Effect of Hypertonic Glucose, Urea and PVP on the Production and Absorption of Cerebrospinal Fluid

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INTRODUCTION

The treatment of cerebrospinal hypertension is one of the important problems in the neurosurgical field. For this purpose, hypertonic glucose solutions have been used for a long time. Neverthless, it was observed by Bullock and his coworkers[4] that a rebound rise in cerebrospinal fluid pressure occured following the transient fall.

In 1927 Fremont-Smith and Forbes[5] observed a remarkable decrease in cerebrospinal fluid pressure in cat following intraperitoneal administration of a hypertonic urea solution. In 1928, Wolff and Forbes[19] noticed the same effect from this agent following its intravenous injection in the cat. This valuable dehydrating agent was abandoned for the following three decades insitep of its outstanding effect.

Since the demonstration by Smyth and associates[15] in monkey (1950), and Javid and Settlage[10] in human subjects (1956), that the intravenous injection of hypertonic urea produced a remarkable decline in cerebrospinal fluid pressure without any untoward incidents, it has come into general use in the neurological and neurosurgical clinic. Particularly, as the effect of the hypertonic urea appears promptly following administration and produces a marked reduction in the brain volume, it has recently been used in brain operations.

On the other hand, polyvinylpyrrolidon (PVP), a nonbiological artificial colloid, has also been used as a cerebrospinal hypotensor since it was produced by Reppe in 1940. Further studies on this agent have been carried out by Wesse and associates.[18] According to them, PVP is not only useful as a substitute for blood plasma but its colloid osmotic properties also make it useful as a diuretic. In this connection, many favorable reports have been published on the clinical use of PVP in cerebrospinal hypertension.

It is the purpose of this study to estimate, using the radioisotope ^{32}P, the effect of both of the avove mentioned hypertonic dehydrating agents as well as of hypertonic glucose solution on the production and absorption of cerebrospinal fluid in normal animals and in those subjected to compression of the brain.

METHOD

Unanesthetized normal rabbits weighing approximately 3 kg. were used in this experiment. In order to determine the turnover rate of the radioisotope from blood to cerebrospinal fluid (CSF), 500 microcuries of ^{32}P were given intravenously, immediately after the intravenous injection of the dehydrating agent. Samples of CSF not exceeding 0.3 ml. were withdrawn by means of cisternal puncture at 30, 60, 120, and 180 min. after injection of ^{32}P. CSF samples which were mixed with blood due to technical failure of the puncture were never used for measurement.

For the determination of the turnover rate of ^{32}P from CSF to blood, 100 microcuries of ^{32}P were given intracisternally immediately after the intravenous administration of each dehydrating agent. Blood samples were collected from the jugular vein at 15, 30, 60, 120, and 180 min. after the injection of ^{32}P.

For the measurement of radioactivity, 0.1 ml. of CSF or blood samples was put into assay dish and dried for 24 hours in an incubator at 60°C. The radioactivity of each sample was determined using a Geiger-Mueller counter. The rate of turnover was expressed directly by average value of count/min. in each CSF or blood sample, and compared with control value. The 4 ml. per Kg. of 50 % glucose solution, 30 % urea solution, and 6 % PVP (of 12,000 molecular weight, Pereston-N), were used as dehydrating agents. The urea solution was prepared just before injection by dissolving the urea in 5 % glucose. These injections thus provided, per Kg. of rabbit, 11 mM of glucose, 20 mM of urea, or 0.02 mM of PVP.

Experiments were carried out on three groups, i.e. normal animals, a group of animals immediately after brain compression, and another after a 24 hour period of brain compression. The rubber balloon method described by Ishii and his cowerkers[8] was used to produce brain compression. Twenty four hours after insertion of the balloon into the epidural space, the balloon was slowly filled with 0.5 ml. increments of saline. If the increments exceeded this limit, the animals had severe convulsion and other serious symptoms leading eventually to death.

For the purpose of estimating the condition of the brain which had been subjected to balloon compression, measurement of the water content of the brain was carried out as well as histological study. The brain was removed as quickly as possible after sacrificing the rabbit, and samples of fresh tissue from symmetrical regions in both hemispheres were weighed (W_1). After drying for three days in an oven at 100°C, the samples were weighed again (W_2). Water content of the brain was given as following formula.

$$\text{Water Cantent } (\%) = \frac{W_1 - W_2}{W_1} \times 100$$

For histological purposes the brain materials were treated by formalin preparation and hematoxylin-eosin stain.

RESULTS

1. Normal animals

(a) Turnover of ^{32}P from blood to CSF

The turnover rate of ^{32}P from blood to CSF is shown in Table 1. Curves of turnover rate for the controls and following injection of each of the 3 solutions are shown in Fig. 1.

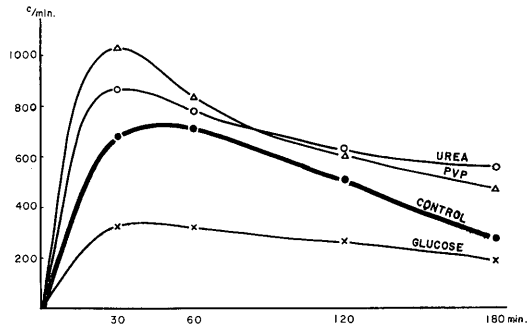


Fig. 1. Follow up of mean values in the turnover of ^{32}P from blood to CSF (production rate) in normal animal following intravenous administration of different hypertonic solutions.

Table 1. Appearance of ^{32}P in CSF Following Intravenous Injection (500μc) in normal rabbit

Administered Solution	Body Weight (Kg.)	Count/min. in 0.1ml. CSF 30min.	60min.	120min.	180min.
50% Glucose	2.6	157	167	137	108
	2.7	162	123	98	94
	3.0	453	387	304	211
	2.7	373	562	461	315
	2.8	493	399	341	205
	Mean Value	327.6	327.0	268.2	186.6
30% Urea	3.0	580	787	532	475
	3.0	962	676	386	236
	2.8	965	634	544	471
	3.0	960	838	819	681
	3.0	862	962	875	937
	Mean Value	865.8	779.0	631.2	560.0
PVP	2.9	1183	747	571	387
	2.9	1367	890	607	451
	2.7	1164	870	613	535
	2.6	931	984	651	529
	2.7	748	691	565	449
	Mean Value	1078.6	836.4	601.4	470.2
None (Control)	2.5	648	711	493	311
	2.7	783	740	833	638
	2.8	656	1039	594	537
	3.0	548	485	410	292
	2.5	677	647	498	456
	3.0	729	1122	557	493
	2.8	692	572	399	263
	3.0	654	532	422	314
	2.8	637	614	456	273
	2.7	714	614	361	293
	Mean Value	677.4	707.5	502.3	387.0

Conspicuous decrease of turnover rate of CSF throughout the experiment was noted in the group receiving hypertonic glucose, while slight increase as compared with control level was observed in the groups receiving hypertonic urea or PVP. The level of turnover rate with glucose was approximately half of that of the control group at each time point. This difference between the glucose group and the other two groups suggests that there is a difference in the mechanism of action of these solutes at the blood-CSF barrier.

(b) Turnover of ^{32}P from CSF to blood.

The turnover rate of ^{32}P from CSF to blood is shown in Table 2. Curves of turnover rates for the controls, and following injection of each of the 3 solutions are shown in Fig. 2.

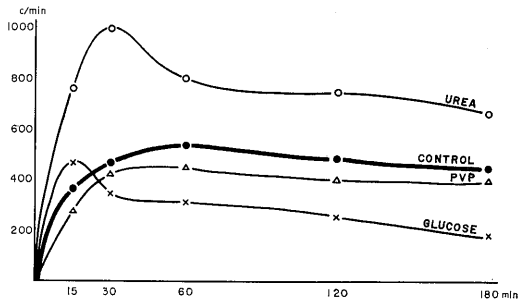


Fig. 2. Follow up of mean values in the turnover of ^{32}P from CSF to blood (absorption rate) in normal animal following intravenous administration of different hypertonic solutions.

Table 2. Appearance of ^{32}P in Blood Following Intracisternal Injection (100μc) in Normal Rabbit

Administered Solution	Body Weight (Kg.)	Count/min. in 0.1 ml. Blood 15min.	30min.	60min.	120min.	180min.
50% Glucose	2.8	528	390	390	292	118
	2.6	459	346	296	240	149
	2.7	448	250	236	219	206
	2.6	493	424	351	279	223
	2.7	424	336	303	264	221
	Mean Value	471.4	349.2	315.2	258.8	183.4
30% Urea	2.8	1154	1477	1202	1054	985
	2.5	1005	1534	971	829	840
	2.6	602	432	422	435	360
	2.6	598	854	705	510	507
	2.9	808	1071	991	868	798
	2.8	401	548	483	780	461
	Mean Value	761.3	986.0	795.7	746.0	658.5
PVP	2.8	317	584	544	890	865
	2.9	220	393	323	284	204
	2.5	319	504	389	386	308
	2.5	233	303	392	357	305
	2.8	316	470	314	243	416
	2.8	249	275	675	222	252
	Mean Value	275.7	421.5	439.5	397.0	391.7
None (Control)	2.6	519	579	626	526	310
	2.5	428	461	523	559	493
	2.8	331	461	469	459	649
	2.7	261	353	519	429	380
	2.5	287	493	549	391	432
	Mean Value	365.2	469.4	537.2	472.8	452.8

A remarkable increase in the turnover rate was noted in the animals receiving hypertonic urea, a rapidly attained high turnover being followed by a gradual decline. In this series, the turnover rate was almost twice as high as in the controls throughout the experiment, and the period of maximum appearance of ^{32}P in blood was earlier than that of the controls. On the other hand, the turnover rate in the series receiving hypertonic glucose was decreased relative to the controls except for an initial slight increase, the difference between the two groups becoming larger as time went on. The curve for the group receiving PVP was the same as for the controls.

2. Immediately after brain compression

(a) Turnover of ^{32}P from blood to CSF

The turnover rate of ^{32}P from blood to CSF is shown in Table 3 and Fig. 3.

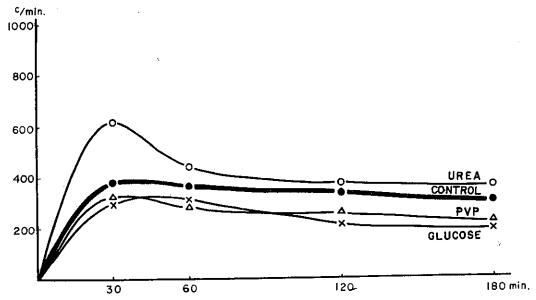


Fig. 3. Follow up of mean values in the turnover of ^{32}P from blood to CSF (production rate) in animal immediately after brain compression following intravenous administration of different hypertonic solutions.

Table 3. Appearance of ^{32}P in CSF Following Intravenous Injection (500μc) in Rabbit Subjected to Brain Compression: Immediately after Compression.

Administered Solution	Body Weight (Kg.)	Count/min. in 0.1 ml. CSF 30min.	60min.	120min.	180min.
50% Glucose	2.5	392	520	263	213
	2.7	313	269	209	176
	2.5	252	201	178	158
	2.8	228	275	212	229
	Mean Value	296.3	316.3	215.5	194.0
30% Urea	2.7	737	360	280	427
	2.6	576	540	561	431
	2.6	591	403	279	258
	2.8	582	437	410	341
	Mean Value	625.1	435.0	382.5	364.3
PVP	2.6	238	259	299	217
	2.6	381	318	240	235
	2.7	365	283	238	225
	2.7	261	241	228	225
	Mean Value	311.3	275.3	251.3	225.5
None (Control)	2.9	250	270	224	276
	2.6	377	266	299	314
	2.5	518	577	542	379
	2.6	380	328	283	257
	Mean Value	381.3	360.3	337.0	306.5

In the control group, the concentration of ^{32}P in CSF reached a maximum by 30 minutes and thereafter continued until 180 minutes at almost the same level. The turnover rates following injection of glucose or PVP were parallel to, but slightly less than the controls. Following injection of urea, there was a transient increase in the rate of turnover, following which the experimental group behaved similarly to the controls.

(b) Turnover of ^{32}P from CSF to blood

The turnover rate of ^{32}P from CSF to blood is shown in Table 4 and Fig. 4.

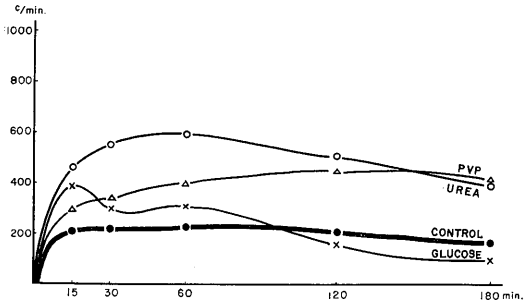


Fig. 4. Follow up of mean values in the turnover of ^{32}P from CSF to blood (absorption rate) in animal immediately after brain compression following intravenous administration of different hypertonic slutions.

Table 4. Appearance of ^{32}P in Blood Following Intracisternal Injection (100μC) in Rabbit Subjected to Brain Compression: Immediately after Compression.

Administered Solution	Body Weight (Kg.)	Count/min. in 0.1 ml. Blood 15min.	30min.	60min.	120min.	180min.
50% Glucose	2.5	381	229	208	182	173
	2.5	551	369	442	134	62
	2.6	321	303	322	99	46
	2.7	356	275	291	160	103
	2.8	331	330	298	190	128
	Mean Value	388.0	301.2	312.2	153.0	102.4
30% Urea	2.5	563	1068	597	461	261
	2.5	350	327	395	248	196
	2.5	346	283	724	712	574
	2.5	331	375	534	425	410
	2.8	696	694	691	696	542
	Mean Value	457.2	549.4	588.2	508.4	396.6
PVP	2.5	356	437	558	855	630
	2.5	299	296	371	391	493
	3.0	236	215	270	260	259
	2.7	354	358	318	259	242
	2.7	247	267	444	434	405
	Mean Value	298.4	314.6	392.2	445.8	405.8
None (Control)	2.5	269	311	366	266	114
	2.5	286	281	205	227	121
	3.0	141	173	185	165	147
	2.6	152	104	115	94	87
	2.5	252	298	275	251	277
	2.5	215	191	269	286	239
	2.5	114	174	226	175	205
	Mean Value	204.1	218.9	234.4	209.1	170.0

In the control group, the level of ^{32}P in the blood remained almost constant between 15 and 180 minutes with a maximum concentration of ^{32}P in the blood being obtained at 60 min. In both the urea and the PVP groups, a high rate of appearance of ^{32}P in the blood was noted, the concentration of ^{32}P in the blood being low at first with PVP but progressively increasing, whereas, with urea, it reached a peak at 60 minutes and then decreased. In the glucose group, however, a considerable increase of turnover from CSF to blood relative to the control rate was noted at first. The curve then crossed that of the controls at about 100 minutes point and was somewhat lower thereafter.

3. After a 24 hour period of brain compression

(a) Turnover of ^{32}P from blood to CSF

The turnover rate of ^{32}P from blood to CSF is demonstrated in Table 5 and Fig. 5.

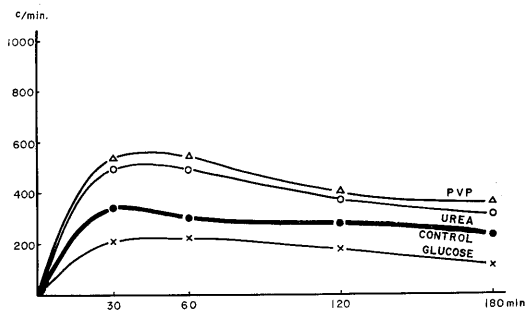


Fig. 5. Follow up of mean values in the turnover of ^{32}P from blood to CSF (production rate) in animal after a 24 hour period of brain compression following intravenous administration of different hypertonic solutions.

Table 5. Appearance of ^{32}P in CSF Following Intravenous Injection (500μc) in Rabbit Subjected to Brain Compression: After a 24 Hour Period of Compression.

Administered Solution	Body Weight (Kg.)	Count/min. in 0.1 ml. CSF 30min.	60min.	120min.	180min.
50% Glucose	2.7	113	100	97	82
	2.5	177	334	140	100
	2.6	331	316	343	211
	2.6	223	154	136	80
	Mean Value	211.0	226.0	179.0	118.3
30% Urea	2.6	571	435	299	211
	2.5	397	326	318	263
	2.7	520	675	464	391
	2.5	497	537	514	394
	Mean Value	496.3	493.3	373.8	314.8
PVP	2.8	775	674	532	442
	2.6	554	587	472	396
	2.9	480	618	302	349
	2.9	348	309	301	250
	Mean Value	539.3	547.0	401.8	359.3
None (Control)	3.0	357	308	267	166
	2.7	317	226	216	193
	2.5	389	403	426	404
	2.5	332	267	242	166
	Mean Value	348.8	301.0	287.8	232.3

The level of the rate in control group was almost equal to that of the control group immediately after brain compression. The level of glucose group was consistently low as compared with the control level. However the levels of both the urea and PVP groups were slightly increased relative to the controls.

(b) Turnover of ^{32}P from CSF to blood

The turnover rate of ^{32}P from CSF to blood is shown in Table 6. The blood level of ^{32}P in the control group increased up to 60 min. with a pattern similar to that of the control group of normal animals.

The average values of the turnover rates for each group are shown in Fig. 6.

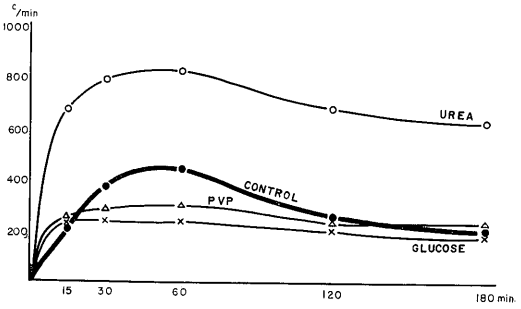


Fig. 6. Follow up of mean values in the turnover of ^{32}P from CSF to blood (absorption rate) in animal after a 24 hour period of brain compression following intravenous administration of different hypertonic solutions.

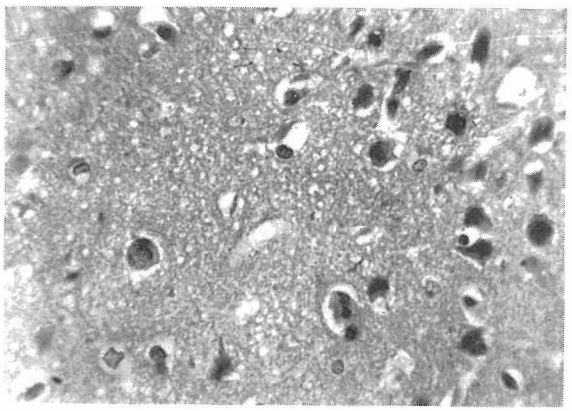
Table 6. Appearance of ^{32}P in Blood Following Intracisternal Injection (100μc) in Rabbit Subjected to Brain Compression: After a 24 Hour Period of Compression.

Administered Solution	Body Weight (Kg.)	Count/min. in 0.1 ml. Blood 15min.	30min.	60min.	120min.	180min.
50% Glucose	3.0	199	211	290	226	222
	2.5	195	225	203	200	248
	2.8	253	256	219	185	154
	2.7	242	273	242	210	148
	Mean Value	222.3	241.3	238.5	205.3	193.0
30% Urea	3.0	651	600	804	683	607
	3.0	708	857	935	756	526
	3.0	679	716	779	615	761
	2.8	512	767	861	659	638
	2.8	851	1032	739	728	638
	Mean Value	680.2	794.4	823.6	688.2	634.0
PVP	2.8	275	260	242	233	209
	2.6	272	348	434	298	272
	2.7	198	252	274	220	230
	2.8	198	253	261	236	226
	Mean Value	235.8	278.3	302.8	246.8	234.3
None (Control)	3.0	171	226	294	120	108
	3.0	174	311	585	265	176
	2.7	268	684	658	382	304
	2.6	212	409	381	295	217
	2.6	223	263	310	225	209
	Mean Value	209.6	378.6	445.6	257.4	202.8

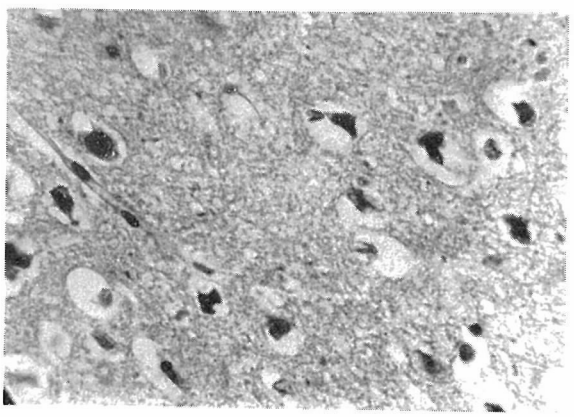
Conspicuous elevation of the level in urea group was noted in all phases of the experiment, running parallel with control group but with the levels two to three times as high. On the other hand, in the glucose group, the level was slightly lower than the controls, while of the PVP group was almost the same as the control.

(c) Water content and histological study of the brain.

Water content of the brain after 24 hours from the beginning of the brain compression was 77.53 %, while that of the normal brain was 75.80 % as shown in Table 7 and 8, the difference between them being no more than 1.73 %. On the other hand, histological findings of both normal and postcompression brain showed no remarkable difference. (Fig. 7)



normal



after a 24 hour period of brain compression.

Fig. 7. Histological findings of the cerebral cortex in normal animal and the state after a 24 hour period of brain compression.

Table 7. Water Content of Normal Rabbit Brain

Body Weight (Kg.)	Water Content in Cortex (%) Left Hemisphere	Right Hemisphere	Difference Between Both Sides (%)
2.5	76.11	72.47	3.64
2.7	74.91	74.73	0.18
2.5	77.86	77.60	0.26
2.8	75.90	76.88	0.98
Mean Value	76.20	75.41	1.27
	Average 75.80%		

Table 8. Water Content of Rabbit Brain after a 24 Hour Period of Compression

Body Weight (Kg.)	Water Content in Cortex (%) Compressed Side	Opposite Side	Difference Between Both Sides (%)
2.8	78.03	77.28	0.75
2.7	77.78	77.12	0.66
2.5	76.54	76.47	0.07
2.7	77.95	77.62	0.73
Mean Value	77.83	77.24	0.55
	Average 77.53 (%)		

DISCUSSION

Since the introduction of radioisotopes into the study of the circulation of cerebrospinal fluid, many discoveries have been made in this field, especially about the sites in which CSF is produced or absorbed. This tracer is also useful for investigating the effect of drugs which may alter the dynamics of CSF.

Turnover of ^{32}P from blood to CSF or from CSF to blood has often been used as an estimation of the rate of production or absorption of CSF. The question arises, however, whether the turnover rate of ^{32}P may represent the rate of production or absorption of CSF. In this concern, we should consider how large amount of ^{32}P penetrates into the brain tissue after intravenous or intracisternal injection during a period designated in the experiments.

The amount of radioactive phosphate which enters the brain from the blood circulation is very small.[3] Only a small fraction of ^{32}P, approximately 0.02% of the total amount given parenterally is deposited in the brain in the first twelve hours following the injection. Both diffusion from plasma to cells and uptake of inorganic phosphate into organic combination are slow.[14]

Bakay summarized the concept about the fate of ^{32}P introduced into general blood circulation.[1] According to him, blood-brain barrier slows down the diffusion of phosphate ions from the plasma, while at the same time phosphate ions pass through the choroid plexus into the ventricular fluid in greater quantity, although still not as easily as into other body fluid. Once in the CSF, these

ions are taken up rapidly by the central nervous system.

On the other hand, it was demonstrated by many investigators that the considerable amount of ^{32}P was taken up by brain tissue rapidly when it was introduced into CSF. Bakay and Lindberg[2] found that after intracisternal injection, the brain concentrates large amounts of ^{32}P very rapidly. When the concentration curve passed its maximum after 30 min., 20 % of the injected ^{32}P was found in the brain, about a quarter of it being already in organic compounds.

Lindberg and Ernster[13] demonstrated a high deposit of ^{32}P, chiefly in the form of adenosintriphosphate and phosphocreatine, following intracisternal injection. Within two minutes, 40 % of the intracisternally administrated phosphate was found in organic linkage; and at eight hours, 70 %.

From above evidences, it is unlikely that the rate of turnover of ^{32}P injected either intravenously or intracisternally is regarded as a direct indication of bulk formation or absorption of CSF. In spite of these shortcomings, radioactive phosphate has still been employed as a measure of CSF dynamics by many investigators because of its easiness in obtaining and handling.

In this study, taking into account these problems, the estimation of the rate of formation or absorption of CSF was made by measuring the turnover rate of ^{32}P, on the standpoint that the former roughly corresponds to the latter unless hypertonic solutions alter the phosphate metabolism within the brain cells. The suitability of ^{32}P as a tracer in the studies of CSF dynamics is examining in our laboratory.

As for the effect of hypertonic glucose solution upon the CSF circulation, it is reasonable to presume, on the basis of recent experiment,[7] that this solution, given intravenously, decreases the production of CSF, contrary to the earlier concept maintained by Weed[17] that the fall of CSF pressure caused by hypertonic glucose solution is due to the dehydration of the brain and CSF.

On the other hand, hypertonic glucose appears to have little effect on normal CSF pressure as demonstrated by both clinical and experimental studies.[16] From this view point, it is necessary to observe not just the production of CSF but all phases of the dynamics of CSF to understand the effect of hypertonic solutions.

In this experiment, it has been possible to explain the disagreement between the studies mentioned above by measuring both the production and absorption of CSF. When 50 % glucose solution was injected intravenously, in normal animals, the rate of production of CSF decreased to half of the control level (Fig. 1). On the other hand, the rate of absorption also decreased to approximately half of the control level following a transient slight increase (Fig. 2). It is clear from these data that, in normal animals, the effect of hypertonic glucose

solution upon CSF pressure is negligible with the exception of a short initial period.

Immediately after subjecting animals to brain compression, however, glucose caused a smaller decrease in the production of CSF relative to the controls, but the effect was of longer duration. At the same time, the duration of the increase in absorption rate, relative to the normal animals, was prolonged for a period of up to 100 minutes.

Consequently, in circumstances in which CSF pressure is acutely increased, the injection of hypertonic glucose may cause some fall in CSF pressure through the combined effects of a decrease in production and an increase in absorption. However, this effect cannot last for more than two hours following injection. This concept is compatible with clinical observations by Takahashi[16] and Ishibashi[7] who found that the effect of an injection of 50 % glucose to lower the intracranial pressure was greater in cases with increased intracranial pressure, and was less without increased pressure.

In animals after a 24 hour period of brain compression, the data were similar to those for normal animals, as far as 50 % glucose was concerned, except for the absence of an initial increase in the absorption rate of CSF. Therefore, in this condition, hypertonic glucose would hardly be expected to cause a fall of CSF pressure, because both the production and absorption rate decreased to almost same extent when compared with the control levels.

From above results, it is suggested that in the brain which has been subjected to mechanical compression of such degree for 24 hours the function of the blood-CSF barrier has been restored in contrast with the acute stage of compression. This view is in accord with the observations on the water content and histological appearance of the brain after a 24 hour period of compression, at which time there was no evidence to support any brain edema.

Concerning hypertonic urea, many favorable reports have been published as to its dramatic effect in decreasing CSF pressure, both experimentally and clinically. In the present experiment, the results appeared to be consistent with these reports: in the animals with urea, the absorption rate of CSF was remarkably high, more than twice as high as the control level in all three groups, though production rates also showed slight increase. Thus, hypertonic urea increased significantly the absorption of CSF, without reference to the initial level of CSF pressure. Hence the net reduction in CSF volume and tension, caused by the hypertonic urea, may be attributed to a marked increase in absorption which overcomes the slight increase in production. Clinically, however, it was reported by Javid[9] on the basis of 700 cases that, the higher the initial CSF pressure, the greater the pressure-reducing effect of urea. Our findings are essentially similar to this report, when a comparison is made, from a hydrodynamic viewpoint,

between results obtained on the normal and postcompression groups.

Previously, the effect of urea to reduce CSF pressure was thought to be due to its diuretic effect. However, it is now believed that the movement of water from the tissue into the blood plays an important role in this mechamism. From this view point, the essential action of urea must be the promotion of CSF absorption, in agreement with our results.

Furthermore, control examination of the present data indicates that, immediately after brain compression, the absorption rate with urea was low compared with the normal animals and with the animals subjected to a 24 hour period of compression ; and that these latter two groups were more or less the same. This may be additional evidence to indicate that the brain having been subjected to compression for 24 hours, is restored approximately to normal with regard to its blood-CSF barrier.

Attention should be paid to the fact that, of these three hypertonic solutions, only urea has a marked effect in decreasing CSF pressure, even under conditions of normal pressure. PVP will be discussed later.

On the basis of these facts, it is suggested that the clinical use of hypertonic urea may be of considerable interest.

PVP differs from glucose and urea in being biological, artificial colloid. Because of its colloidal osmotic properties this agent has recently received consideration clinically for use in cerebrospinal hypertension as a dehydrating agent. From Kuromatsu and Matsuda's clinical report,[11] PVP acted in such a manner that, the higher the CSF pressure, the larger the rate of fall in the pressure observed; and little effect was shown in the cases with normal CSF Pressure. They also noticed that the fall in pressure induced by PVP was maintained for a period of from 30 minutes to 10 hours, following injection in cases with cerebrospinal hypertension. The present experimental results with PVP were essentially similar to their report: In the group immediately after brain compression, the absorption rate of CSF appeared to increase slowly and steadily and remained at more than twice the control level after 3 hours following injection, while the production rate was not changed significantly as compared with control. On the other hand, in the normal group and after 24 hours of brain compression, it seems to have had no remarkable effect on the hydrodynamic state of CSF, since the production of CSF may be considered to be in a state of dynamic equilibrium with its absorption.

Fig. 8 illustrates the production and absorption rates, relative to the control values, following the administration of each of the hypertonic solutions. Differences between rates are indicated by the thickness of the arrows, and comparison of production with absorption indicates the hydrodynamic state of CSF circulation in each group. The right half of this figure indicates the changes in CSF

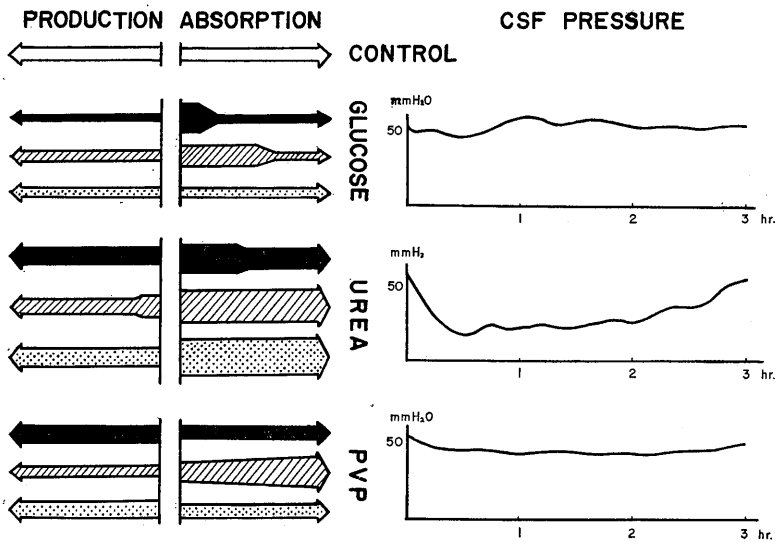


Fig. 8. Left: Illustration of the CSF dynamics under administration of different hypertonic solutions. The thickness of arrows indicates the level of production and absorption rate. Shaded arrow: normal animal. Hatched arrow: immediately after brain compression. Stippled arrow: after a 24 hour period of brain compression. Right: CSF pressure in normal animals following intravenous administration of each solution.

pressure which are actually measured in untreated anesthetized normal rabbits following the intravenous injection of each of the three hypertonic solutions. In general it is important to say that an integrated assesment is necessary in the field of hydrodynamic study of CSF circulation rather than a separate observation of either production or absorption as many investigators have done, i.e. the best method of assesment is to evaluate the difference between production and absorption. This is particularly true of studies to estimate the effect of drugs.

In conclusion, hypertonic urea is the most effective agent of the three hypertonic solutions tested, without reference to the initial level of CSF pressure. Hypertonic glucose and PVP appear to effect the CSF pressure only under the circumstance which pertain immediately after brain compression.

It is interesting that after a 24 hour period of brain compression, hydrodynamic studies as well as measurement of brain water content and histology revealed considerable improvement from the initial impairment in the blood-CSF barrier and no evidence of brain edema. The only possible explanation of this fact is that the function of the brain must have been restored by means of compensatory adjustment to the harmful stimulus resulting from the mechanical compression. Because of this compensation, a presumption may be made that irreversible brain

edema is hardly likely to take place following compression of such degree, contrary to our expectations.

The effect of these hypertonic solutions under circumstances in which the brain develops more severe edema has not been evaluated. Further study of this problem is necessary.

SUMMARY

The effect of three different hypertonic solutions, 50 % glucose, 30 % urea and polivinylpyrrolidon (PVP), on the production and absorption of CSF was studied in the rabbit using the radioisotope, ^{32}P. Experiments were performed in three groups of animals; normal, immediately after brain compression, and after 24 hour period of compression.

From the results obtained by measuring the turnover of ^{32}P from blood to CSF (production rate) and from CSF to blood (absorption rate), an estimate was made of the effect of each solution upon CSF dynamics.

Hypertonic glucose may produce a short lasting decrease in CSF pressure only in the acute compression group, while this effect may be negligible in the remaining two groups. On the other hand, hypertonic urea seems to produce a remarkable fall in the CSF pressure in all three groups, as a result of a conspicuous increase in the absorption of CSF which outweighs the slight increase in production. PVP however appeared to produce a consistent decrease in CSF pressure only in the group subjected to acute compression, since the rate of absorption increased gradually and progressively together with the slight decrease in production in this group. In the remaining two groups, the effect of PVP upon CSF may be negligible as with glucose.

Following a 24 hour period of brain compression, it is suggested from the results that the function of the blood-CSF barrier recovers from the impairment caused by mechanical compression, at least after such very mild compression as was employed in this experiment. Likewise, there is no evidence of brain edema in this condition from the measurement of water content and histological study of the brain.

The hydrodynamics of CSF is too complicated to be understood from the observation of a single phase in the CSF circulation. Any attempt to describe alteration of CSF dynamics must include a consideration of the phases of both production and absorption of CSF simultaneously.

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