CONCLUSION

Neuronal dopamine and serotonin receptors are widely distributed in the central and the peripheral nervous systems at different levels. Dopaminergic and serotonergic systems have crucial role in aldehyde dehydrogenase regulation. Stimulation of autonomic nervous system during ethanol treatment is suggested to be an important factor in regulating the ALDH function. The ALDH enzyme activity was increased in plasma, cerebral cortex, and liver but decreased in cerebellum. The ALDH enzyme affinity was decreased in plasma, brainstem and liver and increased in cerebral cortex and cerebellum. The difference in ALDH activity in brain regions shows the functional regulation of ALDH by the dopaminergic and serotonergic systems at the central level. There is also peripheral level regulation in plasma and liver. Dopamine and serotonin content decreased in liver and brain regions - cerebral cortex, corpus striatum of ethanol treated rats with an increased HVA/DA, 5-HIAA/5-HT turnover rate. Dopamine content decreased in brainstem with an increased HVA/DA turnover rate and serotonin content decreased with an increased 5-HIAA/5-HT turnover rate in the brainstem of ethanol treated rats compared to control. Serotonin content increased in hypothalamus with a decreased 5-HIAA/5-HT turnover rate where as dopamine content decreased in hypothalamus with an increased HVA/DA turnover rate of ethanol treated rats compared to control. Dopamine, serotonin and their metabolic intermediates differentially regulate ethanol craving. Dopamine D2 receptor binding parameters showed a functional increase in cerebellum, hypothalamus, and a decrease in brainstem, cerebral cortex and corpus striatum of ethanol treated rats compared to control. 5-HT2A receptor binding parameters showed a functional increase in corpus striatum, hypothalamus, brainstem and a decrease in cerebral cortex, cerebellum and liver
of ethanol treated rats compared to control. The alterations of DA D$_2$ and 5-HT$_{2A}$ receptor function and gene expression in the cerebellum, hypothalamus, corpus striatum, cerebral cortex play an important role in the sympathetic regulation of ALDH enzyme in ethanol addiction. The differences between ethanol treated and control rats in disposition of DA D$_2$ and 5-HT$_{2A}$ receptors give a clear change in the presynaptic monoamine synthesis and postsynaptic receptor availability during ethanol treatment. The hyperactivity at the frontal cortical region is observed during the EEG analysis support the central effects of ethanol especially at the frontal region. The gene expression pattern of DA D$_2$ and 5-HT$_{2A}$ receptors in the brain regions were in concordance with the receptor alterations. The results from ethanol perfusion study in liver show the dopaminergic and serotonergic functional regulation on ALDH. These alterations in the DA D$_2$ and 5-HT$_{2A}$ receptors of the brain are suggested to play a regulatory role in the liver through sympathetic innervation. In addition, receptor binding studies and Real-Time PCR analysis revealed that DA D$_2$, 5-HT$_{2A}$ receptor functional alterations observed during ethanol treatment clearly gives indication to the ethanol induced gene expression changes, functional interaction between DA D$_2$ and 5-HT$_{2A}$ receptors and their role in ALDH regulation. Brain activity studies using EEG showed a prominent difference in the frontal region of ethanol treated rats.

Thus it is concluded that there is a serotonergic and dopaminergic functional regulation of ALDH activity in the brain regions and liver of ethanol treated rats. Gene expression studies of DA D$_2$ and 5-HT$_{2A}$ studies confirm these observations. Perfusion studies using DA, 5-HT and glucose showed ALDH regulatory function. Brain activity measurement using EEG showed a prominent
frontal brain wave difference. This will have immense clinical significance in the management of ethanol addiction.
SUMMARY

1) Ethanol treated rats were used as a model system to study the dopaminergic and serotonergic functional regulation on the aldehyde dehydrogenase at the molecular level.

2) Ethanol induced aldehyde dehydrogenase activity was observed in liver, plasma and the different brain regions when compared to control.

3) Dopamine and serotonin content decreased in liver and brain regions - cerebral cortex, corpus striatum of ethanol treated rats with an increased HVA/DA, 5-HIAA/5-HT turnover rate.

4) Dopamine content increased in brainstem with an increased HVA/DA turnover rate and serotonin content decreased in brainstem with an increased 5-HIAA/5-HT turnover rate of ethanol treated rats compared to control.

5) Serotonin content increased in hypothalamus with a decreased 5-HIAA/5-HT turnover rate and dopamine content decreased in hypothalamus with an increased HVA/DA turnover rate of ethanol treated rats compared to control.

6) Dopamine D2 receptor binding parameters showed a functional increase in cerebellum, hypothalamus, and decrease in brainstem, cerebral cortex and corpus striatum of ethanol treated rats compared to control.
7) 5-HT$_{2A}$ receptor binding parameters showed a functional increase in corpus striatum, hypothalamus, brainstem and decrease in cerebral cortex, cerebellum and liver of ethanol treated rats compared to control.

8) Real-Time PCR analysis of DA D$_2$, 5-HT$_{2A}$ receptor confirmed the receptor data.

9) Real-Time PCR analysis of ALDH showed an increased expression in liver and cerebral cortex of ethanol treated rats compared to control.

10) Dopaminergic and serotonergic functional regulation of kinetic parameters of aldehyde dehydrogenase was observed in ethanol treated rats compared to control.

11) A prominent brain activity difference was observed in the frontal cortical region in ethanol treated rats compared to control by EEG analysis.

Thus it is observed that there is a functional regulation of dopamine and serotonin through DA D$_2$ and 5-HT$_{2A}$ receptors in brain regions and liver on ALDH activity. The data suggests the importance of brain neurotransmitter regulatory role on ALDH activity in ethanol treated rats.