

## Original Investigation

# Can Hypo/Hyponatremic Conditions be a Factor for Na Ion Channel Kinetics: Model Study

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**AIM:** Dysnatremic cases are frequently faced in clinical practice. Its macroscopic effects and consequences are well known, but microscopic effects are not well defined. The aim of this study was to reveal the effects of dysnatremia at the cellular level.

**MATERIAL and METHODS:** By using an action potential simulation, the effects of extracellular sodium (Na) concentration on the Na ion channel kinetics were studied. The experimental sets were chosen to mimic hypo/hyponatremic conditions and, in both cases, the degree of the severity was varied.

**RESULTS:** Hyponatremic situations through modifying the axonal Na<sup>+</sup> channels kinetics result in the rundown of the sodium current (I<sub>Na</sub>). The degree of the hyponatremia-dependent effect seen in the Na ion channel is severity dependent, which is more effective in the recovery phase of the ion channel. Hyponatremic conditions, on the other hand, have also affected the Na ion channel activity through modifying the kinetics of the channel. Unlike hyponatremia, the effect seen in hyponatremic conditions was through decreasing the response time of the channel. The degree of the significance of the effect seen on the Na ion channel in the case of the hyponatremia was found to be less destructive compared to the hyponatremic condition.

**CONCLUSION:** The Na channels are susceptible to the changes of the extracellular Na concentrations. Thus, the underestimation of hypo/hyponatremic conditions can put patients in danger and close monitoring of serum Na level might be required.

**KEYWORDS:** Axonal action potential, Ion concentration, Ion channel, Simulation

**INTRODUCTION**

Action potential (AP), a rapid rise and fall in the electrical membrane potential of a neuron, which is commonly called “firing”, is the basis of signal transmission through a single neuron. An adequate amount of neurotransmitter concentration in the synaptic space creates a series of reactions resulting in rapid activation of sodium (Na) channels, which is called the zero phase (depolarization phase). Na<sup>+</sup> currents (I<sub>Na</sub>) -for all of the excitable tissue types- can be named universal depolarizing currents whereas the K<sup>+</sup> currents (I<sub>K</sub>) are repolarizing currents (6).

The all or none characteristic of the AP actually comes from the Na<sup>+</sup> channel's properties. When the graded potential is

adequate to open the Na<sup>+</sup> channel, the AP is generated and transferred throughout the axon length without any change in the configuration. However if the graded potential is not sufficient to open a Na<sup>+</sup> channel, no AP is observed (29).

Na<sup>+</sup> channels have three conformations in their mode of action which are open, inactive and closed. These modes not only determine the formation of the AP, but also determine the frequency response of the AP under continuous stimulation (16).

There are at least two issues that are important in the formation of the current through the ion channel. The first one is the internal properties of the channel (conductivity parameters) and the second one is the ionic gradient across the ion



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channel, i.e. the difference between the ionic concentration in and outside of the membrane.

The disturbance of water-electrolyte balance may be an implication of disorders in different systems, which causes dramatic changes of the Na level in blood plasma, as known as “dysnatremia” (7). If the Na level is reduced below 135 mM it is called hyponatremia. Hypernatremia, on the other hand, is defined a serum Na concentration above 145 mM. Both of them are commonly seen in hospitalized, postoperative and elderly patients (10).

Software simulating biological systems have been frequently utilized especially when direct recordings from the tissue are tricky due to technical difficulties. Such simulated models not only helped understanding the physiological nature, but they also serve as powerful tools during problem solving. Indeed, simulations provide new research politics, parameters and new working conditions on the working systems. It would not have been possible to test some of these new conditions on living systems.

The macroscopic effects of dysnatremia have been previously reported (12,13,22,28) but its microscopic effects are not well defined. In an excitable cell, like a neuron, Na ion currents are important for the induction of the AP. Effects of extracellular [Na+] can be predictable when there is only a single Na channel on the axonal membrane. However, it is important to observe the changes in the presence of the other ion channels.

We tested the effects of extracellular Na+ concentration (hypo/hypernatremia) on the axonal Na+ channel kinetics in the presence of the other ion channels with the help of a modified axonal AP simulation program (3).

**■ MATERIAL and METHODS**

All of the simulation results were obtained from the modified non-commercial LabAXON 5.2 software program (<http://labaxon.software.informer.com/5.2/>). Under the physiological conditions (in terms of ion concentration extracellular space mM: Na= 136-143, K= 4; intracellular space mM: Na= 10, K=120) of the simulation, neuronal Na+ currents and their kinetics were saved on the hard disk of a computer. All recorded data were used for the further analysis of the parameters.

The states of the Na ion channels used for the simulation were the same that we used previously (3). Briefly, 3 closed, 1 open and 4 inactive states were used for the mode of action. In this Markov representation, alpha (α) and beta (β) parameters represents forward and reverse reaction rates respectively. At equilibrium, activations were calculated by  $m = \alpha_m / (\alpha_m + \beta_m)$ , whereas the time constants (Tau) were found by  $\text{Tau}_m = 1 / (\alpha_m + \beta_m)$ . It is known that, Na channels have activation (m) and inactivation (h) parameters. Similar to the activation calculations, equilibrium inactivation was calculated by  $h = \alpha_h / (\alpha_h + \beta_h)$ , and time constant of inactivation was calculated by  $\text{Tau}_h = 1 / (\alpha_h + \beta_h)$ . Na channel currents and the reaction rate constants of the cell membrane at any moment, as follows,

$$I_{Na} = g_{Na} m^3 h (E - E_{Na})$$

$$\alpha_m = \frac{-0.1 * (E + 35)}{e^{-0.1 * (E + 35)} - 1}$$

$$\beta_m = 4 * e^{-\frac{E + 60}{18}}$$

$$\alpha_h = 0.007 * e^{-\frac{E + 60}{20}}$$

$$\beta_h = \frac{1}{e^{-0.1 * (E + 30)} + 1}$$

were calculated in accordance with the literature where g is the conductivity, m is the activation, h is the inactivation, E is the voltage across the membrane, and ENa is the Nernst potential (14-17).

Na currents were recorded by a standard voltage clamp protocol. Briefly, from a holding potential of -100 mV for 5 ms, depolarizing pulses of 10 ms starting from -80 mV to +70 mV with 10 mV increments were applied.

INa activation characteristic was determined by applying 5 ms prepulse within the range -80 to +70 mV in 10 mV increments that were followed by a 0 mV, 10 ms pulse. In each tested potential, maximum current values were measured and then these measured values were fitted by Boltzmann function ( $I/I_{max} = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + \exp((V50 - X) / \text{Slope}))$ ) for the parameters. Its inactivation was established by applying a 10 ms prepulse within the range -80 mV to -10 mV in 10 mV increments that was followed by a +0 mV pulse 5 ms long. Maximum currents were obtained from the protocol and fitted by another Boltzmann function ( $I = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + \exp((X - V50) / \text{Slope}))$ ) for the parameters. For the reactivations, two pulses (0 mV, 5 ms) with increasing interval durations (5-50 ms) were used. Obtained currents were again fitted by an exponential function ( $I = I_0 + (\text{Top} - \text{Bottom}) * (1 - \exp(-\text{Tau} * x))$ ).

In order to test the effects of extracellular Na+ concentrations ([Na+]o) on the Na ion channel kinetics, three set of [Na+]o were organized. The first set was named hyponatremic conditions and divided into mild ([Na+]o=131 mM), moderate ([Na+]o=121 mM) and severe ([Na+]o=110 mM). The second set was named hypernatremic conditions and divided into mild ([Na+]o=147 mM), moderate ([Na+]o=155 mM) and severe ([Na+]o=165 mM) (21,26,27). These two sets results were compared with the third set named the physiological range (PR) and assigned as the average of [Na+]o=136-143 mM.

The average values of the parameters were obtained from the physiological ranges used for the comparison of the data sets. Values were expressed as mean ± standard error of mean (s.e.m).

**■ RESULTS**

Capacitance measurement is a frequently used technique in electrophysiological measurements and/or calculations as a measure of the cell size (4,5). In our simulations, a sub-threshold square-wave (50 μs and 70 mV) pulse is applied to the membrane and capacitive currents are elicited. By integrating these current traces, the total charge amount can be obtained. The capacitance of the cell membrane is then calculated by dividing the total charge amount by the

difference (voltage) in the applied potential ( $C_m = \text{Total } Q / \Delta V$ ). For our simulations, the axon diameter was assumed as 542  $\mu\text{m}$  and the capacitance of this diameter was 0.010 pF.

**Effects of Hyponatremia**

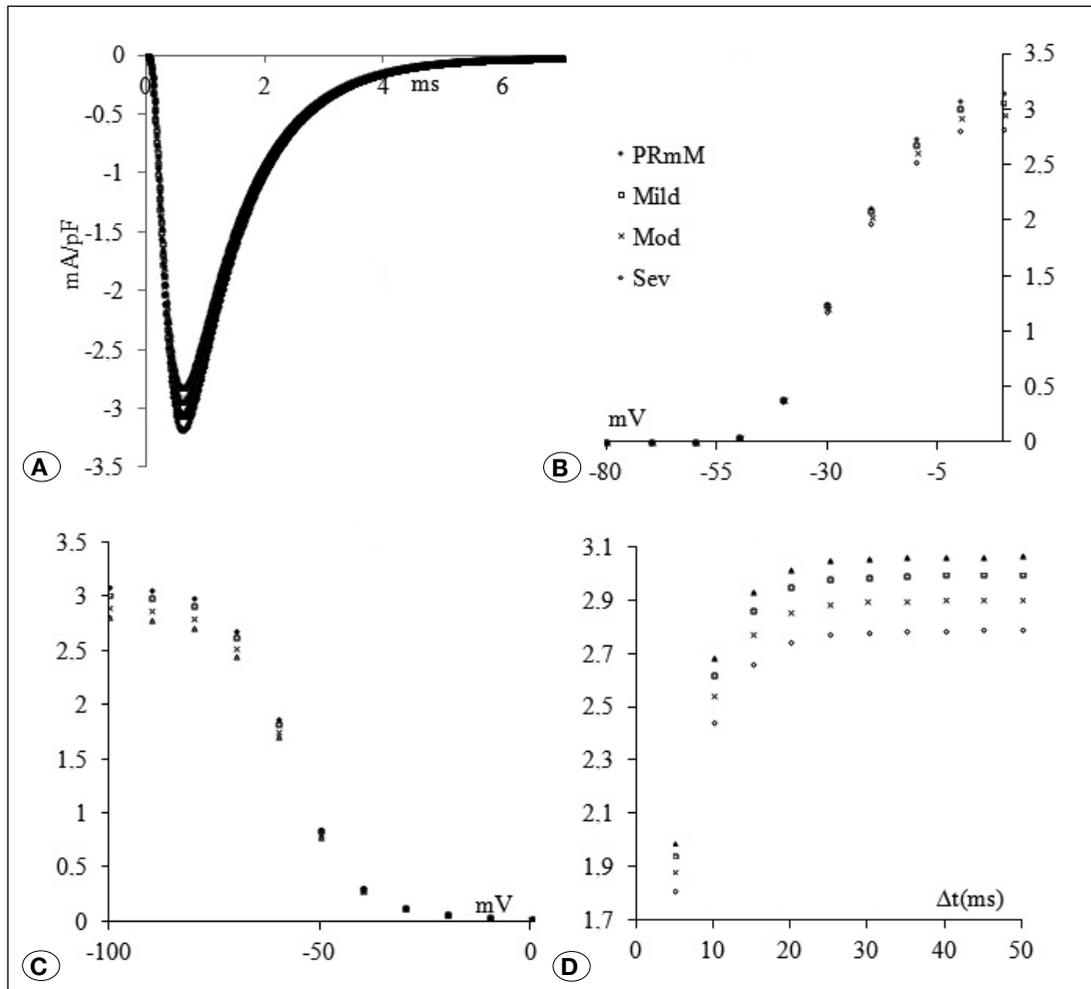
Effects of hyponatremic conditions on the Na<sup>+</sup> channel kinetics are shown in Figure 1. Original current traces of +10 mV voltage clamped (from a holding potential of -100 mV) were given in accordance with the degree of the severity of the hyponatremia (Figure 1A-D). It is obvious that the decrease in [Na<sup>+</sup>]<sub>o</sub> results in the rundown of the peak value of the current (Mild = -3.84%, Moderate = -7.30%, Severe = -11.48%) (Figure 1A). In panel B, activation characteristics of the currents for the different hyponatremic conditions are given (Figure 1A-D). Amongst tested potential differences, significance was found between the -20 mV – 0 mV when compared to physiological range values. The measured activation curve parameters following the fitting procedure ( $R^2=0.99$ ) are summarized in Table I. In parallel to the degree of significance of the hyponatremia, it was seen that activation curves start from more negative values and V<sub>50</sub> values shift to more negative values together with a decrease in the steepness.

Inactivation results are summarized in Figure 1C. In a parallel manner to activation results, potential differences between -100 mV and -60 mV resembled a significant depression compared to the measured physiological values. The results of fitting parameters of the inactivation are given in Table I ( $R^2=0.99$ ). Except for the steepness of the fitted curves, none of the parameters were affected from the hyponatremia. Decrease in the [Na<sup>+</sup>]<sub>o</sub> leads to faster inactivation in the Na<sup>+</sup> channels.

Results of the recovery from inactivation are summarized in Figure 1D. In a severity dependent manner, reactivation values were found to be significantly decreased. Results obtained from exponential fitting of reactivation values are given in Table I ( $R^2=1.00$ ). All the measured parameters were affected. The maximum point of the reactivation values were found to be depressed, together with a slowing down in the kinetics (time constant= $\tau$ ).

**Effects of Hypernatremia**

Effects of mild, moderate and severe hypernatremic conditions on the Na<sup>+</sup> channel currents are presented (Figure 2A). Peak values for these measured currents increase according to the degree of severity (Mild=1.20%, Moderate=3.52%,



**Figure 1:** Na ion channel kinetics under hyponatremic conditions. In the figure, the compared experimental sets are physiological range values (PR), mild ( $[Na^+]_o = 131 \text{ mM}$ ), moderate (mod) ( $[Na^+]_o = 121 \text{ mM}$ ) and severe (sev) ( $[Na^+]_o = 110 \text{ mM}$ ). **A** shows the sample traces of Na currents of these experimental sets. **B, C** and **D** show activation, inactivation and reactivation profiles of the currents based on the records that were detailed in the methods section. Values are expressed as mA/pF in activation, inactivation and reactivation.

Severe=6.26%)(Figure 2A). Also, activation characteristics of the currents for the different hyponatremic conditions are demonstrated in Figure 2B. Amongst the tested potentials, a significant difference was found only at the 0 mV compared to the physiological range values. The results of the fitted parameters are given in Table II ( $R^2=0.99$ ). Although only the 0 mV value was significantly affected from the hypernatremia, our fitting results indicate a significant difference in all of the measured parameters. Matching the degree of significance of the hyponatremia, activation curves starts from more negative values and  $V_{50}$  values shift to more positive potentials together with the increase in the steepness.

Inactivation results, on the other hand, are summarized in Figure 2C. Similar to activation results, potential differences between  $-100$  mV and  $-80$  mV indicate a significant increase compared to the measured physiological values. The results of fitting parameters of the inactivation are given in Table II ( $R^2=0.99$ ). Except for the steepness of the fitted curves, none of the parameters were affected from the hyponatremia. Increase in  $[Na^+]_o$  results in slower inactivation for the mild and moderate states but faster for severe cases.

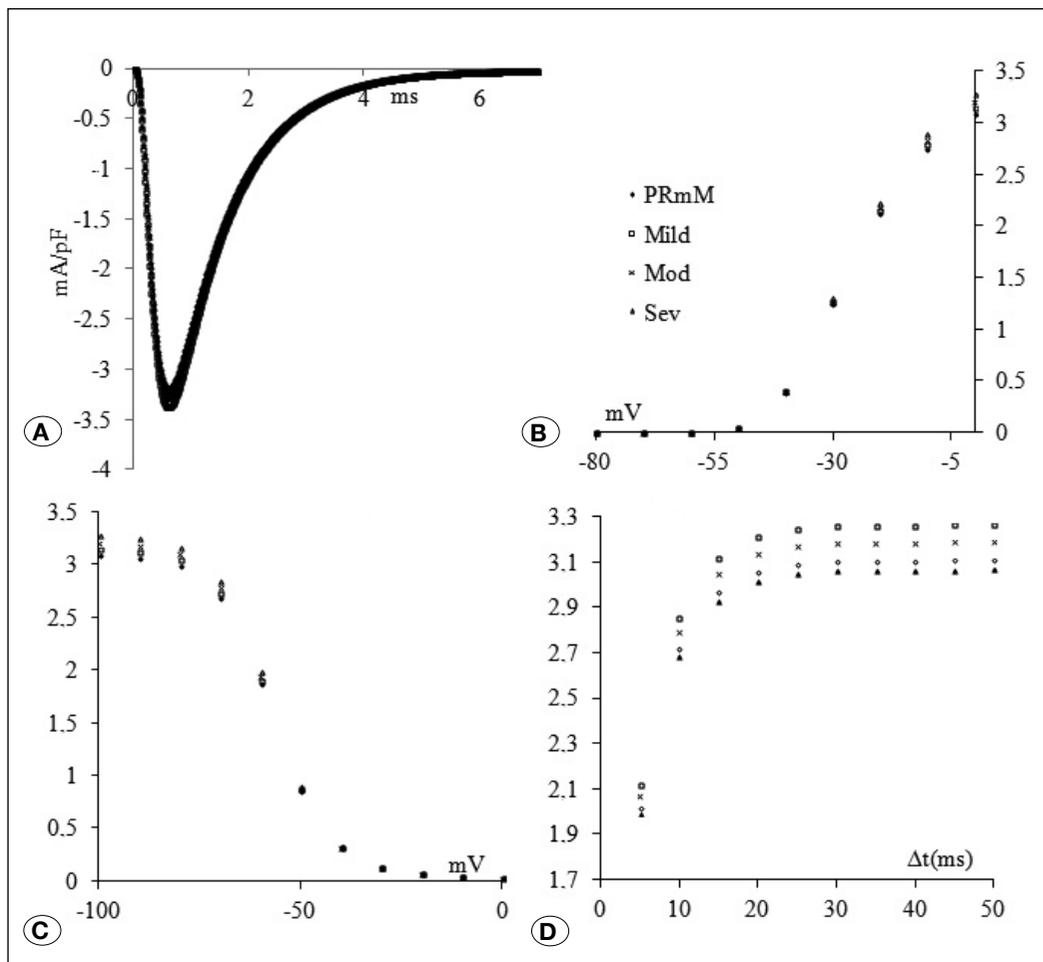
Additionally, results obtained from the reactivation protocol are summarized in Figure 2D. In a severity-dependent manner,

reactivation values were found to be significantly increased. Results obtained from exponential fitting of reactivation values are given in Table II ( $R^2=1.00$ ). Among the measured parameters, no change was found at the starting point of the reactivation. However, the maximum values were found to be increased with faster kinetics only in severe case of the hypernatremia (time constant= $\tau$ ).

■ DISCUSSION

The human body obtains Na through nutrition and loses it primarily in sweat and urine. In principle, the kidneys maintain a reliable level of Na in the body by adjusting the amount excreted in the urine.  $Na^+$  is mostly located in the circulating blood and in the fluid around cells. Besides, the regulation of the osmotic pressure keeping the fluids in a normal balance also plays a key role in normal nerve and muscle conduction facilities (18,23).

Small changes in plasma Na level may be seen in the metabolism. If the change is dramatic and persistent, its underestimation affects the prognosis, and causes coma and even death (1,9). It is reported that hyponatremia may affect the prognosis of some pathologies such as renal cell carcinoma, liver cirrhosis, congestive heart failure, head trauma and subarachnoid hemorrhage (8,11,19,28).



**Figure 2:** Na ion channel kinetics under hypernatremic conditions. In the figure, the compared experimental sets are physiological range values (PR), mild ( $[Na^+]_o=147$  mM), moderate (mod) ( $[Na^+]_o=155$  mM) and severe (sev) ( $[Na^+]_o=165$  mM). **A** shows the sample traces of Na currents of these experimental sets. **B, C** and **D** show activation, inactivation and reactivation profiles of the currents based on the records that were detailed in the methods section. Values are expressed as mA/pF in activation, inactivation and reactivation.

**Table I:** Fitting Parameters for Activation, Inactivation and Reactivations of Ina under Hyponatremic Conditions. The Compared Experimental Sets in the Table are Physiological Range Values (PR), Mild ( $[Na^+]_o=131$  mM), Moderate (mod) ( $[Na^+]_o=121$  mM) and Severe (sev) ( $[Na^+]_o=110$  mM)

<b>Activation</b>				
	<b>Bottom</b>	<b>V50</b>	<b>Slope</b>	<b>R<sup>2</sup></b>
<b>PR</b>	-0.043±0.000	-26.061±0.016	8.009±0.008	0.999
<b>Mild</b>	-0.04047*	-26.25	7.925*	0.999
<b>Moderate</b>	-0.03773*	-26.48*	7.812*	0.999
<b>Severe</b>	-0.03456*	-26.79*	7.674*	0.999
<b>Inactivation</b>				
	<b>Bottom</b>	<b>V50</b>	<b>Slope</b>	<b>R<sup>2</sup></b>
<b>PR</b>	1.525±0.003	-57.123±0.001	7.090±0.001	0.999
<b>Mild</b>	1.519*	-57.122	7.092*	0.999
<b>Moderate</b>	1.524*	-57.120*	7.090*	0.999
<b>Severe</b>	1.534*	-57.120*	7.089*	0.999
<b>Reactivation</b>				
	<b>Bottom</b>	<b>Top</b>	<b>Tau</b>	<b>R<sup>2</sup></b>
<b>PR</b>	0.035±0.001	3.079±0.006	4.825±0.001	1
<b>Mild</b>	0.034*	2.995*	4.828*	1
<b>Moderate</b>	0.028*	2.902*	4.822*	1
<b>Severe</b>	0.033*	2.791*	4.821*	1

**Table II:** Fitting Parameters for Activation, Inactivation and Reactivations of Ina under Hypernatremic Conditions. The Compared Experimental Sets in the Table are Physiological Range Values (PR), mild ( $[Na^+]_o=147$  mM), Moderate (mod) ( $[Na^+]_o=155$  mM) and Severe (sev) ( $[Na^+]_o=165$  mM)

<b>Activation</b>				
	<b>Bottom</b>	<b>V50</b>	<b>Slope</b>	<b>R<sup>2</sup></b>
<b>PR</b>	-0.043±0.000	-26.061±0.016	8.009±0.008	0.999
<b>Mild</b>	-0.044*	-25.91	8.076*	0.999
<b>Moderate</b>	-0.046*	-25.76*	8.147*	0.999
<b>Severe</b>	-0.048*	-25.60*	8.217*	0.999
<b>Inactivation</b>				
	<b>Bottom</b>	<b>V50</b>	<b>Slope</b>	<b>R<sup>2</sup></b>
<b>PR</b>	1.525±0.003	-57.123±0.001	7.090±0.001	0.999
<b>Mild</b>	1.522	-57.12	7.093*	0.999
<b>Moderate</b>	1.530	-57.12	7.087*	0.999
<b>Severe</b>	1.523	-57.12	7.091*	0.999
<b>Reactivation</b>				
	<b>Bottom</b>	<b>Top</b>	<b>Tau</b>	<b>R<sup>2</sup></b>
<b>PR</b>	0.032±0.001	3.069±0.006	4.825±0.001	1
<b>Mild</b>	0.032	3.130*	4.825	1
<b>Moderate</b>	0.034	3.192*	4.824	1
<b>Severe</b>	0.032	3.265*	4.821*	1

The kidney is usually involved in dysnatremic conditions. However, the most vulnerable organ is the brain due to its adaptation mechanisms to hypo/hypernatremic conditions. These may cause cerebral edema and increased intracranial pressure or loss of organic osmolytes of brain content and disruption of the tight junctions (20). The effect of dysnatremia on the peripheral nervous system has not been studied extensively (2,24). It is reported that hyponatremia results in a decrease in the nerve conduction, which can be explained by the lower electrochemical gradient due to reduced extracellular Na concentration. Although the correction of dysnatremia is very important, rapid correction causes central pontine and extrapontine myelinolysis and necrosis in several brain regions. The higher the speed of correction, the greater the damage (20).

Many of the clinical studies dealing with the hyponatremic conditions have reported decreased conduction velocities that are location-independent for the motor and sensorial nerves (2,25). Our previous and the new results have shown that hyponatremic situations, through modifying the axonal Na<sup>+</sup> channels kinetics, result in the rundown of the I<sub>Na</sub>. Once the current density is decreased, it also reflects itself in the measured compound action potentials -via affecting the single fiber action potential- in human conduction velocity measurements. Indeed, the degree of the hyponatremia-dependent effect seen in the in the sodium ion channel, is severity-dependent, being more effective in the recovery phase of the ion channel.

Hypernatremic conditions, on the other hand, have also affected the Na ion channel activity through modifying the kinetics of the channel. Unlike hyponatremia, the effect seen in the hypernatremia condition was through decreasing the response time (increased excitability) of the channel. However, the degree of the significance of the effect seen on the Na ion channel in the case of the hypernatremia was found to be less destructive compared to the hyponatremic condition. For each of the cases for the Na ion concentration effects, further investigations seem to be needed for better treatment strategies.

## ■ CONCLUSIONS

Na ion channel activity is much more susceptible to the changes in the extracellular Na ion concentrations in either way. Susceptibility of the Na channel kinetics -being much more pronounced for the hyponatremic state- makes hyponatremic conditions more dangerous for the patients. Although how the low extracellular Na ion concentration modifies the channel protein molecular biology needs further investigations, we highly recommend close monitoring of the serum Na level following surgery especially in intensive care units.

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