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# Regional Glucose Metabolism in Mouse Brain Following ACTH Peptides and Naloxone

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DUNN, A. J. AND R. W. HURD. *Regional glucose metabolism in mouse brain following ACTH peptides and naloxone.* PHARMAC. BIOCHEM. BEHAV. 17(1) 37–41, 1982.—Following intracerebroventricular (ICV) injection of $ACTH_{1-24}$ significant decreases in 2-deoxyglucose (2DG) uptake were observed in frontal cortex and pyriform cortex, and an increase in thalamus. No such changes were observed following ICV $MSH/ACTH_{4-10}$. Regional changes in 2DG uptake in olfactory bulb, pyriform cortex, thalamus and cerebellum were significantly correlated with the excessive grooming induced by $ACTH_{1-24}$. Grooming behavior not induced by $ACTH_{1-24}$ was not correlated with 2DG changes in any of these regions. Naloxone treatment did not significantly alter the regional pattern of 2DG uptake. In naloxone-pretreated mice $ACTH_{1-24}$ did not induce significant changes in regional 2DG uptake. Following a series of footshocks, 2DG uptake increased in the hypothalamus, tectum and hippocampus. This pattern of changes is different from that observed following ICV $ACTH_{1-24}$ and cannot therefore be attributed to ACTH secretion during the stress.

Deoxyglucose ACTH $ACTH_{1-24}$ $MSH/ACTH_{4-10}$ Naloxone Footshock

SOKOLOFF *et al.* [11] pioneered the use of radiolabelled 2-deoxyglucose (2DG) to measure the regional uptake of glucose in the brain. Theoretical considerations suggest that the glucose uptake by a neuron should be related to its activity, and experience with this technique suggests that it can be used to relate cerebral anatomy to function [10,11]. Using a modification of Sokoloff's procedure, more suited for behavioral studies, we have recently reported regionally specific changes in 2DG accumulation in response to intracerebroventricular (ICV) $ACTH_{1-24}$ and lysine vasopressin [3]. In the case of $ACTH_{1-24}$, some of these changes were significantly correlated with the excessive grooming induced by the peptide. Thus it was not possible to tell whether the 2DG uptake changes were related to the direct action(s) of the peptide or reflected the grooming behavior. In an attempt to resolve this we have now studied the regional 2DG accumulation following ICV $MSH/ACTH_{4-10}$, a peptide that does not elicit grooming. We also studied regional 2DG accumulation following ICV $ACTH_{1-24}$ in animals pretreated with naloxone which prevents the induction of grooming [4,13].

## METHOD

CD-1 male mice (20–30 g) were obtained from Charles River Laboratories. $MSH/ACTH_{4-10}$ and $ACTH_{1-24}$ were gifts from Organon International B.V. (Oss, The Netherlands). Naloxone was a gift from Endo Laboratories. [1-$^3$H]2-Deoxyglucose (18.2 Ci/mmole) was obtained from Amersham-Searle, Inc.

Prior to each experiment mice were surgically prepared with plastic cannulae (Clay Adams PE-50) in each lateral cerebral ventricle as previously described [4,6] after which they were housed individually. Intracerebral injections were performed using a 10 $\mu$l Unimetrics microsyringe designed so that the tip just emerged into the lateral ventricle. Peptides were dissolved in 0.9% saline containing $10^{-3}$ M HCl and injected in a volume of 1 $\mu$l into each ventricle for a total dose of 1 $\mu$g $MSH/ACTH_{4-10}$ or $ACTH_{1-24}$. Naloxone (1 mg/kg) and [$^3$H]2DG (10 $\mu$Ci/animal) were injected SC at the back of the neck. The predominant behavior was scored by an independent observer every 30 sec during the 2DG incorporation period (i.e., a time-sampling procedure) as previously described [3]. Grooming scores are the total number of observations in which grooming was the predominant behavior (out of a possible 80 scores).

Forty minutes after [$^3$H]deoxyglucose injection, mice were killed by decapitation, and regional 2DG uptake determined as previously described [3]. Briefly, freehand dissected brain regions were transferred to preweighed pieces of weighing paper and dried before reweighing. Tritium content was then determined after solubilization of the tissue with Soluene 350 (Packard Instrument Co.). The specific activity (dpm/mg dry weight) determined for each dissected brain region was normalized by dividing by the specific activity for the whole brain, determined by adding together the weights and radioactivities for each piece of that brain including the residual tissue. This yielded a relative specific activity (RSA), reflecting the relative 2DG uptake for each region. The validation for this modification of the original

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TABLE 1

REGIONAL CHANGES IN [$^3$H]DEOXYGLUCOSE UPTAKE FOLLOWING ICV $ACTH_{1-24}$

| Region | Relative Specific Activity: Saline (n=54) | $ACTH^{1-24}$ (n=44) | % Change |
|---|---|---|---|
| Olfactory Bulb‡ | 1.29 ± 0.03 | 1.24 ± 0.03 | −5 |
| Frontal Cortex | 1.19 ± 0.02 | 1.13 ± 0.02* | −5 |
| Parietal Cortex | 1.20 ± 0.02 | 1.17 ± 0.02 | −2 |
| Occipital Cortex | 1.20 ± 0.02 | 1.14 ± 0.03 | −5 |
| Pyriform Cortex‡ | 1.08 ± 0.02 | 1.02 ± 0.01† | −6 |
| N. Accumbens | 1.09 ± 0.03 | 1.05 ± 0.03 | −3 |
| Amygdala | 0.84 ± 0.02 | 0.78 ± 0.02 | −6 |
| Striatum | 0.95 ± 0.01 | 0.97 ± 0.01 | +2 |
| Septum | 0.94 ± 0.02 | 0.88 ± 0.02 | −7 |
| Hippocampus | 0.97 ± 0.02 | 0.97 ± 0.02 | 0 |
| Dorsal§ | 0.94 ± 0.02 | 0.93 ± 0.03 | −2 |
| Ventral§ | 0.98 ± 0.03 | 0.98 ± 0.03 | 0 |
| Thalamus‡ | 0.96 ± 0.01 | 1.00 ± 0.01* | +4 |
| Hypothalamus | 0.93 ± 0.01 | 0.90 ± 0.01 | −3 |
| Tectum | 0.93 ± 0.01 | 0.93 ± 0.02 | 0 |
| Tegmentum | 0.90 ± 0.01 | 0.90 ± 0.01 | 0 |
| Cerebellum‡ | 0.96 ± 0.01 | 1.00 ± 0.01 | +4 |

Deoxyglucose uptake (dpm/mg) in each region is expressed relative to the whole brain uptake to give a relative specific activity (mean ± S.E.M.).

$ACTH_{1-24}$ (1 μg, ICV) was injected 10 min before [$^3$H]deoxyglucose. The results are the combined data from six separate experiments.

*Significantly different from saline, $p<0.05$, †$p<0.01$ (two-factor ANOVA).

‡Significantly correlated with grooming score ($p<0.05$); n=number of animals.

§Data from four experiments only.

TABLE 2

REGIONAL CHANGES IN [$^3$H]DEOXYGLUCOSE UPTAKE FOLLOWING ICV $MSH/ACTH_{4-10}$

| Region | Relative Specific Activity: Saline (n=29) | $MSH/ACTH_{4-10}$ (n=30) | % Change |
|---|---|---|---|
| Olfactory Bulb | 1.25 ± 0.04 | 1.28 ± 0.04 | +3 |
| Frontal Cortex | 1.17 ± 0.03 | 1.16 ± 0.03 | −1 |
| Parietal Cortex | 1.18 ± 0.03 | 1.18 ± 0.03 | 0 |
| Occipital Cortex | 1.20 ± 0.04 | 1.14 ± 0.03 | −5 |
| Pyriform Cortex | 1.08 ± 0.03 | 1.07 ± 0.02 | 0 |
| N. Accumbens | 1.11 ± 0.04 | 1.18 ± 0.05 | +6 |
| Amygdala | 0.87 ± 0.03 | 0.90 ± 0.04 | +4 |
| Striatum | 0.93 ± 0.01 | 0.94 ± 0.01 | +1 |
| Septum | 0.97 ± 0.03 | 0.95 ± 0.03 | −2 |
| Hippocampus | 0.98 ± 0.02 | 0.98 ± 0.02 | 0 |
| Dorsal§ | 0.97 ± 0.03 | 0.98 ± 0.04 | +1 |
| Ventral§ | 1.00 ± 0.03 | 1.02 ± 0.02 | +2 |
| Thalamus | 0.98 ± 0.02 | 0.99 ± 0.01 | +1 |
| Hypothalamus | 0.92 ± 0.02 | 0.91 ± 0.01 | −1 |
| Tectum | 0.93 ± 0.02 | 0.97 ± 0.01 | +4 |
| Tegmentum | 0.90 ± 0.01 | 0.91 ± 0.01 | +1 |
| Cerebellum | 0.98 ± 0.02 | 0.96 ± 0.01 | −2 |

Deoxyglucose relative specific activity (mean ± S.E.M.). $MSH/ACTH_{4-10}$ (1 μg, ICV) was injected 10 min before [$^3$H]deoxyglucose. The results are the combined data from three experiments. None of the changess was statistically significant.

§Data from two experiments only.

Sokoloff procedure was presented in full and discussed previously [3] and resembles that of Meibach *et al.* [8].

Statistical analyses were performed by multifactor analysis of variance (ANOVA) using the SAS programmed package on the Amdahl computer of the Florida North East Regional Data Center. Data from replicate experiments have been pooled to increase the confidence of the results. Because of significant inter-experiment variance, experiment number was included as a factor in these analyses. Thus in most cases the model was 2DG uptake as a function of experiment number and treatment. In the experiment of Table 3, two treatment factors were included (±naloxone and $\pm ACTH_{1-24}$). Correlations between grooming scores and regional 2DG uptake were derived from partial correlation coefficients using the MANOVA section of the SAS package. This was necessary to allow the combination of data from separate experiments, not possible in a simple regression analysis without some arbitrary normalization factor. Animals were excluded from the analysis only if data from more than two brain regions were missing (due to experimental losses) or in the absence of a behavioral response as indicated in the text.

## RESULTS

In Table 1 are shown the combined data from six separate experiments on the effects of ICV $ACTH_{1-24}$ on regional $^3$H uptake. For analysis of variance, $ACTH_{1-24}$-injected animals that showed grooming scores of less than 25% were excluded because these animals were presumed to have received ineffective injections. Statistically significant changes were observed in three brain regions: decreases in frontal cortex, $F=5.2$, $p=0.025$, and pyriform cortex, $F=7.1$, $p<0.01$; and an increase in thalamus, $F=5.6$, $p=0.02$. In addition, there was an increase in the cerebellum that was not quite significant, $F=3.0$, $p=0.09$. These results compare well with those found previously [3], with the notable exception of frontal cortex in which there was no change in the earlier study. While in both studies uptake in the olfactory bulb was decreased and that in the thalamus increased, the former was statistically significant only in the earlier study, and the latter only in the present study.

In addition, we tested the correlation between the regional changes of $^3$H uptake and the grooming scores. Significant correlationss were found for olfactory bulb, $r_{129}=-0.20$, $p<0.05$, pyriform cortex, $r_{131}=-0.31$, $p<0.005$, thalamus, $r_{131}=0.24$, $p<0.01$, and cerebellum, $r_{131}=0.25$, $p<0.01$. A correlation in occipital cortex was not quite significant, $r_{130}=-0.16$, $p=0.07$. Once again this parallels the earlier data [3], although the correlations in the thalamus and olfactory bulb were not statistically significant in that study. These data thus confirm the consistency of the peptide-induced changes, especially for pyriform cortex.

In Table 2 are presented the combined data from three separate experiments with ICV $MSH/ACTH_{4-10}$. $MSH/ACTH_{4-10}$ did not significantly increase the grooming

TABLE 3

REGIONAL CHANGES IN [$^3$H]DEOXYGLUCOSE UPTAKE FOLLOWING ICV $ACTH_{1-24}$ ± NALOXONE

| Region | Relative Specific Activity | | | | | | |
|---|---|---|---|---|---|---|---|
| | Saline (n=26) | Naloxone (n=29) | %Δ | $ACTH_{1-24}$ (n=24) | %Δ | Naloxone + $ACTH_{1-24}$ (n=29) | %Δ |
| Olfactory Bulb† | 1.35 ± 0.06 | 1.33 ± 0.04 | −1 | 1.24 ± 0.04 | −8 | 1.32 ± 0.04 | −2 |
| Frontal Cortex | 1.20 ± 0.02 | 1.21 ± 0.02 | 0 | 1.15 ± 0.02 | −5 | 1.22 ± 0.03 | +1 |
| Parietal Cortex | 1.22 ± 0.04 | 1.18 ± 0.02 | −3 | 1.19 ± 0.03 | −3 | 1.21 ± 0.02 | −1 |
| Occipital Cortex | 1.21 ± 0.03 | 1.17 ± 0.02 | −4 | 1.16 ± 0.04 | −4 | 1.17 ± 0.02 | −3 |
| Pyriform Cortex† | 1.09 ± 0.02 | 1.09 ± 0.03 | 0 | 1.03 ± 0.02 | −5 | 1.05 ± 0.02 | −3 |
| N. Accumbens† | 1.07 ± 0.04 | 1.07 ± 0.04 | 0 | 0.99 ± 0.04 | −7 | 1.10 ± 0.04 | +3 |
| Amygdala | 0.80 ± 0.02 | 0.82 ± 0.03 | +2 | 0.79 ± 0.03 | −2 | 0.81 ± 0.02 | 0 |
| Striatum | 0.97 ± 0.02 | 0.98 ± 0.01 | +1 | 0.98 ± 0.01 | +1 | 0.97 ± 0.01 | 0 |
| Septum | 0.91 ± 0.02 | 0.94 ± 0.03 | +3 | 0.86 ± 0.02 | −5 | 0.91 ± 0.03 | 0 |
| Hippocampus | 0.96 ± 0.03 | 0.94 ± 0.02 | −2 | 0.98 ± 0.03 | +2 | 0.94 ± 0.02 | −2 |
| Dorsal§ | 0.92 ± 0.03 | 0.93 ± 0.04 | +1 | 0.91 ± 0.04 | −2 | 0.88 ± 0.03 | −5 |
| Ventral§ | 0.97 ± 0.05 | 0.98 ± 0.04 | +1 | 0.98 ± 0.05 | +2 | 0.96 ± 0.03 | 0 |
| Thalamus | 0.93 ± 0.02 | 0.95 ± 0.02 | +2 | 1.00 ± 0.02* | +7 | 0.95 ± 0.02 | +2 |
| Hypothalamus | 0.93 ± 0.02 | 0.93 ± 0.01 | 0 | 0.90 ± 0.01 | −3 | 0.91 ± 0.01 | −2 |
| Tectum | 0.93 ± 0.02 | 0.92 ± 0.02 | −1 | 0.91 ± 0.02 | −3 | 0.90 ± 0.02 | −4 |
| Tegmentum | 0.90 ± 0.02 | 0.88 ± 0.01 | −1 | 0.89 ± 0.01 | 0 | 0.92 ± 0.03 | +3 |
| Cerebellum† | 0.94 ± 0.02 | 0.95 ± 0.01 | +1 | 0.99 ± 0.02 | +5 | 0.97 ± 0.02 | +3 |

Deoxyglucose relative specific activity (mean ± S.E.M.). $ACTH_{1-24}$ (1 μg) or saline was injected ICV and naloxone (1 mg/kg) or saline, SC 10 min before [$^3$H]deoxyglucose. Data are the combined results of three experiments.

*Significantly different from saline, $p<0.05$, (3-factor ANOVA).

†Regional deoxyglucose uptake significantly correlated with grooming score ($p<0.05$).

§Data from only two experiments.

scores (saline: 12±2%, MSH/$ACTH_{4-10}$: 11±2%). In contrast to the data obtained with $ACTH_{1-24}$, none of the regions showed significant changes in [$^3$H]2DG uptake. This was also true of each single experiment; no significant changes were observed in any region. The only change that approached significance was the increase in the tectum, F=3.4, $p=0.07$, a change not observed after $ACTH_{1-24}$. Of particular interest is the absence of changes in pyriform cortex or thalamus, and the small (not significant) changes in the olfactory bulb and cerebellum in the direction opposite to those observed with $ACTH_{1-24}$. Thus the changes observed with $ACTH_{1-24}$ are not associated with the "core" 4–10 sequence of ACTH.

Naloxone pretreatment prevents the excessive grooming induced by $ACTH_{1-24}$ [4,13]. Therefore, it was of interest to test the effect of naloxone on the changes in 2DG uptake induced by $ACTH_{1-24}$. Using a Latin Square design, we could also test the effects of naloxone alone. Thus each animal received an ICV injection of $ACTH_{1-24}$ or saline and an SC injection of naloxone (1 mg/kg) or saline.

The combined results of three experiments are shown in Table 3. Naloxone alone did not significantly alter the 2DG uptake in any brain region. This was true whether naloxone was included as a treatment factor in the analysis of variance, or whether the naloxone (ICV saline) group was compared independently with the saline (ICV saline) group. $ACTH_{1-24}$ induced changes in the same directions as those observed in Table 1 although these were less significant. Pyriform cortex uptake was decreased, F(3,104)=3.5, $p<0.07$, and that in the cerebellum, F(3,104)=2.7, $p=0.10$, increased. Testing the $ACTH_{1-24}$ (SC saline) group against the saline (SC saline) group alone, the increase in thalamus, F=9.4, $p<0.01$, was significant, and the decreases in frontal cortex, F=3.51, $p<0.07$, and pyriform cortex, F=3.9, $p<0.06$, nearly so. By contrast when the $ACTH_{1-24}$-naloxone group was tested against the saline-saline group none of the changes was even close to significance. Examining the regions individually, the naloxone appears to attenuate the $ACTH_{1-24}$-induced changes. This is true in all the responsive regions: olfactory bulb, frontal cortex, pyriform cortex, thalamus and cerebellum. Unfortunately, because no statistically significant changes were observed between the $ACTH_{1-24}$ (SC saline) and $ACTH_{1-24}$ (SC naloxone) groups, these data are inconclusive.

It was also of interest to determine whether the 2DG uptake changes induced by ACTH relate to those observed during stress. Previously we reported that footshock treatment increased 2DG uptake in the hypothalamus and brain stem, and decreased it in parietal cortex [1]. We repeated this experiment with footshock analyzing the regions we used for the ACTH studies. The results (Table 4), resemble those of the earlier study in that hypothalamic 2DG uptake was increased, F=6.1, $p<0.02$. However, the decrease in parietal cortex was not replicated and a decrease in 2DG uptake in the tectum, F=6.6, $p<0.02$, was also observed. If the statistical analysis was performed on the combined results of the earlier two experiments [1] and the present one (Table 4), significant increases were also observed in occipital cortex (+7%, $p<0.02$) and hippocampus (+6%, $p<0.01$). The important finding is that none of these changes parallel

TABLE 4
REGIONAL CHANGES IN [$^3$H]DEOXYGLUCOSE UPTAKE FOLLOWING FOOTSHOCK

| Region | Relative Specific Activity Quiet (n=9) | Footshock (n=8) | % Change |
|---|---|---|---|
| Olfactory Bulb | 1.16 ± 0.03 | 1.16 ± 0.03 | −1 |
| Frontal Cortex | 1.32 ± 0.02 | 1.28 ± 0.02 | −3 |
| Parietal Cortex | 1.37 ± 0.03 | 1.45 ± 0.04 | +6 |
| Occipital Cortex | 1.23 ± 0.05 | 1.34 ± 0.04 | +9 |
| Pyriform Cortex | 1.07 ± 0.04 | 1.05 ± 0.04 | −2 |
| N. Accumbens | 1.11 ± 0.05 | 1.15 ± 0.09 | +4 |
| Amygdala | 0.75 ± 0.03 | 0.74 ± 0.03 | −1 |
| Striatum | 1.05 ± 0.02 | 1.04 ± 0.02 | −1 |
| Septum | 0.98 ± 0.05 | 1.06 ± 0.05 | +8 |
| Hippocampus | 0.90 ± 0.02 | 0.96 ± 0.02 | +7 |
| Thalamus | 1.06 ± 0.02 | 1.04 ± 0.03 | −1 |
| Hypothalamus | 0.88 ± 0.02 | 0.94 ± 0.02* | +7 |
| Tectum | 0.95 ± 0.03 | 0.87 ± 0.02* | −9 |
| Tegmentum | 0.95 ± 0.02 | 0.97 ± 0.02 | +2 |
| Cerebellum | 0.98 ± 0.02 | 0.99 ± 0.01 | −6 |

Mice were given a 15 min period of footshock (20 shocks, 0.3 mA, 1 sec duration). [$^3$H]Deoxyglucose was injected immediately before the footshock period.
*Significantly different from quiet, $p<0.05$ (ANOVA).

any observed with $ACTH_{1-24}$. Thus, the responses to footshock cannot be ascribed to release of ACTH.

## DISCUSSION

The present results confirm our earlier finding that ICV $ACTH_{1-24}$ causes regionally specific changes in [$^3$H]2DG uptake in mouse brain, in particular a relative decrease in pyriform cortex. However, because ICV $MSH/ACTH_{4-10}$ treatment resulted in none of the changes seen with $ACTH_{1-24}$, we can conclude that the changes are not related to behavioral activities shared by $MSH/ACTH_{4-10}$ and $ACTH_{1-24}$ [12]. Indeed, no 2DG uptake changes were observed that could be associated with behavioral activities of $MSH/ACTH_{4-10}$. This is consistent with our earlier data using peripheral injections of this peptide [1]. Thus if changes do occur with $MSH/ACTH_{4-10}$, they are either too small or too anatomically discrete to be detected by our procedure.

Because naloxone prevents $ACTH_{1-24}$-induced grooming and the appearance of 2DG uptake changes, it might be concluded that the 2DG changes reflect the excessive grooming. However, the data are less than convincing on this point. In particular, there were no significant differences between the $ACTH_{1-24}$-saline and $ACTH_{1-24}$-naloxone groups. Inspection of the data suggests that insofar as the regions normally responding to $ACTH_{1-24}$ are concerned, the changes in pyriform cortex and cerebellum may persist, but be diminished.

However, it is important that naloxone did not produce any significant changes in [$^3$H]2DG uptake. This would suggest either that under the conditions of our experiment levels of endorphin release are low, or that they have relatively small effects on regional neuronal activity.

An important question is whether the regional changes observed following ICV $ACTH_{1-24}$ are related to direct actions of the peptide or to the expression of grooming behavior. The very high correlation obtained between the changes in pyriform cortex [$^3$H]2DG uptake and the grooming scores suggests the latter interpretation. However, we also examined our data to test for correlations between pyriform cortex $^3$H accumulation and grooming scores in animals not treated with $ACTH_{1-24}$. In this case the correlation was far from statistically significant, $r_{59}=-0.17$, $p=0.3$. This suggests (but does not prove) that pyriform cortex may only be involved in the grooming induced by $ACTH_{1-24}$ and not endogenous grooming.

The decrease in frontal cortex 2DG uptake may well parallel the increased synthesis of dopamine observed in this region following ICV $ACTH_{1-24}$ [2]. This would be consistent with an inhibitory role for dopamine in that region. However, studies of frontal cortex 2DG uptake following lesions of the dopaminergic input with 6-hydroxydopamine have shown decreases, suggesting that the input is excitatory [7,9]. It is possible that this result reflects an artifact of the 6-hydroxydopamine treatment (e.g., postsynaptic supersensitivity) because the decreased glucose utilization seen in the frontal cortex of schizophrenics is reversed by neuroleptic treatment [5], suggesting that, at least in humans, the dopaminergic input is inhibitory.

We have also confirmed our earlier effects of footshock on regional 2DG uptake in the hypothalamus, but not in parietal cortex [1]. The present results suggest that none of these regional changes is attributable to ACTH release during the stress.

The present data indicate that regionally specific changes in glucose metabolism do occur following intracerebroventricular injection of peptides and may be related to the induction of specific behaviors. However we failed to find any effect following $MSH/ACTH_{4-10}$ injected either SC or ICV.

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