by a number of stimuli and brain neurotransmitters, norepinephrine (14, 54, 72), histamine (53), and excitatory amino acids (47) have been directly implicated in peripheral release of oxytocin from the neurohypophysis specifically in response to suckling. More recent studies have investigated the roles of these agents in release of central oxytocin during lactation.

Norepinephrine

While early studies firmly established that activation of CNS noradrenergic systems is critical for secretion of systemic oxytocin during lactation (14, 54, 72) and parturition (25), the role of this neurotransmitter system in regulation of intranuclear oxytocin during reproductive states has only recently been investigated. Using microdialysis, we demonstrated that norepinephrine is released in the PVN in response to suckling offspring (5), and it was associated with increased intranuclear oxytocin (40, 42, 43). These data suggested that norepinephrine is involved in both central and peripheral oxytocin release during suckling.

Results from additional studies support this proposal. Administration of either an α- or β-adrenergic antagonist by retrodialysis prevents local oxytocin release in the PVN during suckling (5). Furthermore, local stimulation in the PVN of either receptor subtype with specific α- or β-adrenergic agonists induces intranuclear oxytocin release in nonsuckled rats (5). These data demonstrate that, similar to systemic secretion of oxytocin in lactation, intranuclear oxytocin release during suckling is dependent on activation of central noradrenergic systems. These data are consistent with the proposal that the suckling offspring activate central noradrenergic pathways to magnocellular nuclei inducing intranuclear release of oxytocin and that it is the central oxytocin release that is essential for systemic oxytocin secretion. However, the involvement of both α- and β-adrenergic receptors suggests this regulation is complex.

Histamine

In addition to norepinephrine, activation of central histaminergic systems is essential for normal secretion of peripheral oxytocin during lactation (53). We evaluated the contribution of central histamine receptor stimulation to release of intranuclear oxytocin in lactating rats (4). Similar to norepinephrine, extracellular histamine concentrations in the PVN are increased during suckling (4). Furthermore, local administration of either an H1 or an H2 antagonist into the PVN by retrodialysis prevents suckling-induced release of intranuclear oxytocin. These data demonstrate that activation of central histamine H1 and H2 receptors in magnocellular nuclei is evoked by the cutaneous stimulation of the suckling offspring, and is necessary for intranuclear release of oxytocin, as well as the subsequent systemic secretion of the hormone.

Since central noradrenergic receptors modulate responses evoked by a number of other neurotransmitter systems, we also investigated the effects of noradrenergic blockade in histamine-evoked release of central and systemic oxytocin (6). Local administration of histamine into the PVN by retrodialysis induces release of both intranuclear and systemic oxytocin. However, when the noradrenergic antagonist phentolamine was included in the dialysis fluid, both systemic and intranuclear oxytocin release were prevented (6). These results demonstrate that central noradrenergic receptor stimulation is necessary for histamine-induced release of oxytocin. This relationship is similar to that demonstrated for histaminergic release of vasopressin secretion, which is also mediated by adrenergic receptor stimulation (3). These data suggest that suckling-induced activation of CNS histamine release stimulates the norepinephrine secretion necessary for intranuclear oxytocin and the resultant peripheral release of the hormone.

Excitatory Amino Acids

Pharmacological studies in lactating rats have provided evidence that glutamate can stimulate systemic oxytocin release via an action at the AMPA receptor subtype and that this stimulatory effect is essential for suckling-induced systemic oxytocin release (47). As appears to be the case with histamine described above, the glutamatergic system also interacts with norepinephrine. Thus, Parker and Crowley (46) found that the stimulatory effect of an AMPA agonist on systemic oxytocin release could be prevented by α1-adrenergic receptor blockade. de Kock CP et al. (17) have provided evidence, using hypothalamic slices from lactating rats ex vivo, that glutamate increases dendritic oxytocin release. This, in turn, suppresses GABA release by a presynaptic action and results in enhanced activity in the oxytocin neurosecretory system. However, when glutamate is applied locally to the PVN by retrodialysis in vivo, intranuclear oxytocin concentration did not increase, although the peptide was released systemically (24). These data suggest that, unlike both norepinephrine and histamine, glutamate may induce pulsatile release of central oxytocin, which is not detected using the extended sampling periods required by microdialysis. Alternatively, glutamate may directly induce systemic release of oxytocin, independent of a stimulatory action on intranuclear oxytocin. Although it is clear that excitatory amino acid neurotransmission is necessary for systemic release of oxytocin in response to suckling and is mediated by noradrenergic receptor activation, the precise role of excitatory amino acids in release of oxytocin within the magnocellular nuclei and reconciling the in vitro (17) with in vivo findings (24) will require further investigation.

Taken together, these data suggest that stimulation of several central neurotransmitter systems appear necessary for intranuclear release of oxytocin and subsequent peripheral secretion in response to suckling. Furthermore, norepinephrine release in...
the magnocellular nuclei may be the final common pathway necessary for intranuclear oxytocin release during lactation.

**Neurochemical Mediators of Central Oxytocin Release During Gestation**

The three neurotransmitter systems described above are directly implicated in regulating intranuclear oxytocin release during lactation. Control of dendritic and somatic oxytocin secretion from magnocellular neurons is less well characterized during gestation. However, although basal release of intranuclear oxytocin does not appear to increase during gestation (20, 34, 43, 74), there is evidence that responsiveness of central oxytocin is enhanced, and that norepinephrine and opioids interact to regulate intranuclear oxytocin during this stage of reproduction.

**Norepinephrine**

Both release of central norepinephrine and intranuclear oxytocin secretion in response to noradrenergic stimulation are increased in pregnancy. Specifically, recent studies demonstrate that norepinephrine release in the dorsal SON following both stimulation of magnocellular neuron axons and intraventricular cholecystokinin is significantly greater in pregnant animals on gestation days 21 and 22, compared with gestation day 20 and with virgin animals (70). Furthermore, responses of intranuclear oxytocin to the excitatory effects of noradrenergic receptor activation are enhanced during gestation. We found that local administration of the α1-adrenergic agonist, phenylephrine, evoked a greater response in both intranuclear and systemic oxytocin release in Sprague-Dawley dams during late pregnancy than in midgestation, or in nonpregnant, ovariectomized female rats (34). These findings demonstrate that although basal extracellular oxytocin levels are not increased during gestation, both central norepinephrine release and the intranuclear oxytocin response to excitatory adrenergic stimulation in magnocellular nuclei are potentiated. The effects of pregnancy on central histamine and excitatory amino acid release and the associated responses of intranuclear oxytocin have not yet been investigated.

In addition to increased neurotransmitter release and responsiveness to excitatory stimulation, other adaptations suggest enhanced activity of the central oxytocin system during gestation. Using autoradiography, we found that oxytocin receptor binding is significantly greater in late gestation than in midgestation, and binding in both periods was greater than that observed in ovariectomized, virgin control animals (7). These data suggest that there is a progressive increase in oxytocin receptor binding over the course of gestation, which may represent increased receptor numbers. Although the functional significance of enhanced oxytocin receptor stimulation due to increased noradrenergic sensitivity and receptor binding during pregnancy has not been completely defined, there is evidence that it is critical for pregnancy-related adaptations necessary for normal systemic oxytocin release during parturition and lactation. Even if dendritic oxytocin release were to remain the same during pregnancy, the increased binding would suggest that oxytocin receptor activation could be enhanced.

**Opioids**

In addition to norepinephrine, a second neurochemical system has been implicated in regulation of dendritic oxytocin release during gestation. As reviewed extensively (52), there is considerable evidence for opioid inhibition of systemic oxytocin release during late gestation. That this may extend to intranuclear release of oxytocin is suggested by the observation that the opioid antagonist naloxone increased oxytocin concentrations in the SON during this period (20). In another study by this group, however, naloxone failed to increase intranuclear oxytocin release during parturition (43). These findings are consistent with the proposal that endogenous opioids provide an important inhibitory influence on central oxytocin secretion in the days immediately prior to parturition, but that this restraint may diminish on the day of parturition itself (52).

These data indicate that during the latter stages of pregnancy, prior to parturition, noradrenergic and opioid systems interact to regulate intranuclear oxytocin release. These findings suggest that opioid inhibition of central oxytocin secretion during the late stages of gestation may be necessary to prevent premature systemic oxytocin release, which could be induced by noradrenergic systems. Furthermore, release from this opioid inhibition may then allow the norepinephrine-mediated central and systemic oxytocin secretion necessary for normal parturition.

It should be noted that the relative influence of excitatory and inhibitory control mechanisms regulating central oxytocin release is probably not constant over the course of gestation. It is likely that excitatory influences predominate during early and midgestation to evoke the adaptations necessary to prepare the system for the demands of parturition and lactation. As parturition approaches, the inhibitory effects of opioids may predominate to diminish systemic oxytocin release that could result in premature uterine contractions. The roles of other neurochemical systems in central oxytocin release during late gestation and parturition have not yet been investigated.

**Role of Intranuclear Oxytocin During Gestation**

While actions of intranuclear oxytocin during parturition and lactation have been extensively studied, the role of this system during gestation is less well understood. During pregnancy, the central oxytocin system undergoes several adaptations necessary for normal function during parturition and lactation, including increased oxytocin gene expression, morphological changes in and around oxytocin neurons, and altered electrophysiological response characteristics in magnocellular oxytocin neurons. There is functional evidence that stimulation of central oxytocin neurons during gestation is critical for establishing the response patterns and intensity required for appropriate oxytocin secretion during parturition and lactation. When pregnant Sprague-Dawley rats receive continuous intracerebroventricular administration of a selective oxytocin receptor antagonist beginning on gestation day 12 and ending immediately following parturition, the timing of systemic oxytocin release to suckling throughout lactation is altered, milk delivery is reduced, and consequently the growth rate in the developing offspring is depressed (33). However, no aspect of parturition or maternal/pup behavior was altered by this treatment. These data indicate that central oxytocin receptor stim-
ulation during mid and late gestation is essential for establishing normal oxytocin response characteristics during lactation.

The mechanisms through which oxytocin receptor stimulation during gestation alters systemic release of oxytocin in response to suckling during lactation are unknown. However, we propose that intranuclear release of oxytocin during pregnancy is a critical prerequisite for one or more of the adaptive changes that prepare magnocellular oxytocin neurons for the demands of parturition and lactation. CNS oxytocin has been implicated in several of the well-characterized adaptations that occur during gestation, as reviewed below.

**Increased Oxytocin Gene Expression and Neural Lobe Oxytocin Content**

Oxytocin mRNA expression has been measured during pregnancy, parturition, and lactation. Most studies (e.g., Refs. 1, 12, 26, 35, 56, 57, 75, 77), but not all (e.g., Refs. 19 and 79), report increased oxytocin gene expression during late gestation compared with early gestation or cycling animals. The increased oxytocin mRNA expression during this period is associated with increased hormone storage in the neural lobe (18, 51), perhaps in anticipation of the demands of parturition. It is likely that the changing ovarian hormone milieu of late pregnancy (i.e., gradually increasing estradiol and fall in progesterone) is important for increasing oxytocin mRNA expression, since mimicking these changes in ovariectomized rats also increases oxytocin mRNA in the hypothalamus (12). That ovarian hormones may increase oxytocin gene expression via an action of intranuclear oxytocin is suggested by the observation that oxytocin receptor blockade prevented the increase in oxytocin mRNA induced by a pregnancy-mimicking ovarian hormone treatment (48).

During lactation, central oxytocin receptor stimulation is necessary for enhanced oxytocin mRNA expression, as administration of a selective oxytocin receptor antagonist during this period reduced oxytocin mRNA expression (55). We have evaluated the effects of continuous, central infusion of an oxytocin receptor antagonist during mid and late gestation on the progressive increase in oxytocin mRNA observed during this period. Blockade of oxytocin receptors during gestation had no effect on the progressive increase in either oxytocin mRNA or neural lobe oxytocin during the course of pregnancy. This suggests that a central action of oxytocin is not involved in mediating the increased oxytocin expression in late gestation, in contrast to its importance during lactation. Thus, taken together, these data indicate that increased oxytocin gene expression is mediated by different mechanisms during gestation and lactation. Furthermore, these findings suggest that there are additional, redundant mechanisms that increase oxytocin mRNA during normal gestation that are not duplicated by ovarian hormone treatments designed to mimic pregnancy.

**Morphological Adaptations**

Profound anatomical changes in the oxytocin magnocellular system develop during gestation and persist throughout lactation. These include synaptic remodeling (68), increases in neuronal appositions and glial retraction (64, 65), and increased incidence of dye coupling suggestive of gap junctions (23). The anatomical alterations are clearly present by late gestation (21, 38, 64), and some may be evident by midgestation (day 15) (69). Several studies have suggested that at least some of the morphological changes characteristic of lactation are mediated by central actions of oxytocin (31, 37, 66, 67). For example, central administration of exogenous oxytocin in primaparous nonpregnant, nonlactating rats induced reversible changes in the soma and dendrites of magnocellular oxytocin neurons that could be prevented by administration of an oxytocin antagonist (67). Oxytocin also induces this plasticity in ovariectomized females treated with estrogen (37). Finally, oxytocin can induce these changes directly in hypothalamic slices taken from pregnant rats (31), as well as directly affecting GABAergic synaptic activity (66). These data indicate that oxytocin receptor stimulation, probably in combination with changes in estrogen and progesterone, is essential for the anatomical adaptations that occur during gestation and could account for changes in sensitivity and patterning of oxytocin release during parturition and lactation. However, the effect of centrally administered oxytocin antagonists on the normal morphological plasticity observed during pregnancy and lactation has not been assessed.

**Decreased Inhibition by GABA**

A series of papers by Brussaard and coworkers (9–11, 27) has revealed intriguing actions of intranuclear oxytocin release and interrelationships with other important neuromessengers during the period encompassing late pregnancy, parturition, and lactation, when dendritic nuclear release may be most critical. In brief, these investigators have shown that the largely inhibitory GABAergic control over magnocellular oxytocin neurons undergoes a striking plasticity during this period. In late gestation, when systemic and intranuclear release of oxytocin is low, the stoichiometry and clustering of GABA-A receptors subunits is configured such that this receptor is very sensitive to the facilitatory modulation exerted by the progesterone metabolite/neurosteroid allopregnanolone, the levels of which are high until late pregnancy, reflecting, in part, high circulating titers of progesterone. However, closer to the time of parturition, when there are a number of intrinsic structural and functional changes in the magnocellular oxytocin system, as reviewed above (32, 64), the dendritically released oxytocin reduces the sensitivity of GABA-A receptors to allopregnanolone, and the underlying mechanism appears to involve a phosphorylation event mediated by protein kinase C (27). The functional consequence of this alteration is that the oxytocin system becomes at least partially disinhibited from GABAergic influence prior to the secretory demands of parturition and lactation, which may be a natural constraint against inappropriate oxytocin release that could lead to premature uterine contractions.

Subsequently, during lactation, oxytocin further suppresses inhibitory GABAergic tone via a presynaptic effect that reduces release of GABA. This may, in turn, result from the excitatory influence of glutamate via NMDA receptors on intranuclear oxytocin release, which then acts as a retrograde messenger to inhibit GABA release (16, 17). A second example of retrograde messaging by dendritically released oxytocin may be on release of norepinephrine (15), which clearly exerts an obligatory excitatory influence on both systemic and dendritic oxytocin release (13).
Electrophysiological Properties of Oxytocin Neurons

As mentioned above, dendritic release of oxytocin within the SON and PVN appears critical to the coordinated bursting of oxytocin neurons adopted during lactation. The initial instigation of this release is likely driven by sensory afferents involving noradrenergic and glutamatergic signaling activated by suckling (13). This locally released oxytocin then appears to further promote its own release (39). Oxytocin facilitates recruitment of oxytocin neurons into the coordinated bursting pattern, and oxytocin antagonists severely disrupt this activity (29). The site of oxytocin’s action critical for this effect is not certain, and may involve both pre- and postsynaptic actions (28, 45, 59, 60, 75) and multiple signaling pathways.

Oxytocin receptor stimulation during gestation has been shown to alter plasticity of oxytocin neuron electrical and synaptic properties. Investigations of the membrane properties of oxytocin neurons during pregnancy and lactation have revealed changes in spike afterpotentials that would shape bursting activity. Depolarizing afterpotentials (DAPs) increase in incidence in oxytocin neurons by late pregnancy, whereas typically only a minority of oxytocin neurons (and a majority of VP neurons) exhibit these potentials (61). An increase in DAP expression would make oxytocin neurons more excitable (2), but it is not certain how long this effect persists into lactation, because by midlactation DAP incidence is not significantly different from virgin rats (58). The most consistent changes are in two varieties of Ca²⁺-dependent hyperpolarizing afterpotentials (AHPs), both of which would gate firing rate and the slower of which would more likely regulate burst length (58, 61–63). During lactation at least, these changes are not due to an increased Ca²⁺ current density but are related either to a change in AHP channel density or the interaction between Ca²⁺ and the Ca²⁺ sensor on the AHP channels. Although at first glance this result seems counterintuitive, increased AHPs are understandable when it is realized that the mammary gland desensitizes to prolonged oxytocin exposure, so short bursts of activity are needed for the discrete, bolus release of hormone during milk ejection to obtain maximally efficient milk ejection.

The AHP changes appear related to centrally released oxytocin, since intraventricular administration of a specific oxytocin antagonist during pregnancy completely blocked the normal plasticity of AHPs observed in late pregnant rats, without affecting VP neurons (63); the same treatment disrupts the timing of oxytocin release to suckling and reduces pup weight gain (33). The effect of the oxytocin antagonist is not acute, as it has no influence on AHPs when applied directly to slices from pregnant rats. Thus, oxytocin exerts long-term changes in protein expression and/or trafficking in addition to its acute neuromodulatory roles on membrane or synaptic properties. This is consistent with oxytocin’s ability to mimic morphological plasticity associated with central oxytocin activity both in vivo (67) and in vitro (31, 66), as well as with oxytocin’s persistent effects on long-term potentiation and memory during lactation (71). These latter effects appear mediated by oxytocin receptor coupling to MAP-kinase pathways and the upregulation of cAMP responsive element binding protein.

Conclusions

Figure 1 is a schematic diagram summarizing the neurotransmitter systems and predominant effects of central oxytocin in magnocellular nuclei during gestation and lactation. During lactation, intranuclear release of oxytocin within the PVN and SON has autocrine and paracrine effects on magnocellular oxytocin neurons that initiate and establish the pulsatile temporal pattern of systemic oxytocin secretion in response to suckling. Activation of noradrenergic, histaminergic, and possibly, glutamatergic, receptor systems in the magnocellular nuclei are necessary for suckling-induced release of central oxytocin during lactation. In addition, it appears that histamine, and possibly glutamate, induces release of intranuclear oxytocin by stimulating norepinephrine release.

It has been demonstrated that, similar to lactation, norepinephrine stimulates intranuclear oxytocin release during gestation, and opioids may have an inhibitory influence during the later stages of pregnancy. While the importance of central oxytocin during suckling on secretion into the systemic circulation has been well characterized, its role during gestation has been less thoroughly investigated. Because oxytocin receptor blockade specifically during pregnancy significantly alters systemic oxytocin secretion during lactation, actions of intranuclear oxytocin during gestation may be critical for programming the oxytocin system for the enhanced release anticipated during lactation. For example, the available evidence suggests that oxytocin receptor stimulation during gestation contributes to morphological changes in oxytocin neurons, disinhibition of oxytocin neurons in response to GABA, and to induction of specific membrane characteristics of oxytocin neurons that occur during gestation. However, stimulation of central oxytocin receptors does not appear to be essential for increased hypothalamic oxytocin mRNA, and oxytocin content in the neural lobe during normal pregnancy.

Taken together, these observations indicate that intranuclear release of oxytocin within the magnocellular nuclei, which is under stimulatory control by norepinephrine during both gestation and lactation, is necessary for the normal pattern of systemic oxytocin release in response to suckling. This pattern of release, in turn, is essential for providing adequate nutrition to the suckling offspring.

Fig. 1. Schematic representation of neurotransmitters directly implicated in regulation of intranuclear oxytocin release in magnocellular neurons, and responses to oxytocin receptor stimulation during gestation and lactation (symbols). EEA, excitatory amino acids; GABA, γ-aminobutyric acid; HA, histamine; NE, norepinephrine; OT, oxytocin.
GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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