Published in final edited form as:

Placenta. 2015 February ; 36(2): 115–120. doi:10.1016/j.placenta.2014.12.009.

PET/CT Imaging Reveals Unrivaled Placental Avidity for Glucose Compared to Other Tissues

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Abstract

Introduction—The goal of this study was to define the kinetics of glucose transport from maternal blood to placenta to fetus using real time imaging.

Methods—Positron emission tomography (PET) imaging of the glucose tracer [¹⁸F]fluorodeoxyglucose (FDG) was used to temporally and spatially define, *in vivo*, the kinetics of glucose transport from maternal blood into placentae and fetuses, in the late gestational gravid rat. Computed tomography (CT), with intravenous contrast, co-registered to the PET images allowed anatomic differentiation of placentae from fetal and maternal tissues.

Results—FDG was rapidly taken up by placentae and subsequently appeared in fetuses with minimal temporal lag. FDG standardized uptake values in placentae and fetuses approached that of maternal brain. In both anesthetized and awake dams, one quarter of the administered FDG ultimately was accrued in the collective fetuses and placentae. Accordingly, kinetic modeling demonstrated that the placentae had very high avidity for FDG, 2-fold greater than that of the fetus and maternal brain, when accounting for the fact that fetal FDG necessarily must first be taken up by placentae. Consistent with this, placental expression of *glucose transporter 1* exceeded that of all other tissues.

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Discussion—Fetal and placental tissues place a substantial glucose metabolic burden on the mother, owing to very high avidity of placenta for glucose coupled with the large relative mass of fetal and placental tissues.

Conclusions—The placenta has a tremendous capacity to uptake and transport glucose. PET/CT imaging is an ideal means to study metabolite transport kinetics in the fetoplacental unit.

Introduction

The fetus depends on placental transport of glucose from the maternal circulation [1–3]. Aberrant glucose transport leads to complications including altered birth weight, neonatal hypoglycemia, and respiratory distress syndrome [4,5].

The net transport of glucose is from the mother to placenta and placenta to fetus. Placental glucose can be metabolized, returned to maternal circulation, or transported to the fetal circulation [6]. Fetal circulating glucose can be taken up and metabolized by fetal tissues or returned to the placenta [7]. By contrast, 2-deoxyglucose and [¹⁸F]fluorodeoxyglucose (FDG) are not metabolized beyond phosphorylation [8]. Thus, these deoxyglucose compounds are commonly used glucose transport tracers [9,10].

FDG transport in pregnant rats has been studied by positron emission tomography (PET) [11,12], though without spatially resolving placental from fetal tissues. Herein, co-registered computed tomography (CT) employing a contrast agent that does not cross the placenta [13] is used to anatomically distinguish fetal, placental, and maternal tissue in gravid rats. This enables determination of separate glucose uptake kinetics for placenta versus fetal tissues. It was hypothesized that this approach would permit quantification of the total FDG flux through the placenta including the FDG which ultimately accumulates in the fetus, thus providing a more complete description of the glucose handling properties of the placenta.

Methods

Animals

Experimentation was performed within the regulations of the Animal Welfare Act and the National Institutes of Health Guide for the Care and Use of Laboratory Animals and was approved by the Institutional Animal Care and Use Committee of the University of Iowa. Timed, pregnant rats (Hsd:Sprague Dawley SD; Harlan Laboratories, Inc., Indianapolis, IN) underwent placement of left femoral artery and vein catheters on gestational day 18 (GD18). Saline containing 2 U/ml heparin was infused at 10 μ L/min from GD18 to GD20 via both catheters.

PET/CT Imaging

After overnight fast, three GD20 rats were anesthetized with isoflurane (4% induction, 2% maintenance) delivered in oxygen (Medical grade) [12]. Anesthetized rats were placed supine on a heated bed in the gantry of an Inveon (Siemens Knoxville, TN) preclinical PET/CT/SPECT (Inveon Acquisition Workplace, version 1.5). FDG, 1411 ± 210 μ Ci/kg, was infused through the femoral vein catheter over 2 minutes. Dynamic PET imaging,

focused on the abdomen (tail base through inferior thorax), was initiated at the start of the FDG infusion (Figure 1A) and maintained in continuous listmode data acquisition for 90 minutes, comprised of 9 60 sec, 3 120 sec, and 15 300 sec frames. Blood samples, 50 µl from femoral artery catheter or tail capillary, were collected during the dynamic PET at 0, 5, 10, 15, 20, 25, 30, 40, 50, 60, and 90 minutes after FDG administration. Thereafter, without repositioning, contrast (10 mL/kg iohexol 300 mg/mL) was infused into the left femoral vein over 10 min. Ten minutes after completed contrast infusion, undisturbed dams were euthanized by intravenous pentobarbital. Ten minutes thereafter, a CT (50 kV, 500 µA, 99 microns, 360° rotation in 360 steps) was acquired. A final, whole-body PET was acquired in two 10 min segments, caudal then cranial, with overlap in the superior-abdomen for reconstruction. Each PET was coupled to an attenuation correction CT acquired in the same scanner workflow. Each acquired PET image consisted of a 128×128×159 matrix at a voxel size of 0.8×0.8×0.8mm; CT image, a 1024×1024×1024 matrix at a voxel size of 0.1×0.1×0.1mm. Maternal tissues, fetuses, and placentae were collected by Caesarean section, blotted, and weighed. Decay corrected FDG in serum and tissues was determined by calibrated γ NaI well-counter (905 series, Maestro software, Ortec, Oak Ridge, TN) [11,12].

Image Analysis

Decay-corrected PET images were reconstructed using filtered back-projection, a Ramp filter (FBP/Ramp) with scatter correction and CT-based attenuation correction. Contrast enhanced CT data were reconstructed using a down sample factor of 2, bilinear interpolation, Shepp-Logan reconstruction filter, and a beam hardening correction. PET images were co-registered to CT data (PFUSION tool, PMOD Technologies, Zurich, Switzerland). Volumes-of-Interest (VOIs) were manually defined on the contrast enhanced CT. Six-to-ten fetoplacental units (FPU) were defined per scanned dam, chosen randomly from FPU that were spatially non-adjacent to the bladder's highly intense FDG accumulation. Standardized uptake values (SUV) were determined from PET (SUV_{PET}) and well-counter (SUV_{well}) measures of radioactivity [11]. Time-activity curves (TACs) were constructed from dynamic PET data and scaled in SUV units.

Kinetic Modeling

Patlak modeling determines the net transfer rate of FDG into tissues that exhibit irreversible tracer accumulation [14] and has been applied to the FPU taken as a whole [11]. Here, a Patlak model treating the fetus and placenta as distinct entities has been derived as detailed in Supplemental Methods. This model accounts for the fact that fetal FDG necessarily first enters the placenta. The resultant Patlak rates are

$$K_{patlak,fetal} = \frac{k_1 k_5 k_7}{(k_2 + k_3 + k_5)(k_6 + k_7) - k_5 k_6}$$

and

$$K_{patlak,placental} = \frac{k_1(k_5 k_7 + k_3 k_6 + k_3 k_7)}{(k_2 + k_3 + k_5)(k_6 + k_7) - k_5 k_6} = K_{patlak,fetal} + K_{patlak,placenta-alone}$$

where $K_{Patlak,fetal}$, $K_{Patlak,placenta-alone}$ and $K_{Patlak,placental}$ are the net influx rate constants for FDG accumulation in the fetus, in placenta-alone (i.e. neglecting fetal FDG), and for total FDG accumulation mediated by the placenta (i.e. considering fetal FDG), respectively. Serum ^{18}F specific activity was used as the input function for Patlak modeling. Manual blood sampling was not rapid enough to adequately capture the peak ^{18}F activity that occurred with the FDG infusion. Therefore, a hybrid input function (SUV_{hyb}) was constructed in which FDG concentrations prior to the first serum sample were image-derived whereas subsequent FDG concentrations were derived from serum sampling.

Fractional uptake rates (K_{FUR}) were calculated as described [11], except for placenta where the considerations discussed above regarding $K_{Patlak,placental}$ apply. Thus analogously, the total K_{FUR} mediated by each placenta was determined from the rate observed in that placenta alone plus its corresponding fetus: $K_{FUR,placental} = K_{FUR,placenta-alone} + K_{FUR,fetal}$. Using this newly derived approach, well counter data from published PET experiments (N=11 pregnant dams) [11] under identical control conditions were utilized in addition to the fresh data collected for this study.

FDG Studies in the Awake State

To examine potential confounding of FPU metabolism by anesthesia, four dams were studied in the awake state. These awake studies were identical to anesthetized studies except as follows. A femoral artery catheter was not placed. No anesthesia was administered on the day of imaging. After FDG administration via femoral vein catheter, dams were left undisturbed. CT contrast was administered 95 min after FDG administration, with euthanasia by pentobarbital infusion 5 minutes thereafter. CT and whole-body PET were then performed as in the anesthetized studies.

Glucose Transport 1 Gene Expression

Glucose transporter 1 (GLUT1) expression levels were mined from public gene expression profiling data of mouse and human tissues [15,16]. Data was obtained from <http://biogps.org/gene/20525/> (accessed May 2, 2013). Mouse “1” data was from GEO accession #GSE10246, probe set 1426599_a_at. Mouse “2” data was from GEO accession #GSE1133, probe set gnflm02785_a_at. Human data was from GEO accession #GSE1133, probe set 201250_s_at.

Statistical Analyses

The statistical significance of pairwise comparisons was determined by Student's t-tests and of comparisons between multiple groups determined by one-way ANOVA followed by Tukey's HSD test for pairwise significance. Correlation between groups was assessed by Pearson's product-moment coefficient. Means $\pm$ standard error of measurement are reported.

Results

Radiographic Distinction of Placental from Fetal Tissues

Placentae, compared to fetuses, demonstrated increased density on contrast-enhanced CT (Figure 2A). Fetuses were identified using the fetal skeleton as a landmark. To test the

accuracy of fetal/placental radiographic discrimination, CT identified VOIs were compared to the weighed mass of each fetus and placenta, assuming a density of 1 g/cm³ for placentae [17,18] and fetuses [19]. Mean fetal and placental volumes were 3.4±0.1 cm³ and 0.7±0.04 cm³ by CT and 3.7±0.1 cm³ and 0.6±0.02 cm³ by weight/density, respectively (p=non-significant, paired t-test, N=24 FPU, 3 dams). CT volumes and weight/density measures were highly correlated (p<0.001, N=24 placentae and 24 fetuses, 3 dams). Example co-registrations of PET and CT are shown in Figure 2A,B. All rats remained euglycemic during study (Table 1).

Temporal Disposition of Glucose Tracer

Dynamic PET imaging encompassed only abdominal structures. PET confirmed rapid FDG infusion, evidenced by the catheter and inferior vena cava TACs (Figure 3A). As expected from dilution of infusate into venous blood, FDG intensity in the inferior vena cava was less than in the catheter. SUV_{hyb} serum TACs showed a singular peak with subsequent decay. The kidneys and bladder quickly accumulated FDG consistent with urinary clearance of FDG. Placentae also accumulated FDG rapidly, achieving an SUV_{PET} of over 2 by 15 minutes, with minor increases thereafter. Fetal FDG exhibited a similar TAC, albeit shifted later in time and ultimately achieving a lower SUV_{PET} than in placentae. Importantly, there was no decrement of placental or fetal SUV_{PET} over time. Liver SUV_{PET} initially increased but then rapidly diminished. There was minimal FDG accumulation in skeletal muscle. Representative images from the dynamic PET allowed visualization of these findings (Figure 3B).

Final, Whole-Body Glucose Tracer Disposition

Final FDG disposition was assessed by whole-body PET (Figure 3C), 140 minutes after FDG administration, accomplished in two overlapped bed positions sufficient to scan the entire rat neglecting the tail. Fetal FDG concentrations (SUV_{PET}) were lower than that of placenta concentrations (Figure 4A). Placental SUV_{PET} values rivaled that of the maternal brain. The accumulated fraction of the administered FDG dose was greater for each fetus compared to its corresponding placenta (Figure 4B). Total FDG was greater per fetus than in the maternal heart and brain. Summing across all pups and placentae, the accumulated FDG amounted to 26±2% of the administered FDG dose (Table 2). SUV_{well} was highly correlated with SUV_{PET} (Figure 4C).

FDG Avidity and Glucose Metabolism

Supporting Patlak modeling assumptions, FDG irreversibly accumulated in placentae and fetuses as evidenced by no decrement over time in their SUV_{PET} (Figure 3A). This indicates that k_4 and k_8 are negligible over the time frame studied. A Patlak-based model accounting for the fact that all fetal FDG necessarily was first transported into its corresponding placenta (Supplemental Methods) was used to determine the net FDG influx rates into placentae and fetuses, yielding $K_{Patlak,placental}$ and $K_{Patlak,fetal}$. $K_{Patlak,placental}$ was 2-fold greater than $K_{Patlak,fetal}$ (0.025±0.001 mL/cm³/min versus 0.010±0.0006 respectively), which was markedly greater than $K_{Patlak,skeletal-muscle}$ (0.001±0.0002) (Figure 5A). Maternal liver was not subject to Patlak analysis, as it does not irreversibly trap FDG. Fractional

uptake rates (K_{FUR}) determined from well-counter data allowing assessment of tissues outside the dynamic PET imaging view. K_{FUR} was highest in placenta, over 2-fold less in fetuses and maternal brain and heart, and even less in maternal skeletal muscle (Figure 5B).

K_{FUR} and K_{Patlak} are dependent on tracer concentrations rather than total tracer amounts, and thus are in some sense agnostic of the total FDG transported by the placenta. Because placenta were 6.5 ± 0.1 -fold smaller than their fetuses (N=101 FPU, 7 dams), placenta necessarily transport, per gram, considerable total glucose. In fact, the total FDG flux per gram tissue was greater for placenta than any other tissue, for example 9.5 ± 1.4 (N=14 dams, 122 FPU) fold-higher than maternal brain (Figure 5C).

FDG Avidity in the Awake State

Because anesthesia, including isoflurane [20], affects glucose metabolism, we also studied pregnant rats in the awake state. The awake rats underwent a similar protocol, except that PET imaging while awake was not possible, precluding determination of TACs and Patlak analysis. As expected, FDG accumulation was greater in the brain and skeletal muscle of awake rats, visually evident when comparing whole body PET images from the two states (Supplemental Figure 1). Despite increased competition for FDG uptake incurred by the awake brain and active muscle, the %FDG dose accumulated per fetus (Table 2) rivaled brain (Supplemental Figure 2A). Interestingly, placental %FDG dose accumulation was less in the awake than in the anesthetized state (Table 2). However, total %FDG dose accumulation across all fetuses and placenta was nearly identical in the awake and anesthetized states (Table 2). Placental $K_{FUR,well}$ rivaled that of brain (1.02 ± 0.1 fold relative to brain, Supplemental Figure 2B). Taken together, these suggest that during the increased FDG competition of the awake state, placenta maintain high avidity for glucose but increasingly shunt FDG to the fetus rather than retaining the FDG. Just as in the anesthetized state, FDG flux was far higher in placenta compared to brain (3.21 ± 0.26 fold relative to brain, Supplemental Figure 2C), fetus, heart, and hindlimb muscle.

Placental Size is Not Limiting for Fetal FDG Accumulation

The above data suggest that placenta have an immense kinetic capacity to transport maternal glucose to the fetus. If this is the case, then placental size should not be a limiting factor in fetal FDG accumulation. Rather, fetal FDG accumulation should be driven by fetal needs, which should be in part related to fetal size. Accordingly, fetal size explained 35% of the within-dam variance in fetal FDG accumulation ($r=0.59$, $P<0.00001$, N=7 dams, 101 FPU) (Supplemental Figure 3A). By contrast, placental size explained only 4% of the within-dam variance in fetal FDG accumulation ($r=0.20$, $P<0.005$, N=7 dams, 101 FPU) (Supplemental Figure 3B). These results suggest that placental size is not a major factor determining glucose transport to the fetus.

GLUT1 Gene Expression

The predominant glucose transporter expressed in placenta is GLUT1[21]. GLUT1 is also highly expressed in brain where it is vital to glucose uptake [22]. Based on the PET results, it was hypothesized that GLUT1 would be more highly expressed in placenta than other tissues. Consistent with this, GLUT1 expression was greatest in placenta relative to all of the

78–96 tissues (including brain) examined in each of three expression datasets from mice and humans (Figure 5D).

Discussion

The fetoplacental unit places a significant glucose metabolic burden on the gravid mother. PET imaging has previously determined FDG uptake into rat uterine-fetal-placental tissues as a combined unit [11]. The current study extends this capability by spatially resolving placenta from fetus. This approach reveals that placental FDG flux is far greater than could be ascertained without resolving placenta from fetus.

Just as in prior studies, much of the glucose entering the placenta is retained within the FPU [6,10]. Placenta is thought to have virtually no glucose-6-phosphatase activity [10,23] precluding FDG dephosphorylation. Recent evidence, though, suggests that *glucose-6-phosphatase 3*, a more widely expressed enzyme, is expressed at midrange levels in the placenta [24]. However, the present results suggest virtually no FDG phosphatase activity in the placenta under the time frame studied (~1.5 hours).

As in prior studies [11,12], there was a good correlation between PET-based and excised tissue γ NaI well-counter based measurements of FDG accumulation. The current SUV_{PET} of 1.7 ± 0.1 g/cm³ for fetuses is consistent with prior findings of SUV_{PET} of 1.3 for uterine horn [11]. The slightly lower prior value might be expected due to inclusion of non-fetal and non-placental tissues (e.g. amniotic fluid) in whole uterine horn volumes. Likewise, the current $SUV_{placenta}$ of 2.4 ± 0.1 is consistent with human placenta ($SUV=2.5$) [25]. The current K_{Patlak} of 0.01 ± 0.001 and 0.02 ± 0.001 mL/cm³/min for fetuses and placentae are consistent with that previously observed for the aggregate uterine horn at 0.02 mL/cm³/min [11].

CT imaging underestimated total fetal volumes by 7%, likely due to conservative manual VOI under-identification of fetal tissues. This conservative approach was deemed preferable to its opposite which risks that non-fetal tissues be included in the fetal VOIs. Postmortem placental weights were smaller than CT-based placental volumes by 30%. This discrepancy is not unexpected as the vascular placentae lost blood (i.e. deflated) upon removal from the mother prior to weighing. It is appropriate to use the deflated weight when comparing to postmortem FDG determination since both involve placenta not engorged with blood.

Though glucose metabolic rate can be estimated from FDG-PET for select tissues, this was not determinable for placentae due to the myriad of placental FDG fates. Likewise, fetal glucose metabolic rates were not calculated due to lack of relevant lumped constant estimates for fetal tissues other than brain [26]. The present approach does not inform regarding the metabolic fates of glucose in the placenta and fetus such as oxidation [27], conversion to lactate or fructose [6], and incorporation into placental glycogen [28].

Placentae and especially fetuses are of considerable mass in late gestation. This, coupled with their high avidity for glucose, results in significant total FDG accumulation. Placentae and fetuses are thus a high glucose metabolic burden to the mother, accounting for 24–26% of the total administered FDG dose in the awake and anesthetized states. In humans, similar

to rats, the placenta is far smaller (~5-fold) than the fetus [29]. This highlights the placental task, to transport glucose to a much larger entity. Correspondingly, placental FDG flux rates per gram are unrivaled by other tissues. GLUT1 expression in placenta likely mediates this capacity. Since human placenta also expresses high levels of GLUT1, the present results are likely applicable to human pregnancy.

In summary, PET/CT is an exceptional approach for the determination of placental and fetal avidity for glucose *in vivo*. This approach demonstrates the remarkable avidity of placenta for glucose.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the University of Iowa PET center for preparation of radiolabeled FDG.

This work was supported by grants NIH R01-DK097820 (to A.W.N.), Fraternal Order of Eagles Diabetes Research Center grant (to A.W.N.), NIH P30 CA086862 (cancer center support grant for the University of Iowa Small Animal Imaging Core), and NIH T35 HL007485 (Medical Student Research Program, A.B.S.).

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Highlights

- Placental-fetal transport of glucose-tracer was imaged in real time using PET/CT
- A kinetic model of glucose transport from the placenta to fetus was developed
- Avidity of placenta for glucose transport is greater than all other tissues examined
- Placental size is not a limiting factor in glucose transport to the fetus

Figure 1. Experimental protocol and kinetic model

(A) Timeline indicating the chronology of PET/CT imaging under anesthesia. The initial PET, 0–90 minutes, was focused on the abdomen. The infusion of FDG and CT contrast (“cont”) are indicated. Euthanasia (“E”) occurred at 130 minutes. The final PET, 170–210 minutes, consisted of a caudal view focused on the abdomen followed by a cranial view focused on the thorax and head. (B) Patlak compartmental model of FDG disposition in the FPU. As detailed in the text, collected data indicate that k_4 and k_8 are negligible and thus shown in lighter grey.

Figure 2. Co-registration of PET and CT imaging

PET images are taken from the summed frame (i.e. time-integrated) of the 0–90 minute scan. The CT is intravenous contrast enhanced. (A) Coronal section of co-registered CT, PET, and PET CT images are shown for an identified [P]lacental [F]etal unit which was adjacent to a [K]idney. (B) Co-registered CT and PET coronal section of the entire abdomen, including the [B]ladder. (C) Maximum intensity projection of the 0–90 minute PET.

Figure 3. Temporal FDG disposition

(A) Time-activity curves representing SUV_{PET} or SUV_{hyb} for the indicate volumes of interest or serum, respectively. (B) Maximum intensity projections demonstrating the evolution of FDG accumulation at 2, 4, 6, and 90 minutes. IVC = inferior vena cava. (C) Final FDG disposition at 140 minutes as shown by maximum intensity projection of whole-body PET.

Figure 4. Final FDG accumulation in select tissues

(A) Standardized uptake values (SUV) based on final whole body PET imaging. Letters indicate groups that did not differ statistically ($P<0.05$ by ANOVA, $N=3$ dams, 24 FPU). (B) Percentage of total injected FDG dose, by tissue, determined by final whole body PET imaging. Fetal / placental position is indicated, numbered consecutively from the cervical end of each uterine horn ($n=3$ dams, 2–5 FPU per position). Identical letters indicate groups that did not differ statistically ($P<0.05$ by ANOVA, $N=3$ dams, 24 FPU). (C) Correlation of SUV values determined from final whole body PET imaging (SUV_{PET}) versus γ -counter measurements of dissected tissues or serum (SUV_{well}), ($R^2=0.86$, $N=104$, $P<0.0001$).

Figure 5.

(A) K_{Patlak} for fetal, placental, and muscle tissues. Identical letters indicate groups that did not differ statistically ($P < 0.0005$ by ANOVA, $N = 3$ dams, 24 FPU). (B) Relative $K_{FUR,well}$ (normalized to brain $K_{FUR,well}$) of the indicated tissues. Identical letters indicate groups that did not differ statistically ($P < 0.05$ by ANOVA, $N = 14$ dams). (C) Relative FDG flux per gram of tissue, calculated from well-counter data. For placentae, total FDG flux included the FDG in the placenta plus that in the related fetus. Identical letters indicate groups that did not differ statistically ($P < 0.0001$ by ANOVA, $N = 14$ dams). (D) GLUT1 (official gene symbol is Slc2a1) expression in the indicated tissues, normalizing to expression in brain tissues. "n.m." - not measured.

Table 1

Maternal details.

	<i>units</i>	Anesthetized	Awake	<i>P</i> -value
# Dams		3	4	
# Fetuses		43	53	
Weight	<i>g</i>	319 ± 5	343 ± 13	0.20
Blood glucose	<i>mg/dL</i>	85.7 ± 8	49.3 ± 7	0.02
FDG Dose	<i>μCi</i>	448 ± 61	495 ± 31	0.49

Blood glucose was measured just before PET imaging was initiated. Bold indicates statistical significance. *P*-values refer to statistical significance of differences between the anesthetized and awake states

Table 2

Percentage of total FDG accumulated across all placentae and fetuses.

	Anesthetized	Awake	<i>P</i> -value
Percent of administered FDG dose			
All placentae	4.6 ± 0.3%	3.6 ± 0.2%	0.02
All fetuses	21.2 ± 1.9%	20.0 ± 1.5%	0.99
All F+P	25.8 ± 1.7%	23.6 ± 1.7%	0.68

“F+P” signifies all fetuses plus placentae. Bold indicates statistical significance. *P*-values refer to statistical significance of differences between the anesthetized and awake states. Anesthetized: N=43 FPU, 3 dams. Awake: N=58 FPU, 4 dams.