Hindbrain cytoglucopenia-induced increases in systemic blood glucose levels by 2-deoxyglucose depend on intact astrocytes and adenosine release

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Rogers RC, Ritter S, Hermann GE. Hindbrain cytoglucopenia-induced increases in systemic blood glucose levels by 2-deoxyglucose depend on intact astrocytes and adenosine release. Am J Physiol Regul Integr Comp Physiol 310: R1102–R1108, 2016. First published April 13, 2016; doi:10.1152/ajpregu.00493.2015.—The hindbrain contains critical neurocircuitry responsible for generating defensive physiological responses to hypoglycemia. This counter-regulatory response (CRR) is evoked by local hindbrain cytoglucopenia that causes an autonomously mediated increase in blood glucose, feeding behavior, and accelerated digestion; that is, actions that restore glucose homeostasis. Recent reports suggest that CRR may be initially triggered by astrocytes in the hindbrain. The present studies in thioptobarbital-anesthetized rats show that exposure of the fourth ventricle (4V) to 2-deoxyglucose (2DG; 15 μmol) produced a 35% increase in circulating glucose relative to baseline levels. While the 4V application of the astrocytic signal blocker, fluorocitrate (FC; 5 mmol), alone, had no effect on blood glucose levels, 2DG-induced increases in glucose were blocked by 4V FC. The 4V effect of 2DG to increase glycemia was also blocked by the pretreatment with caffeine (nonselective adenosine antagonist) or a potent adenosine A1 antagonist (8-cyclopentyl-1,3-dipropylxanthine; DPCPX) but not the NMDA antagonist (MK-801). These results suggest that CNS detection of hypoglicemia is mediated by astrocytes and that astrocytic release of adenosine that occurs after hypoglycemia may cause the activation of downstream neural circuits that drive CRR.

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GLUCOSE IS THE PRIMARY ENERGY source for cellular metabolism, especially for neurons. Thus, the maintenance of appropriate serum glucose levels is critical for brain function and survival. It is no surprise that there are multiple, overlapping glucoregulatory systems with sensors in the periphery as well as the CNS that function to balance energy influx and energy expenditure, as well as caloric regulation, adjustment of metabolic rate, nutrient balance, food preference, and circadian rhythms (6, 54, 60, 70, 74). Glucoprivic feeding is elicited in animals receiving large chronic doses of leptin, i.e., a situation signaling extreme metabolic repletion (76). On the other hand, destruction of medullary neurons critical to the expression of the CRR does not significantly affect daily feeding behavior (38). The advantage of such a system in the management of a physiological emergency is that it retains its sensitivity to the defended parameter under practically all other physiological circumstances (20, 51, 61, 74) This exclusivity of CRR circuitry can help identify CRR vs. non-CRR metabolic and feeding control elements. CRR circuit elements are probably not affected by, for example, leptin or α-melanocyte-stimulating hormone (α-MSH) inputs, while non-CRR regulatory feeding and metabolic control elements are biased in their response to glucoprivic stimuli in the presence of signals corresponding to repletion state (20, 51, 61, 74).

Recent data from our laboratory as well as others (36, 45, 47, 49) suggest that detection of a low-glucose state by brain stem astrocytes could be the trigger to the initiation of CRR. For example, transgenic mice in which GLUT2 transporter (a critical component of most glucodetection mechanisms) has been knocked out, do not increase glucagon secretion in response to hypoglycemia (i.e., one of the components of the CRR). However, such defects in eliciting CRR can be “rescued” by the selective reexpression of GLUT2 in astrocytes, but not neurons (10, 45). Our recent live-cell calcium (Ca2+) imaging studies demonstrated that astrocytes in NST increase cytoplasmic Ca2+ in response to decreases in glucose concentration. Exposure to 2-deoxyglucose (2DG) reduces cellular glucose utilization and elicits a similar increase in cytoplasmic Ca2+ in NST astrocytes (47).

Our in vivo, neurophysiological studies showed that this 2DG-induced glucoprivic challenge lowers the excitability of inhibitory “gastric” vago-vagal reflex sensory neurons in the NST. Gastric-NST neurons strongly inhibit gastric parasympathetic excitatory neurons in the dorsal motor nucleus of the vagus (DMN) as part of their role in the control of gastric motility. So, the reduction of NST activity by glucoprivic stimuli leads to a sharp increase in DMN firing activity resulting in an increase in gastric motility (36). This modulatory effect of glucoprivic conditions on NST neurons appears to be dependent on normal, functioning astrocytes. Further studies in intact animals verified that both dorsal medullary and systemic
glucoprivation significantly increases gastric motility (36), as would be expected given the inhibitory nature of dorsal medul- lary vago-vagal reflex control (63). Significantly, astrocyte inactivation blocked this gastric component of the CRR (36). These in vivo and ex vivo results explain century-old observ- ations connecting acute food deprivation and hypoglycemia with increased gastric motility and accelerated digestion in CRR (9, 13, 18, 67).

Therefore, we tested the hypothesis that medullary astro- cytes are also necessary for the CRR-mediated increase in blood glucose in response to hindbrain cytoglucopenia. Fourth ventricular administration of the cytoglucopenia-inducing agent 2DG into thiobutabarbital-anesthetized rats was used to elicit the CRR effect on plasma glucose levels. Preexposure of the fourth ventricle to a selective blocker of astrocytic metabo- tropic signaling, fluorocitrate (71), was used to evaluate astro- cytic involvement in CNS glucodetection circuits that drive different aspects of CRR. Pharmacologic intervention of known gliotransmission pathways involving either glutamate or adenosine was then performed.

It has been estimated that about half of the overall, inte- grated response to hypoglycemia is driven by peripheral ner- vous inputs, primarily from the portal/mesenteric afferents (20) with inputs to this hindbrain neurocircuitry. Therefore, we tested the hypothesis that medullary astrocytes are also neces- sary for the CRR-mediated increase in blood glucose following systemic glucoprivation.

MATERIALS AND METHODS

All experimental procedures were conducted with the approval of the Pennington Biomedical Research Center’s Institutional Animal Care and Use Committee and were performed according to the guidelines set forth by the National Institutes of Health. Long-Evans rats of either sex (females = 26; males = 28; body weight between 250 and 450 g; age range 4–6 mo) obtained from the Pennington Biomedical Research breeding colony were used in these studies. Animals were housed in a temperature-controlled room under 12:12-h light-dark cycle and provided water and food ad libitum.

Animals were deeply anesthetized with thiobutabarbital [Inactin; Sigma Aldrich, St. Louis, MO; 150 mg/kg ip; long-term anesthesia with minimal interference on autonomic reflexes (7)] and secured in a stereotactic frame. Using aseptic techniques, we exposed the floor of the fourth ventricle (4V) by removing the occipital skull plate and opening the foramen magnum; dura and arachnoid layers were re- tracted. Once all preparatory surgery was complete, systemic glucose levels were monitored via blood samples obtained by tail-vein punctures every 30 min. Glucose concentrations of the 3–4-μl blood droplets were determined with Freestyle Lite glucose test strips and glucometer (Abbott Diabetes Care, Alameda, CA). To ensure that baseline blood glucose levels were stable, samples were taken at 0, 30, and 60 min after all preoperative surgery was complete. Baseline levels of blood glucose (mg/dl) within each group were averaged and compared in a one-way ANOVA (Fig. 1). At the 60-min point, each animal was exposed to one of the following 4V experimental condi- tions: 1) control: 10 μl of either saline (n = 5) or 1:4 DMSO/saline (n = 5) (i.e., vehicle for MK-801, caffeine, or DPCPX); total n = 10; 2) fluorocitrate (FC; astrocytic metabotropic signal blocker; Sigma Aldrich) alone [5 nmol in 10 μl; (21, 33, 43, 68)]; n = 5, 3) 2DG (Sigma Aldrich) alone [18 μmol in 10 μl; (14, 36)]; n = 6, 4) FC followed 30 min later by 2DG (FC+2DG); n = 5, 5) caffeine alone (nonselective adenosine receptor antagonist; Sigma; 130 nmol in 6 μl; Ref. 59); n = 5, 6) caffeine followed 30 min later by 2DG (caffeine+2DG); n = 5, 7) A1-specific adenosine antagonist: 8-cyclopentyl-1,3-dipropylxanthine [DPCPX; Sigma; 2 nmol in 2 μl (41)] followed 30 min later by 2DG (DPCPX+2DG); n = 5, and 8) MK801 [nonselective NMDA antagonist, Sigma; 18 nmol in 10 μl (12)] followed 30 min later by 2DG (MK801+2DG); n = 5.

Although other, previous studies of central 2DG effects have used awake rats equipped with chronic ventricular cannulas to deliver the challenge (15, 77), we chose instead to use thiobutabarbital-anesthe- tized rats and direct application of agents to the floor of the fourth ventricle to match our recent physiological studies of hindbrain 2DG cytoglucopenia effects on gastric motility and gastric vago-vagal reflex circuitry (36). Additionally, we used the same amount of 2DG in both the motility (36) and these blood glucose studies (i.e., 3 mg = 18 μmol). This amount of centrally administered 2DG is a fraction of that used in previous awake studies [i.e., 60–80 μmol iv (15, 77)].

The 1:4 DMSO/Saline Group served as a control for both those groups that required the partial DMSO solution as a vehicle (i.e., MK-801, caffeine, or DPCPX), as well as a control for the osmolality challenge of 2DG alone.

Blood glucose levels were monitored every 30 min for a minimum of 180 min. Kinetics of the glycemic responses are shown in Fig. 2. For statistical analysis, changes in blood glucose levels were expressed as percent changes relative to baseline for each individual animal. Thus, each animal served as its own control. These normal- ized values of maximal percent change in blood glucose levels for each animal were averaged and subjected to a one-way analysis of variance followed by Dunnett’s post hoc tests for statistical signifi- cance (P < 0.05). In a subset of rats (n = 4 males, 4 females), all preparations were as described above, including anesthesia and open cranium. The hindbrain was treated either with saline or FC; the 2DG challenge (15, 77), we chose instead to use thiobutabarbital-anesthe- tized rats and direct application of agents to the floor of the fourth ventricle to match our recent physiological studies of hindbrain 2DG cytoglucopenia effects on gastric motility and gastric vago-vagal reflex circuitry (36). Additionally, we used the same amount of 2DG in both the motility (36) and these blood glucose studies (i.e., 3 mg = 18 μmol). This amount of centrally administered 2DG is a fraction of that used in previous awake studies [i.e., 60–80 μmol iv (15, 77)].

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RESULTS

Individual baseline blood glucose levels ranged from 70 to 95 mg/dl (overall average ± SE = 80.3 ± 0.8 mg/dl; Fig. 1) in these nondeprived, anesthetized rats. There were no signif-

![Graph](image_url)

Fig. 2. Changes in blood glucose levels in response to fourth ventricular application of 2-deoxyglucose (2DG). A: fourth ventricular exposure to 2DG, in the thiobutabarbital-anesthetized rat, produced significant elevations in blood glucose levels relative to baseline levels (% change) peaking within 150 min after fourth ventricle (4V) application. However, 4V pretreatment of FC blocked the effect of subsequent 2DG to increase blood glucose. (2DG was applied at time 0). B: fourth ventricular application of vehicle controls (saline or 1:4 DMSO/saline), FC alone, or caffeine alone, had no effect on glucose levels (Figs. 2B and 3). However, pretreatment of the fourth ventricle with FC blocked the effect of subsequent 2DG to increase blood glucose. (2DG was applied at time 0).

![Graph](image_url)

Fig. 3. Fourth ventricular exposure to 2DG, in the thiobutabarbital-anesthetized rat. Maximal percent change in blood glucose levels relative to baseline levels were averaged within each group. Maximal peak responses for the 2DG-alone group averaged 36.0 ± 7.4% change. While 4V application of vehicle controls (saline or 1:4 DMSO/saline) or FC (alone) or caffeine (alone; data shown in Fig 2B) had no effect on glucose levels, pretreatment of the 4V with FC blocked the effect of subsequent 2DG to increase blood glucose (FC/2DG: 3.1 ± 2.0%). Similarly, pretreatment with caffeine or DPCPX suppressed the glycemic effects of 2DG (caffeine/2DG = 5.7 ± 2.8%; DPCPX/2DG = 11.1 ± 2.4%). In contrast, the NMDA antagonist MK801 did not block the 2DG effect to increase blood glucose (MK801/2DG = 22.2 ± 6.4%). One-way ANOVA $F_{7,38} = 9.78, P < 0.0001$; Dunnett’s post hoc test *$P < 0.05$.

Similar to previous reports in the glucoprivic effects of 2DG to elicit elevations in blood glucose levels (15, 20, 38, 62, 74, 77), exposure of the dorsal medulla to 18 μmol 2DG produced significant elevations (% change) in blood glucose levels relative to baseline levels starting within 90 min of the challenge (Fig. 2A) and peaking at ~150 min after 4V application. Maximal percent change in blood glucose levels was determined for each animal based on their individual baseline and peak responses. Maximal peak responses for the 2DG-alone group averaged 36.0 ± 7.4% change (Fig. 3).

Fourth ventricular application of vehicle controls (saline or 1:4 DMSO/saline), FC alone, or caffeine alone, had no effect on glucose levels (Figs. 2B and 3). However, pretreatment of the fourth ventricle with FC blocked the effect of subsequent 2DG to increase blood glucose. (2DG was applied at time 0).
2DG to increase blood glucose (FC + 2DG: 3.1 ± 2.0%; Figs. 2A and 3). Similarly, pretreatment with the adenosine antagonists, caffeine and DPCPX, suppressed the glycemic effects of 2DG (caffeine + 2DG = 5.7 ± 2.8%; DPCPX + 2DG = 11.1 ± 2.4%; Figs. 2C and 3). In contrast, the NMDA antagonist, MK801, did not block the 2DG effect to increase blood glucose (MK801 + 2DG = 22.2 ± 6.4% change relative to baseline; Figs. 2C and 3). One-way ANOVA ($F_{7,38} = 9.78, P < 0.0001$) and the Dunnett’s post hoc test (*$P < 0.05$) were performed.

Subcutaneous 2DG (100 mg·kg$^{-1}$·ml$^{-1}$) elicited increased blood glucose levels (Fig. 4) similar to that reported by Smith et al. (66). Pretreatment with fourth ventricular FC (5 nmol) 30 min prior to subcutaneous delivery of 2DG significantly suppressed the hyperglycemic effect of systemic 2DG ($t = 3.074; P = 0.02$; Fig. 4B).

**DISCUSSION**

Our data show that 4V exposure to 2DG in thiobutabarbital-anesthetized rats can elicit the expected elevation in blood glucose of CRR, as has been previously reported in response to intracranial or peripheral challenges in the awake animal (15, 20, 38, 62, 74, 77). This centrally induced CRR effect on glycemia was blocked by exposure of the 4V to fluorocitrate, a selective blocker of astrocyte metabolic signaling and gliotransmission (71). Thus, these data are consistent with the hypothesis that hindbrain astrocytes are important components of CNS glucodetection circuits that drive multiple aspects of CRR (36, 45, 47). Further, the 4V application of adenosine receptor antagonists (caffeine and the A1 antagonist, DPCPX) also suppressed the hindbrain 2DG effect to initiate CRR. This is in contrast to the lack of effect of the NMDA antagonist (MK801) to suppress the 2DG-evoked increase in glycemia. Thus, these data suggest that astrocytes are important sensors of low-glucose availability (central 2DG-induced glycemia). In turn, astrocytes are probably signaling this “hypoglycemic condition” to appropriate neurons in the hindbrain neurocircuity involved in CRR reflexes via purinergic agonists, such as adenosine. Fourth ventricular FC also suppresses the effect of systemic 2DG to provoke hyperglycemia. Together, these data suggest that astrocytes in the hindbrain are not only necessary for the detection of hindbrain cytoglucopenia but are also important for the accurate integration of cytoglucopenia information from the periphery.

Astrocytes are the most abundant cells within the central nervous system. A single astrocyte may contact thousands of synapses and, along with presynaptic terminals and postsynaptic neurons, will form what has been termed the “tripartite synapse” (4, 11, 31, 32, 57), in which synaptic efficacy is regulated by astrocytes, as well as the postsynaptic responsiveness to afferent input and neuronal excitability. Astrocytes are, themselves, subject to modulation by most of the “classic” neurotransmitters (e.g., glutamate, norepinephrine) that are released from neuronal presynaptic terminals (34, 48, 71), as well as gliotransmitters released by other astrocytes (30). Additionally, hormones, circulating factors, such as thrombin, changes in endogenous physiological signals such as O₂/CO₂ or pH, and changes (particularly, reductions) in glucose concentration or metabolic availability can all increase astrocytic calcium levels (3, 5, 26, 29, 35, 39, 47). This increase in astrocytic calcium is coupled to a release of gliotransmitters in processes similar to neurotransmission (31, 32, 57). Glutamate, ATP, adenosine, and D-serine are among the agents now accepted as gliotransmitters (2, 5, 17, 23, 44, 55).

The astrocytic release of adenosine may be especially relevant to the connection between astrocytic glucodetection and the activation of downstream CRR mechanisms. There is good evidence that adenosine is released rapidly within the CNS in response to glucoprivation (69). A number of downstream effects of CNS hypoglycemia are known to be blocked by antagonists to the A1 adenosine receptor (52, 69). There are at least two mechanisms by which astrocytes subjected to hypoglycemia could increase the adenosine concentration in the vicinity of neurons. First, adenosine can be released directly from astrocytes through reversible equilibrating nucleoside transporters in the cell membrane (50), a release that is not coupled to cytoplasmic calcium. This would occur as a consequence of the exhaustion of cytoplasmic ATP and the buildup of adenosine. Second, ATP released by calcium-dependent gliotransmission after detection of low extracellular glucose is readily converted to adenosine via the action of ectonucleotidases (4, 40). This sort of astrocyte purinergic gliotransmission has already been implicated in chemoreflex regulation of respiration (22). Adenosine release from astrocytes in response to metabolic stress is well documented. However, the mechanism connecting adenosine release, ATP catabolism, and astrocyte calcium signaling remains controversial (43). While glucose-
nia-driven adenosine release from neurons might also occur, if that neuronal source were the predominant mechanism for the subsequent CRR response, then the astrocyte metabolic blocker, FC, should not have had the effect to block 2DG-induced increases in blood glucose.

Adenosine acting on the A1 receptor typically causes neuronal inhibition (24, 64). Such inhibition of neuronal activity would explain our observations on glucoprivation effects on gastric vago-vagal control of motility. Glucoprivation causes a dramatic increase in gastric motility (9, 13, 14, 36). This effect on gastric motility is dependent on intact astrocyte signaling (36). Glucoprivic stimuli (e.g., 2DG) cause NST neurons to be less excitable and less excited by vagal afferent inputs from the gut. NST neurons receiving vagal afferent inputs from the gut, in turn, powerfully inhibit neurons in the DMN that are responsible for activating gastric motility (36, 63). Therefore, it is possible that adenosine release from glucosensitive astrocytes could be responsible for the inhibition of gastric vagal NST neurons and the consequent increase in DMN-mediated gastric motility. Further, it is also possible that adenosine inhibition of NST neurons could also release ventrolateral medullary neurons from tonic inhibition, thus increasing downstream sympathetic activity. These medullary neurons are well known to be involved in the control of sympathetic activity that impinges on cardiovascular as well as glycemic control (61, 72).

The attribution of these glucoprivic sensing effects on astrocytes is due to the specificity of fluorocitrate (FC) to suppress astrocytic function. Although high doses (micromolar amounts) of FC can derange astrocyte mitochondrial function and have secondary repercussions for neuronal activity [e.g., resulting in seizures or death as a result of the withdrawal of the stabilizing influences of glia over neuronal excitability (27, 37, 58)], nanomolar amounts (as used in our studies) are astrocyte-specific and entirely reversible (16, 71). The specificity of action of FC in glial cells is supported by several, now classic, biochemical observations. First, glial cells avidly take up and metabolize FC, while neurons do not (16, 53). FC is an aconitase inhibitor (16); the metabolic result of which is rapid accumulation of citrate. This effect is not observed in neurons (75). Furthermore, in live-cell imaging studies, we have shown that FC at nanomolar doses: 1) only inhibits astrocytes, 2) specifically inhibits metabolotropic and not ionotropic pathways of astrocytes, and 3) is reversed within minutes of washout (71).

Mechanistic explanations of FC-astrocyte inhibition are rooted in classic biochemical studies (16, 42). Buffa and Peters (8) were among the first to observe the metabolic overflow of citrate following FC exposure. Citrate is a potent cation chelator, and these early authors postulated that an overflow of citrate would disturb cellular excitability through the inactivation of calcium. This theory obtained currency with the observation that FC effects can be mimicked by the application of calcium chelators which are, themselves, buffered by the co-application of excess calcium (37). It is now believed that the FC-induced increase in intracellular citrate produces a buffering of calcium, as well as magnesium and manganese ions. This effect may be responsible for not only the elimination of calcium-dependent gliotransmission but also for the blockade of glia-specific metabolic pathways dependent on these cations (16, 25, 42, 56).

**Perspectives and Significance**

The present study suggests that astrocytes are important sensors of low glucose availability. In turn, astrocytes are probably signaling this “hypoglycemic condition” to appropriate neurons in the hindbrain neurocircuity involved in CRR reflexes via purinergic agonists, such as adenosine. Together, these data suggest that astrocytes in the hindbrain are not only necessary for the detection of hindbrain cytoglucopenia but are also important for the accurate integration of cytoglucopenia information from the periphery.

There is now good evidence that astrocytes in the NST and other circumventricular regions perform important functions as chemosensors. NST astrocytes have been suspected of having a sensitivity to acute glucoprivation (78). This concept was supported by the work of Marty et al. (45, 46), as well as our own (47, 49), showing that astrocytes may be essential to the detection and initiation of physiological reactions to rapid reductions in glucose availability to the brain. The anatomical relationships between the vascular supply, blood cells, and the neuropil certainly suggest that astrocytes occupy a “favored” (i.e., gateway) position from the perspective of monitoring material flux into the brain. Glial cells, including astrocytes, literally form vascular-neuropil and ventricular-neuropil diffusion barriers. But these cells also possess transporters that allow the penetration of even large-sized signal molecules, such as cytokines into the neuronal matrix. Additionally, small nutrient molecules, such as glucose, ions, and blood gases access the neuropil by passing through or around astrocytes. Thus, this arrangement places glial cells in an ideal position to detect the fluxes of physiologically critical solutes and exert early influence on adjacent neural systems dedicated to homeostatic regulation of these agents (19). In addition to the counter-regulatory control of glucose homeostasis, glial cells have also been identified as critical detectors of PCO2 for respiratory control by the ventral medulla (28) and sodium ions for salt intake control by the subfornical organ (65, 73). Evidence is accumulating that glia may be important for the detection of different sensory modalities (e.g., PCO2, pH, and blood glucose levels) and transmitting sensory information to the relevant neural networks involved with the maintenance of homeostasis (19, 28).

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

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