The Effect of Osmotic Pressure on the Production of Cerebrospinal Fluid

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Summary

The effect of the osmotic gradient between plasma and CSF on the rate of CSF formation was studied in rabbits using the ventriculo-cisternal perfusion technique. The rate of formation of CSF in the control animals with isosmolar perfusion was found to be 10.9 ± 0.5 μl/min.

In order to raise the plasma osmolality, 20% mannitol was intravenously administered as a bolus after a steady-state condition of perfusion was attained. Rapid readjustment of plasma osmolality was observed after the mannitol injection, though the osmotic gradient was reversed for CSF formation throughout the 3-hour period of perfusion. In spite of such an adverse osmotic gradient, the rate of the bulk formation of CSF was still maintained by more than 50% of the control value.

Hypertonic perfusion was performed by adding NaCl or monosaccharides into the perfusion fluid. A remarkable increase in the rate of formation of CSF was observed in the NaCl perfusion, after a steady state was achieved in the perfusion system, while in the monosaccharide perfusion, the increase in the rate of formation of CSF was not only less marked but also of shorter duration, despite the increased osmolality of the perfusate.

In face of the experimentally imposed osmotic gradient between both sides of the choroidal epithelium, the osmotic flow of water across the ependyma may take part in the mechanism of CSF production. However, when such an osmotic gradient is produced by nonelectrolytes, homeostatic regulation of CSF formation may take place. In such a mechanism, Na+ ion is likely to play a role as a regulatory factor.

Key words:
cerebrospinal fluid, homeostasis, mannitol, osmotic gradient, osmotic pressure, production rate

Introduction

The mechanism of cerebrospinal fluid (CSF) production has been studied by many investigators in recent decades. Although most of them agreed that the secretory process by the choroidal epithelium plays an important role in the formation of CSF,1.11.12.18) osmotic flow has also been reported to have some relation in the production of CSF.19.30) On the other hand, it is known that osmolarity in the CSF is remarkably constant and also is strictly regulated with regard to blood values.28)

The osmolarity of body fluid depends mainly upon the concentration of Na+. In a steady state, CSF Na+ is equilibrated in the slightly higher level than in plasma Na+.12) If this equilibrium is disturbed by acute changes in electrolytes in body fluids, the osmotic imbalance between blood and CSF may cause an impairment of water metabolism within the central nervous system (CNS), such as edema or dehydration, leading to severe damages of CNS functions. For instance, hyponatremia due to the cerebral salt wasting syndrome or “inappropriate secretion of antidiuretic hormone” readily brings about impairment of consciousness.

Furthermore, Bowsher5) suggested that the development of hydrocephalus is an osmotic process in which excess sodium in the fluid from the choroid plexus is presumed to attract water in order to render itself isotonic with the plasma and the tissue fluids of the neuraxis.

In this context, investigation of the possible
role of osmotic flow in the formation of CSF may be fundamental in order to elucidate pathogenesis of various disease relating disturbance in water metabolism within CNS or CSF circulation. This study was designed to investigate changes in the rate of CSF formation in experimental conditions in which osmolarity was raised in the compartment on either side of the choroidal epithelium using the ventriculo-cisternal perfusion technique in rabbits.

Materials and Methods

Adult albino rabbits of both sexes, weighing 2.5–3.5 kg were used. Animals were anesthetized by intravenous sodium pentobarbiturate, at 15 mg/kg, with additional doses given as necessary. Tracheostomy was performed and an endotracheal tube was inserted and connected to a small animal respirator. The rate and volume of respiration were adjusted to maintain normal blood gas and pH values. The rabbit was placed in a stereotaxic instrument and the head was tightly fixed. The left femoral artery was catheterized for blood sampling and pressure monitoring with a strain gauge transducer (Nihon Kohden, model MPU-0.5).

Surgical Techniques: Through a midline scalp incision, right parietal craniostomy was performed with a twist drill 2 mm in diameter, 1 cm caudal to the coronal suture and 0.8 cm lateral to the midline. The nuchal musculature was then incised in the midline and the deep ligaments were preserved for obtaining the effluent from the cisterna magna.

Ventriculo-cisternal Perfusion: The inflow device consisted of a 21-gauge blunt-tipped needle with attached fine polyethylene tubing, 0.8 mm in diameter, from the 20-ml syringe, which was placed in the infusion pump (Nakagawa Seikodo). The outflow cannula, an 18-gauge needle, was connected to the polyethylene tube which was approximately 2 mm in diameter.

The inflow cannula was driven into the lateral ventricle to a depth which was 0.8 cm from the bone surface with the aid of a micromanipulator. The proper placement of the cannula was assured by the abrupt drop of manometric pressure upon entry into the ventricle. After insertion of the inflow cannula, the twist-drill hole of the skull was sealed with surgical adhesive.

Confirmation of proper placement of the cannula was done by trans-cannular perfusion with dye (Trypan blue) immediately after termination of the experiment. Then the rabbit was sacrificed and the brain was removed. Failure to reach the ventricle was indicated by the absence of ependymal staining. The hydrostatic pressure was monitored by a low-pressure transducer (Nihon Kohden, model LPU-0.1) inserted within the perfusion system throughout the experiment. Cisternal puncture was performed by the outflow cannula through the nuchal ligaments. The height of the outlet of the outflow tube was adjusted in order to maintain the hydrostatic pressure within the range of ±5 cm H₂O. The entire perfusion system is schematically illustrated in Fig. 1.

After the perfusion system was completed, the ventriculo-cisternal perfusion was continued for 2–4 hours with a fixed rate, approximately 46 µl/min. The rate of inflow was measured before and after the perfusion in each experiment. Collection of samples from the outflow tube was done at 15-minute intervals. Since the steady-state condition was reached an hour after the beginning of the perfusion, the first four successive samples were discarded. If blood appeared in the effluent at any time, the experiment was terminated. The quantity of each sample was measured gravimetrically.

Perfusion Fluid: The standard artificial CSF for perfusion was made of 154 mM NaCl, 2.8 mM KCl, 1.1 mM CaCl₂, 0.8 mM MgSO₄, and inulin (80 mg/dl) according to the method of Bradbury and Davson. The osmotic pressure

Fig. 1 Diagramatic representation of the ventriculo-cisternal perfusion system. LV: lateral ventricle, III: third ventricle, A: aqueduct of Sylvius, IV: fourth ventricle, CM: cisterna magna
of the perfusate at each experiment averaged 298 ± 9.2 mOsm/L in the control group and 293 ± 5.6 mOsm/L in the mannitol group.

For the hypertonic perfusions, two kinds of perfusate were prepared: 1) the osmotic pressure of the perfusate was raised to 335 mOsm/L by adding 24 mM NaCl into standard artificial CSF. 2) Hyperosmosis of the perfusate was obtained by adding 40 mM xylose plus 5 mM glucose into the standard artificial CSF, yielding an osmotic pressure of 345 mOsm/L. Care was taken to prevent the total concentration of glucose from exceeding 300 mg/dl because beyond such a concentration, the color of the fluid itself interferes with spectrophotometric measurement.33) (Table 1)

<table>
<thead>
<tr>
<th>Type of Experiment</th>
<th>Number of Experiments</th>
<th>Osmotic Agents Added to Artificial CSF</th>
<th>Osmolarity (mOsm/L)</th>
<th>Concentrations of Electrolytes (mEq/kg H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>(12)</td>
<td>None</td>
<td>298</td>
<td>Na 153.8 ± 1.0 K 2.8 ± 0.1 Cl 158.7 ± 4.2</td>
</tr>
<tr>
<td>NaCl Group</td>
<td>(8)</td>
<td>24 mM NaCl</td>
<td>335</td>
<td>Na 177.8 ± 2.8 K 3.0 ± 0.1 Cl 173.7 ± 7.1</td>
</tr>
<tr>
<td>Xylose-glucose</td>
<td>(8)</td>
<td>40 mM xylose + 5 mM glucose</td>
<td>345</td>
<td>Na 154.8 ± 0.6 K 2.9 ± 0.1 Cl 150.6 ± 2.3</td>
</tr>
</tbody>
</table>

Table 1 Composition of perfusates in control and hypertonic perfusions. Concentration of electrolyte is expressed as mean value ± standard deviation.

Analysis: Estimation of osmotic pressure was performed by the freezing point determination using an osmometer (Advanced Instruments, Inc., model LS). Inulin concentration was determined by the resorcinol-thiourea method.29) A spectrophotometer (Hitachi, model 102) was used for the analysis at the wavelength of 520 nm.

Results

(1) Calculation of CSF Formation Rate

Calculation of CSF formation rate was performed according to the method of Heisey et al.,19) namely that inulin, a molecule of high molecular weight, is barely diffusible across the ependymal linings, and is lost from CSF only by bulk absorption distal to the fourth ventricle. Therefore, the clearance of inulin represents virtually the rate of the bulk absorption of CSF. On the other hand, in the steady-state perfusion system, the rate of bulk formation of CSF is expressed as the outflow-inflow difference plus the bulk absorption. Thus

\[ \dot{V}_f = C_{\text{in}} + \dot{V}_o - \dot{V}_i \]  

(1)  

\[ C_{\text{in}} = \frac{\dot{V}_o c_i - \dot{V}_i c_o}{c_0} \]  

(2)

where \( \dot{V} \) is the formation rate of CSF; \( C_{\text{in}} \), inulin clearance; \( \dot{V}_o \), rate of effluent flow; \( \dot{V}_i \), rate of perfusion; and \( c_i \) and \( c_o \) represent the concentration of inulin in influent and effluent fluid.

(2) Control Group

Ventriculo-cisternal perfusion with standard artificial CSF was performed in 12 animals for a period of 75 minutes after a steady state was reached (Fig. 3). The mean formation rate of CSF was 10.9 ± 0.5 μl/min which compares fa-
vorably with that reported by Bradbury and Davson in rabbits. Slight fluctuation of values at each time interval was observed, but no statistical difference was detected.

(3) **Effect of Intravenous Hypertonic Mannitol Solution**

Consecutive two 15-minute samples were taken after a steady state was achieved and these samples served as its own control in each experiment. The mean rate of normal CSF formation in this series calculated from 16 samplings was $11.3 \pm 0.8 \mu l/min$, which was slightly greater than the mean value in the control group, although statistically not significant.

The rate of formation after mannitol administration is shown in Fig. 2. The formation rate gradually but slightly decreased until an hour after mannitol injection, and maintained a lower rate up to 3 hours. At the peak at 60 minutes after the mannitol injection, the mean formation rate was $5.5 \pm 1.3 \mu l/min$; a 51% decrease from the control level ($p < 0.01$). The two successive decreased rates; $5.7 \pm 1.2$ and $6.7 \pm 1.3\mu l/min$ were followed thereafter; a 50% ($p < 0.01$) and 41% ($p < 0.05$) decrease from the control level respectively. No statistical significance was demonstrated in the decreased rate in all other time periods after the mannitol administration.

The bulk absorption rate (inulin clearance) rapidly increased to reach $32.4 \pm 6.7 \mu l/min$ within 15 minutes after the mannitol injection. This value was 9 times greater than the mean value in the control condition before mannitol injection; $3.6 \pm 1.2 \mu l/min$. The bulk absorption rate then decreased shortly to reach the control level within 30 minutes after the injection, and maintained the same, or a lower level thereafter (not shown in the figure).

Serum osmolarity rapidly increased and reached its maximum level of $314 \pm 2.3 \text{mOsm/L}$ five minutes after the mannitol injection (a 7.1% increase from the control level of $293 \pm 2.6 \text{mOsm/L}$). It then rapidly decreased to reach a plateau level 15 minutes after the mannitol injection, so that osmotic gradient of $9 \sim 14 \text{mOsm}$ was maintained between blood and perfusate during a period from 15 minutes to 3 hours after the mannitol administration (Fig. 2).

The hematocrit of femoral arterial blood slightly decreased concomitantly during the short period in which serum osmolarity was increased, probably reflecting the dilution of blood (Fig. 2). Blood pressure slightly fell after the mannitol administration. The maximal decrease of blood pressure was 10% less than the control level at 45 minutes after the mannitol injection (not shown in the figure).

Cisternal pressure under the mannitol injection was measured in five normal rabbits other than the perfusion series. Pressure decreased rapidly and reached the maximum drop, 41% less than the control level, at 25 minutes after the mannitol injection. The pressure gradually returned to normal level over 3 hours without any rebound rise (Fig. 2).

(4) **Hypertonic Perfusions**

In the NaCl group, the formation rate of CSF markedly increased and remained high throughout the entire experiment (Fig. 3). The mean
formation rate was $23.6 \pm 0.9 \mu l/min$ which represented a 117% increase from the control level ($p < 0.01$).

In contrast to the NaCl group, the xylose-glucose group revealed different results. In the first two sampling periods after a steady state was reached, the formation rate showed a significant increase; 66% and 53.6% increases respectively ($p < 0.01$). However, the values returned to the control level thereafter in spite of continuous maintenance of the osmotic gradient of approximately 45 mOsm between blood and perfusate. (Fig. 3).

**Fig. 3** Rate of CSF formation of the ventriculo-cisternal perfusion with isotonic and hypertonic perfusates. The measurements started 60 minutes after the beginning of the perfusion, when a steady state was attained. The mean values of CSF formation rates are plotted at the mid-point of each 15-minute sampling interval. Broken line with triangles: hypertonic NaCl perfusion; Dotted line with open circles: hypertonic xylose-glucose perfusions; Solid line with closed circles: isotonic perfusions (control group). The vertical bars represent the standard errors.

Bulk absorption (inulin clearance) also increased in the rates corresponding to the increase in the bulk formation; mean values of the bulk absorption was $5.1 \pm 0.8 \mu l/min$ in the controls, $11.7 \pm 1.1 \mu l/min$ in NaCl group, and $7.7 \pm 1.5 \mu l/min$ in xylose-glucose group (not shown in the figure).

**Discussion**

Under normal conditions, plasma and CSF are almost isotonic in various animals (Table 2). In the present experiments, the estimated mean values of osmotic pressure in both fluids were somewhat different between two sets of control series, while the ratios for osmolarities of CSF vs plasma ($R_{CSF}$) were almost identical. Therefore, isosmolality was maintained on both sides of the choroidal epithelium in the control condition, in which state the osmotic influence upon the formation of CSF may be negligible. In such a situation, it is conceivable that the CSF is produced by secretion. The mechanism for such an isosmolar secretion has been explained by postulating an active transport of ions across the choroidal epithelium. Water would be transferred rapidly into the ventricle by diffusion with ions so that an approximately isosmolar flow would be achieved in the steady state.

Heisey et al. first investigated the correlation of the rate of formation of CSF with osmotic gradients between plasma and CSF using the technique of ventriculo-cisternal perfusion in the goat. Welch et al. also demonstrated an increase in bulk flow into hypertonic fluid bathing the choroid plexus. From these observations, it is clear that the rate of formation of CSF is sensitively influenced by an osmotic milieu outside the choroid plexus. However, the concept of a secretory property of the choroid plexus would be incompatible with the fact that the rate of CSF formation depends upon an osmotic gradient. Therefore, osmotic flow through the ependymal walls of the ventricles might be considered a contributing source of fluid, as Heisey et al. suggested, although the choroid plexus still has the major role in CSF production. Transependymal bulk formation of CSF was also demonstrated by Pollay and Curl using aqueductal perfusion in rabbits.

Concerning the osmotic flow in face of experimentally imposed osmotic gradient between both sides of the choroidal epithelium, Heisey et al. and DiMattio et al. found that there was a linear correlation between the magnitude of osmotic gradient and the bulk flow rate. However, their results were based on the single estimation of the bulk flow rate in a steady-state situation of various levels of plasma or CSF osmolarity and not on a dynamic study in pursuit of time course under such altered osmotic gradient as ours.

In the present experiment, hypertonic mannitol was injected as a bolus so that complete inhibition of CSF formation, as DiMattio and coworkers observed in their experiments with continuous hypertonic infusion, did not occur.
because of a rapid readjustment of plasma osmolarity leading to lowering the osmotic gradient between both fluids by dilution of the blood. However, plasma osmolarity was continuously raised so as to maintain a higher osmolality in the plasma than in the perfusate. In such a steady-state condition, in which state there was an osmotic gradient favoring flow of fluid back into the blood, bulk flow of the fluid into the ventricle was still continued to more than 50% of the control level. Such mechanism of up-hill water transport for the bulk formation of CSF was also shown by Heisey et al.191 and Welch et al.32)

In the earlier experiments in our laboratory, we observed a remarkable increase in the turnover rate of $^{32}$P from CSF to blood after intravenous injection of hypertonic urea.21) A remarkable transient increase in the bulk absorption rate (inulin clearance), as much as 9 times greater than the control level, was also observed shortly after the intravenous administration of mannitol in the present experiment. Such an increased rate of bulk absorption may represent extraction of water from the brain and CSF compartments into blood, thus causing a 40% fall of CSF pressure. In spite of such an acute and intense dehydration of the CNS, the calculated rate of bulk formation of CSF was unchanged from the control level during the corresponding period of increased absorption, presumably reflecting a homeostatic regulation of CSF formation against an acute dehydration. A significant decrease in bulk formation took place with some delay after the increased rate of bulk absorption was reversed. Such a decreased rate of CSF formation continued up to 3 hours until the cisternal pressure recovered to the control level, probably resulting from an adverse osmotic gradient.

Although we did not measure the electrolyte concentration in plasma, Wise31) reported an 11.6% fall of Na$^+$ concentration in serum in a patient at the conclusion of the infusion of hypertonic mannitol, at which point the osmotic gradient between CSF and serum was determined as 27 mOsm. Such difference in concentrations of Na$^+$ ion between these two fluids may possibly explain the continuation of CSF formation against an adverse osmotic gradient.

In the second part of the present study, the intraventricular osmotic pressure was enhanced by adding different osmotic agents, salt and monosaccharide, into the perfusion fluid. Consequently, the rate of CSF formation increased to twice that of the control level in the NaCl group, while increases in the rate were less marked and of shorter duration in the xylose-glucose group despite the fact that the resulting osmotic gradient was greater in the latter than in the former group.

Accounting for the different results from the two series of hypertonic perfusions, a different osmotic response of these two osmotic agents, ionic and non-ionic, to the CSF production system should be considered. Since molecules of salt and monosaccharide seem to be easily permeable to the ependyma, diffusion of these molecules into the brain extracellular fluid across the ventricular wall might have some effect upon the change of bulk flow rate of CSF.

In order to consider the different attitude of the changes in CSF formation between the two series of experiments, the difference in permeability of the ependymal wall to salt and monosaccharides must be known. Thus, according to Heisey et al.,19) the computed permeability coefficient for $^{24}$Na across the ependyma of the goat is approximately the same as that for urea, while the permeability coefficient for $d$-glucose and $d$-xylose for the rabbit is greater, by four and three times, respectively, than that for urea.9) Since the value for urea in the goat and rabbit appear to be the same order of magnitude, monosaccharide may presumably pass across the ependymal epithelium more easily than Na$^+$ when the ventricle is perfused with a hypertonic solution of these solutes. If so, then, in the case of hypertonic perfusion with monosaccharide, osmotic equilibrium between both sides of the ependyma may be attained more rapidly than in the case with NaCl so that the osmotic influence upon water movement would disappear earlier in monosaccharide perfusion than in NaCl perfusion.

However, experimental evidence exists both in vivo and in vitro supporting the concept of sugar transport including more complex mechanisms such as carrier saturation and competition transport.5,6,7,9,15,17,24) Considering the selectivity involved in the transport mechanism of sugars, it is difficult to reach a single conclusion based on a simple concept of osmotic equilibrium. Therefore, further investigation, includ-
ing analysis of tissue fluid of the brain, is necessary.

In hypertonic perfusions, bulk absorption of CSF (inulin clearance) also increased in the rates corresponding to the increase in the bulk formation, thus preventing the increase in CSF pressure by accumulation of the fluid into the ventricle. A question arises here as to whether penetration of tracer inulin into the brain across the ependyma could, in part, be responsible for enhanced clearance of inulin since experimental evidence suggested that the increased clearance of the nonelectrolytes in the hypertonic perfusion system may have been the result of ependymal cell shrinkage and consequent widening of these intercellular channels. However, this may be not the case since Calhoun et al. found that the clearance of inulin from hypertonic perfusion fluid in the ventricular system of calves was not significantly higher than from isotonic perfusion fluid.

The experimental results demonstrated that in the case of the non-ionic hypertonic perfusion an early readjustment of increased bulk flow of CSF took place in contrast to the ionic hypertonic perfusion. This fact is compatible with participation of the Na⁺ ions in the osmotic regulation and water regulation of CSF. In fact, plasma osmolality and Na⁺ concentration in both effluent and plasma were measured in 6 animals after 105 minutes from the beginning of the hypertonic perfusion in the xylose-glucose group. In the results, plasma osmolarity increased by 20-40 mOsm, and the distribution ratio of Na⁺ for effluent vs plasma decreased to 0.97 from the control value of 1.01. From these observations, it is suggested that an early readjustment of osmotic gradient may occur by means of Na⁺ transfer from the ventricle to blood during non-ionic hypertonic perfusion. Sweet et al. virtually demonstrated that sodium was moving from CSF to blood independently of water in their observations using ⁴Na and D₂O. In this respect, experimental results reported by Ames, Higashi and Nesbett stimulate our interest. They showed that when 10% glucose was infused in the cat, plasma osmolality was not changed in spite of an 11% fall of Na⁺ and Cl⁻ concentration in plasma, being made up by glucose, so that isosmolarity would have been maintained between plasma and CSF. In such situation, no changes were found in Na⁺ and Cl⁻ concentration in the newly formed CSF collected from the exposed choroid plexus.

The role of Na⁺ ions as a regulative factor for osmotic disequilibrium was demonstrated in patients with increasing severe renal failure by Prill. In their cases, in face of hypoosmolarity in CSF with respect to the blood because of increasing retention of urea in the blood, the osmolarity of the CSF is readjusted to that of the blood by a compensatory increase of the Na⁺ ion exchange to the CSF, thus preventing dehydration of the brain.

The interesting features of acute osmotic imbalance between blood and CSF is observable in the “dialysis disequilibrium syndrome” in which severe neurological symptoms develop at the end of, or following, successful hemodialysis of uremic patients. Pappius et al. demonstrated an increase in ventricular pressure during hemodialysis of dogs with experimentally induced uremia owing to osmotically induced movement of water into the CSF compartment. On the other hand, DiMattio et al. showed that acute alteration of serum osmolality affects brain water as well as bulk flow of CSF into the ventricle.

Now evidence has been accumulated indicating a rapid exchange of water between blood and brain across brain capillaries by simple diffusion. When plasma osmolality is altered, there is a relating rapid adjustment of brain osmolality brought about by the appropriate net transport of water across the capillary endothelium. Therefore, it is necessary to take into account the transcapillary as well as transchoroidal and transependymal water transport altogether in order to understand the movement of water in response to altered osmolarity.

**Conclusion**

Our observations in the present study indicated that there might be a regulating mechanism in osmotic flow of the fluid into the ventricle when the osmotic gradient between blood and CSF in either direction is imposed by nonelectrolytes. Absence of such regulation in the bulk formation of CSF in hypertonic NaCl perfusion suggests that the Na⁺ ion itself probably plays a role in the regulatory mechanism of CSF formation through osmoregulation. Con-
considering the rapid and easy diffusion of water across the ependyma, osmotic flow of the fluid in response to changes in the osmotic gradient and regulation of such osmotic flow to some extent are thought to be a homeostatic mechanism against acute hydration or dehydration of the CNS.

Table 2  Osmolarity of plasma and CSF in various animals and data obtained from the present experiments.

<table>
<thead>
<tr>
<th>Species</th>
<th>Plasma</th>
<th>CSF</th>
<th>R&lt;sub&gt;CSF&lt;/sub&gt;</th>
<th>Reporter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>289</td>
<td>289</td>
<td>1.0</td>
<td>Hendry (1962)&lt;sup&gt;40&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dog</td>
<td>299.6</td>
<td>305.2</td>
<td>1.02</td>
<td>Bito &amp; Davson (1966)&lt;sup&gt;91&lt;/sup&gt;</td>
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<tr>
<td>Cat</td>
<td>308.5</td>
<td>314.8</td>
<td>1.02</td>
<td>Davson (1967)&lt;sup&gt;21&lt;/sup&gt;</td>
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<tr>
<td>Rabbit</td>
<td>298.5</td>
<td>305.2</td>
<td>1.02</td>
<td>Davson (1967)&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dogfish</td>
<td>973</td>
<td>986</td>
<td>1.015</td>
<td>Maren (1962)&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rabbit</td>
<td>292.7</td>
<td>293.4*</td>
<td>1.000**</td>
<td>Higashi &amp; Maza (1976)</td>
</tr>
<tr>
<td></td>
<td>± 9.9</td>
<td>± 5.6</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>299.5</td>
<td>298.2*</td>
<td>0.996***</td>
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<td></td>
<td>± 4.6</td>
<td>± 9.2</td>
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<td></td>
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</tbody>
</table>

*Artificial CSF  **Control group  ***Controls in mannitol group

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