hyperpolarization the channel modulation was arranged as follows: Kv7>> TTX-sensitive VGSC=KATP>HCN>KNA>TTX-resistant VGSC≥Cav3; while by the ability to induce depolarization the sequence was Kv7=4-AP-sensitive Kv>>KNA>K2P>>Cav3>>KATP. The strongest and most consistent effect on Em was achieved by manipulating the activity of M-channels. Thus, retigabine (M-channel enhancer) and XE991 (M-channel inhibitor) hyperpolarized and depolarized neurons by approximately 10 mV each. Both drugs had strong reciprocal effect on evoked action potential firing. Results obtained in slices confirmed those obtained from culture. Acute topical application of retigabine, ZD7288 (HCN blocker) and pinacidil (KATP channel enhancer) to DRG in vivo significantly alleviated peripherally-induced pain however, again, retigabine was the most efficacious.
Conclusions: Our study deciphers a toolkit of ion channels that sets Em of nociceptive neuron somata and identifies M-channels as one of the main controllers of nociceptor's excitability.

3859-Pos Board B587
Critical Behavior in the Pancreatic Islet Depends on the Balance Between Cellular Excitability and Electrical Coupling
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The pancreatic islets of Langerhans controls glucose homeostasis through the regulated secretion of insulin. Gap junction channels coordinate membrane depolarization between β-cells in the islet, which coordinates oscillatory [Ca^{2+}] at elevated glucose and suppresses spontaneous [Ca^{2+}] elevations under basal glucose. β-cells are heterogeneous in their glucose-stimulated [Ca^{2+}] and the balance between cellular excitability and coupling in determining the whole-islet response is not well understood. Here we quantify how the electrical response is shaped by the distribution of cellular excitability across the islet and the strength of coupling between cells. We utilize mice that express mutations to the KATP channel that decrease excitability in a population of β-cells, which can be controlled through variable doses of tamoxifen induction of CreER-recombinase, and quantified by GFP coexpression. To compare this defined heterogeneity in cellular excitability with endogenous heterogeneity, we also apply variable concentrations of the KATP-activator diazoxide to uniformly shift cellular excitability. In each case we compare experimental results with predictions from a multicellular coupled oscillator model and a percolating network model of the islet. Upon increased KATP mutant-channel expression there is a sharp transition at ~15% expression between near-normal [Ca^{2+}] and near-complete suppression of [Ca^{2+}]. Thus ~15% of inexcitable cells can control islet electrical activity. This similarly impacts insulin secretion and glucose homeostasis, such that mice transition from euglycemia to diabetes. Similar results are obtained upon diaxoizde treatment indicating this is a general behavior and not specifically dependent on mosaic mutant KATP expression. These results could be described by both mathematical models revealing the fundamental importance of heterogeneity and coupling to islet physiology and glucose homeostasis. This will be important for understanding islet dysfunction caused by mutations that affect the electrical response in diabetes.

3860-Pos Board B588
Qube - High throughput Screening with Genuine Electrophysiology
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A challenge in ion channel drug discovery is the need to screen a large number of compounds and to measure the pharmacology of drug-ion channel interaction. Automated patch clamp (APC) makes it possible to measure the pharmacology of many compounds; however, the throughput required for high throughput screening of compound libraries has been out of reach of the first generation of APC instruments. Screening of large compound libraries has been done using indirect methodologies with higher false positive and false negative errors. The Qube is a 384 channel, gigaohm-seal based APC instrument for recordings from voltage-gated and ligand-gated ion channels. It offers the capability to screen large compound libraries for ion channel block or modulation. Data are obtained with a throughput of more than 30,000 wells tested per 24 hours. In this study, we did high throughput, voltage clamp recordings of $Na_v1.7$, hERG and ASIC1A on the Qube. Recordings were made on the QChip384 planar patch clamp consumable. Here we demonstrate throughput of up to 1500 wells tested per hour with a 95% success rate using multihole QChips. Using Nav1.7 and hERG expressing cells we demonstrate that the recording are stable and have good voltage control for at least 30 minutes. By repetitive alternating additions of high and low pH on the ASIC1A expressing cells, we demonstrate the advantages of the liquid flow system in the QChip: the QChip384 has flow channels and complete wash in/washout and indefinite waste. The capability of the Qube to handle 384 sites simultaneously combined with the QChip384 architecture enable high throughput screening of compounds with the highest output of true, direct electrophysiological recordings with an uncompromised data quality.

3861-Pos Board B589
Current Clamp of Stem Cell Derived Cardiomyocytes on Qpatch
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The U.S. Food and Drug Administration (FDA) guidelines S7B mandate the measurement of inhibition of the human ether-a-go-go-related (hERG) ion channel by new drug candidates as it has been found that drug inhibition of the hERG channel can be associated with cardiac action potential (AP) prolongation and lethal cardiac arrhythmias. However, hERG is only one of multiple ion channels involved in forming the cardiac AP and therefore direct measurement of the cardiac AP has the potential to detect the effects of the candidate drug on multiple ion channels potentially affected. Stem cell-derived cardiomyocytes (SC-CM) or induced pluripotent stem cells (iPS-CM) have many of the phenotypic properties of authentic cardiomyocytes e.g. realistic ventricular action potentials. In this work we show how the QPatch can trigger action potentials using rapid switching from voltage to current clamp during recordings on the iPS-CM. We demonstrate that the current clamp recordings made on this automated patch clamp device are comparable to results obtained on standard manual patch clamp rigs. The integrated low volume glass flow channels of the QPatch minimize the consumption of iPS-CM cells - a valuable and often limiting "consumable". Parallel recordings from up to 48 iPS-CM were made on the QPatch HT with full analysis of action potential parameters including action potential duration and upstroke velocity. We measured assay success rates, the stability of action potentials and pharmacological profiles of reference compounds. Current clamp measurements of these cardiomyocytes offer important information to the understanding of the complex pharmacological effect of compounds on ion channels involved in the AP. Our data presented here clearly demonstrate how automated patch clamp on QPatch can augment the throughput of current clamp to meet new demands in drug discovery.

Muscle: Fiber and Molecular Mechanics and Structure II

3862-Pos Board B590
An Examination of Sarcomere Length Non-Uniformities in Actively Stretched Muscle Myofibrils
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Residual force enhancement (RFE) is a characteristic of skeletal muscle describing the increase in force exhibited following an active stretch on the descending limb of the force-length relationship, compared to the force of an isometric contraction at the final length. It has previously been argued that RFE is a result of instable sarcomeres on the descending limb, causing longer, weaker sarcomeres to lengthen to a greater extent than shorter, stronger sarcomeres, when a myofibril is actively stretched. If this were the mechanism of RFE, then sarcomeres should become more non-uniform in length after an active stretch. The purpose of this study was to investigate length non-uniformities between sarcomeres within a myofibril in isometric contractions pre- and post-active stretch. We hypothesized that sarcomere lengths would be less uniform in the post-stretch condition. Rabbit psoas muscle myofibrils were stretched passively to an average sarcomere length of 3.2 μm. The myofibrils were then activated. Five seconds after full activation, myofibrils were rapidly shortened to an average sarcomere length of 2.4 μm, held at that length for ten seconds and then stretched back to 3.2 μm. Individual sarcomere lengths were then determined during the initial isometric contraction and again following the active stretch. Standard deviations of sarcomere lengths were compared to analyze non-uniformity. Preliminary results gave normalized sarcomere length standard deviations of 5.7 % and 10.2 % for the initial isometric contraction and following active stretch respectively (103 % RFE). This supports the hypothesis that