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Flexible and waterproof micro-sensors to uncover zebrafish circadian rhythms: The next generation of cardiac monitoring for drug screening

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Flexible electronics are the next generation of sensors for mobile health and implantation. Zebrafish (*Danio rerio*) is an emergent strategy for pre-clinical drug development and toxicity testing. To address the confounding effects from sedation of fish and removal from the aquatic habitat for micro-electrocardiogram (μECG) measurements, we developed waterproof and wearable sensors to uncover the circadian variation in heart rate (HR) and heart rate variability (HRV). The parylene-C based ECG sensor consisted of an ultra-soft silicone integrated jacket designed to wrap around the fish during swimming. The Young's modulus of this silicone jacket matched with the fish surface and an extended parylene cable connected the underwater chest electrodes with the out-of water electronics. In addition, embedded micro-glass spheres in the silicone effectively reduced the effective density of the jacket to ~1 g cm^{-3}. These innovations enabled physiological ECG telemetry in the fish's natural habitat without the need for sedation. Furthermore, a set of non-linear signal processing techniques filtered out the breathing and electromagnetic artifacts from the recorded signals. We observed a reduction in mean HR and an increase in HRV over 24 hours at 10 dpa, accompanied by QT prolongation as well as diurnal variations, followed by normalization in mean HR and QT intervals at 26 days post ventricular amputation (dpa). We revealed Amiodarone-mediated QTc prolongation, HR reduction and HRV increase otherwise masked by sedation. The novel features of the flexible silicon jacket for μECG telemetry unraveled the biological clock and normalization of QT intervals at 26 dpa, providing the first evidence of new physiological phenomena during cardiac injury and repair as well as cardiac drug-mediated aberrant rhythms. Thus, the light weight and waterproof design holds promise to advance the next generation of mobile health and drug discovery.

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Potential role of N-benzylcinnamide in inducing neuronal differentiation from human amniotic fluid mesenchymal stem cells

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Neurodegenerative disorders are characterized by chronic and progressive loss of neurons in structure and function related to aging such as Alzheimer's disease, the latter characterized by the degeneration of cholinergic neurons in basal forebrain connected to the cerebral cortex and hippocampus. Amniotic fluid mesenchymal stem cells (AF-MSCs) have been proposed as one of the candidates for stem cell therapy of nervous system disorders. This study demonstrate that incubation of AF-MSCs, obtained from 16-20 week pregnant women with 10 ng/ml bone morphogenetic protein (BMP)-9 for 48 hours in conditioned medium resulted in trans-differentiation to cholinergic neuronal-like cells. This phenomenon could also be obtained with N-benzylcinnamide (PT-3). Pre-treatment for 1 hour with 10 nM PT-3 augmented BMP-9 trans-differentiation effect, elevated βIII-tubulin cell numbers and fluorescence intensity of immunoreactive ChAT, ameliorated BMP-9-related production of reactive oxygen species and enhanced anti-apoptosis status of the neuronal-like cells. The trans-differentiation process was accompanied by increased p53 but decreased Notch1 and SIRT1 (p53 deacetylase) levels and activation of p38, ERK1/2 MAPK and PI3K/Akt pathways, in concert with inactivation of JNK, all of which were accentuated by PT-3 pre-treatment. These findings suggest that N-benzylcinnamide may not provide a useful adjuvant in BMP-9-induced trans-differentiation of AFMSCs into ultimately cholinergic neurons.

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