The proarrhythmogenic role of autonemics and emerging neuromodulation approaches to prevent sudden death in cardiac ion channelopathies

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Abstract

Ventricular arrhythmias in cardiac channelopathies are linked to autonomic triggers, which are sub-optimally targeted in current management strategies. Improved molecular understanding of cardiac channelopathies and cellular autonomic signalling could refine autonomic therapies to target the specific signalling pathways relevant to the specific aetiologies as well as the central nervous system centres involved in the cardiac autonomic regulation.

This review summarizes key anatomical and physiological aspects of the cardiac autonomic nervous system and its impact on ventricular arrhythmias in primary inherited arrhythmia syndromes. Proarrhythmogenic autonomic effects and potential therapeutic targets in defined conditions including the Brugada syndrome, early repolarization syndrome, long QT syndrome, and catecholaminergic polymorphic ventricular tachycardia will be examined. Pharmacological and interventional neuromodulation options for these cardiac channelopathies are discussed.

Promising new targets for cardiac neuromodulation include inhibitory and excitatory G-protein coupled receptors, neuropeptides, chemorepellents/attractants as well as the vagal and sympathetic nuclei in the central nervous system. Novel therapeutic strategies utilizing invasive and non-invasive deep brain/brain stem stimulation as well as the rapidly growing field of chemo-, opto-, or sonogenetics allowing cell-specific targeting to reduce ventricular arrhythmias are presented.

Keywords

Sympathetic • Parasympathetic • Autonomic imbalance • Ventricular arrhythmias • Sudden cardiac death • Brugada syndrome • Early repolarization syndrome • Catecholaminergic polymorphic ventricular tachycardia • Long QT syndrome • Short QT syndrome • Short coupled torsade de pointes

1. Introduction

Sudden cardiac death (SCD) secondary to ventricular arrhythmias (VAs) can affect patients in all age groups, with primary inherited arrhythmia syndromes accounting for up to a third of these events in the young. Sympathetic arousal as well as abnormal parasympathetic tone or an imbalance of the two limbs of the autonomic nervous system (ANS) have been described as an important trigger for VAs in channelopathies. Neuromodulation is a promising yet underutilized treatment modality to prevent arrhythmogenic events in these conditions. Current clinical approaches are limited to general anti-adrenergic therapies including pharmacological betablockade or, in high risk cases, cardiac sympathectomy for patients with long QT or catecholaminergic polymorphic ventricular tachycardia (CPVT). There are no clinically available neuro-modulatory options for patients with vagally induced arrhythmic events, e.g. in Brugada, long QT 3, or early repolarization syndromes.

A number of innovative therapeutic modalities have been proposed to offer tailored modulation of the proarrhythmogenic adrenergic and vagal influences in cardiac channelopathies.

2. Autonomic influences on cardiac electrophysiology

2.1 Anatomy

The ANS is regulated over a complex hierarchical network organized within numerous centres in the cortex, amygdala, hypothalamus, brainstem, spinal level, intrathoracic ganglia, and peripheral target organ with multiple feedback and reflex loops at each level (Figure 1). The vagal nuclei providing preganglionic fibres to the heart are sited in the nucleus ambiguous and dorsal motor nucleus of the medulla oblongata. Key components of the cardiac sympathetic...
Autonomous innervation of the heart: left (yellow): the cell bodies of the post-ganglionic sympathetic neurons are located in the ganglia adjacent to the cervical and thoracic spinal cord, which receive inputs from the dorsal root ganglia of the spinal cord and central nervous system. Their axons travel along the epicardial vascular structures of the heart and penetrate through into the myocardium. The highest density in innervation is located in the subepicardial structures in the atria and base of the ventricles and surrounding the specialized conduction system. There are distinct afferent and efferent parasympathetic and sympathetic neural projections. The afferent nerve endings have numerous functions including their roles as mechano-, chemo-, or nociceptors. Among others, this allows that the afferent sympathetic fibres can provide beat-to-beat information to the central nervous system.7 Right (green): parasympathetic neurons are preganglionic fibres arising from the left and right vagus nerve and synapsing with a dense multiplexed network of ganglia located in the epicardial fat pads. Post-ganglionic fibres cross the AV groove and are thought to then dive intramurally to the subendocardium. Parasympathetic innervation is more heterogenous and was long thought to have little effect on the electrical activity of the ventricle, yet in vivo vagal influence on the ventricle has been highlighted and direct effects of acetylcholine on the ventricular myocardium demonstrated. A schematic representation of the effect of sympathetic and parasympathetic inputs on the action potential (AP) configuration of impulse forming cells is shown: left bottom—key changes following sympathetic stimulation include a steeper phase 4 slope in impulse forming cells, an increase in dV/dt in phase 0 with higher AP amplitude and thus faster conduction velocity, a shortening of the action potential and effective refractory period. Electrophysiological changes are mediated via Gs-protein coupled beta-adreno-receptors inducing intracellular signal cascades via protein kinase A (PKA) interacting with numerous proteins, including key calcium-handling proteins. Right bottom—vagal stimulation antagonizes sympathetic effects and via muscarinic Gi-protein coupled receptors induces changes in intracellular cAMP level and ion channel availability/opening probability. A more detailed description is provided in Supplementary material online, Table S1.

2.2 Physiology

Sympathetic and parasympathetic activity is continuously modulating cardiac electrophysiological properties, electromechanical coupling, and contractile performance. This is complemented by their links to the neurohumoral system (e.g. over the renin angiotensin aldosterone system4–6) and cardiovascular reflexes (e.g. via mechano-receptors in the baroreceptor reflex)7. Their relationship has been described as ‘accentuated antagonism’ (e.g. enhanced effect of vagal stimulation in presence of background sympathetic stimulation) and ‘reciprocal excitation’ (a peripheral component of one division is activated as a consequence of activation of the other).8–10 Both are subject to agonist-promoted desensitization and down-regulation, a regulatory process that diminishes receptor response to continuous or repeated agonist stimulation.11

The dominant effects of the ANS on cardiac electrophysiological properties are summarized in Supplementary material online, Table S1. There is significant anatomical regional heterogeneity and lateralization in innervation as well as intrinsic spatial differences in expression and activity of the autonomically modulated ion channels3,12 translating into regionally distinct action potential characteristics (see Figure 2). Due to these physiological differences in action potential duration (APD) and configuration, the wave of repolarization moves in the opposite direction of depolarization from epicardium to endocardium causing a natural dispersion of repolarization across the ventricular wall, as well as apex to base and right to left.16–18

On a cellular level, the sympathetic effects act via noradrenaline binding to Gs-protein coupled beta-adreno-receptors. Activation of Gs stimulates...
positive chrono-, dromo-, bathmo-, ino-, and lusitropic effects over a complex cascade of intercellular signalling. The parasympathetic influences are transmitted via acetylcholine binding to the muscarinic inhibitory G-protein coupled receptors counterbalancing the sympathetic influences via negative chrono- and dromotropic effects and a tonic inhibitory inotropic effect.

2.3 Pathophysiology of the ANS in SCD

Increased sympathetic and reduced vagal activity, but in certain inherited arrhythmia syndromes also increased parasympathetic activation, has been associated with a propensity of lethal ventricular arrhythmias in a number of cardiovascular diseases.26-22 Although disease-specific mechanisms may dominate in different disorders, in general, the proarrhythmogenic effect of sympathetic stimulation may be attributed to: (i) changes in calcium handling that facilitate delayed after-depolarizations and trigger sustained ventricular arrhythmias,23 (ii) modulation of the APD and repolarization gradients due to heterogeneity in cardiac innervation, and (iii) pathological remodelling of neuronal structures.24,25 More detailed discussion regarding adrenergically driven arrhythmias in inherited arrhythmia syndromes is provided below. Mechanisms of vagally driven arrhythmias associated with LQT3, Brugada syndrome (BrS), and early repolarization syndrome are diverse and discussed below in the respective sections.

3. Management of cardiac channelopathies with focus on neuromodulation

Diagnosis and genetics of CPVT, long QT syndrome (LQTS), BrS, early repolarization syndrome, short QT syndrome (SQT), and idiopathic ventricular fibrillation (VF)26,27 are summarized in Supplementary material online, Table S2. Detailed reviews discussing genetic and clinical background have been published for each channelopathy.28-31 Characteristic ECG features, action potential configurations, and key ion channel alterations associated with these channelopathies are illustrated in Figure 3.

Existing clinically employed treatment options for interventional autonomic neuromodulation are summarized in Figure 4 and include (bilateral or left) cardiac sympathetic denervation, low level vagus nerve stimulation, auricular branch vagus nerve stimulation (VNS) (Tragus Stimulation), baro-reflex activation therapy, renal denervation, and spinal cord stimulation. They have been reviewed for treatment of heart failure, cardiomyopathies, ischaemic heart disease, and atrial fibrillation.34,35 Cardiac sympathectomy and to a lesser degree renal denervation remain the only two clinically employed interventional neuromodulation options in channelopathies.

3.1 Catecholaminergic polymorphic VT

VAs occur secondary to inappropriate cytosolic calcium overload generating delayed after-dopolarization. Several mechanisms of the inappropriate cytosolic calcium release, particularly in the more susceptible Purkinje cells,26,37 and proarrhythmogenic adrenergic changes have been discussed38-40 and are summarized in Figure 5.

In brief, one hypothesis relates to an enhanced basal activity and increased Ca2+ sensitivity decreasing the amount of calcium required for RyR2 activation.41,42 Others suggest a disrupted interaction with the binding protein that stabilizes the receptor in its closed state under physiological circumstances and promotes more frequent RyR2 channel opening.43 A third hypothesized mechanism may be a defective inter-domain folding and pathological interaction between certain domains, which may result in high sensitivity of RyR2 channel agonists and decrease the threshold for opening.44
3.1.1 Pharmacological neuromodulation

To suppress the adrenergic influences, betablockers are recommended for all patients, including for silent carrier of pathogenic mutations. Type and dose of betablocker are important due to differences in pharmacodynamics and pharmacokinetics (including cardioselectivity, half-life, and lipophilicity), concomitant cardiac ion channel modulation, but also ease of dosing regimen (once to three times daily) that may affect compliance. Lower event rates have been reported with nadolol when...
compared to β1 selective betablockers in equivalent doses and should therefore be given preference. The superiority may be due to the low inter-individual pharmacokinetic variability and longer half-life with overall stronger negative chronotropic effect and lower maximum heart rate. If unavailable, most authors recommend propranolol, yet higher inter-individual variability in pharmacokinetics as well as more central nervous system side effects (due to its lipophilic properties) are to be taken into consideration.

Dose titration and efficacy testing should be assessed with exercise testing. Both nadolol and propranolol also exhibit peak sodium current blocking properties (and late current by propranolol) that may further reduce the risk of delayed after-depolarizations via driving the sodium-calcium exchange causing an inward sodium flux to remove calcium overload secondary to the spontaneous calcium release from the SR. The role of carvedilol and nebivolol, which have been associated with suppression of calcium leakage of the cardiac ryanodine receptor, are not well explored. Lastly, preclinical studies suggest that additional alpha-adrenergic blockade may be beneficial in CPVT. In patients with breakthrough arrhythmias while on betablockers, flecainide has been shown to reduce cardiac events regardless of genotype including in a small prospective randomized trial. There is an ongoing debate whether its preventive effect is mediated by a reduction in sodium channel availability or its ryanodine receptor blocking properties suppressing sarcoplasmic reticulum calcium release.

3.1.2 Interventional neuromodulation

For uncontrolled arrhythmias despite maximal medical therapy, cardiac sympathetic denervation (CSD) can be considered to reduce cardiac events and ICD shocks. The anti-arrhythmic mechanism of CSD is thought not only to be due to a reduction in cardiac sympathetic stimulation and release of norepinephrine but also to a reflex increase in vagal efferent activity. CSD largely interrupts the centrally projecting cardiac sympathetic afferents, which ‘normally’ may have an inhibitory effect on the vagal outflow directed to the heart. The resulting vagotonic effect of CSD is likely an important contributor to the anti-arrhythmic mechanism of action. Evidence supporting other interventional neuromodulation approaches is sparse. Isolated case reports of percutaneous renal sympathetic denervation for CPVT as well as ablation of discrete origins of bidirectional ventricular premature ectopics triggering VF in CPVT.
have been published but are not investigated in a larger population. Programming of ICDs needs to focus on minimizing unnecessary shocks with high heart rate detection zones and long delays for shock delivery due to the known increase in adrenergic stress and self-perpetuating electrical storm following ICD shocks.

### 3.2 Long QT syndrome

The LQTS has numerous different subtypes according to the ion channels affected promoting prolonged ventricular repolarization times and accentuate transmural dispersion. Long QT subtypes 1 and 2 are particularly prone to sympathetic stimuli triggering VAs. The heterogeneous sympathetic innervation reported in nuclear imaging studies in LQTS likely further amplifies the arrhythmogenic risk during adrenergic stimulation. LQT1 is associated with a loss of function mutation in $I_{Ks}$ (slowly activating delayed inward rectifier potassium channel) preventing rapid repolarization and action potential shortening in the context of adrenergic drive. This facilitates the occurrence of early after-depolarizations triggering torsade de pointes that can be maintained by re-entry mechanisms and predispose to exercise or stress related cardiac events. The increase spontaneous inward current of calcium over $I_{CaL}$ under adrenergic stress further increases the likelihood of triggered...

![Image of the proposed mechanism of spontaneous calcium release in CPVT](https://example.com/image.png)

**Figure 5** Arrhythmogenesis in CPVT: proposed mechanism of the spontaneous calcium release of the mutant ryanodine receptor (in red, large 'mushroom' shaped homo-tetramer) under adrenergic stimulation are: [1 orange] an enhanced basal activity and increased Ca$^{2+}$ sensitivity decreasing the amount of calcium required for RYR2 activation; [2 purple] a disrupted interaction with the binding protein (FKBP), which stabilizes the receptor in its closed form under physiological circumstances, leads to untimely opening; [3 green] a defective inter-domain folding and pathological interaction between certain domains, which result in high sensitivity of RyR2 channel agonists and decrease the threshold for activation; and [4 blue] calcium overload in the sarcoplasmic reticulum (SR) has been associated with increased triggered activity even in absence of adrenergic drive (store overload induced Ca$^{2+}$ release). The resulting inappropriate diastolic calcium release from the sarco-plasmatic reticulum causes intracellular calcium overload and delayed after-polarization (A) that result in triggered activity (B), most prominently in the more susceptible Purkinje cells than the ventricular myocardium. The ensuing VT with beat-to-beat alternating QRS morphology (C) and cycle length is thought to be the result of alternating foci (termed 'reciprocating bigeminy') developing at different heart rate thresholds, as found in a mouse model with CPVT and suggested in computer models. If more than three foci fire, the bidirectional VT may transition into polymorphic VT. Other studies suggest that spiral wave re-entry may be an important mechanism in CPVT.
activity. The relationship between adrenergic stress and VAs is less prominent in LQT2S (characterized by an abnormal ICaL, the rapidly activating delayed inward rectifier potassium channel). The pathognomonic genotype specific trigger is generally considered to be loud noise while at rest or asleep, \(^{20,75}\) which is associated with a sudden acceleration in heart rate and slower adaptation of repolarization in LQT2. \(^{72}\) Also, an excessive risk in the postpartum period \(^{72}\) is thought to be secondary to the rapid reversal of changes in cardiac haemodynamics, output, and contractility, but importantly also alterations in adrenergic activity in the peripartum period and disrupted sleep patterns. \(^{74,75}\)

General management recommendations include avoidance of QT prolonging medication, electrolyte imbalances, and genotype specific triggers.

### 3.2 Pharmacological neuromodulation

Betablockers are the mainstay in all LQTS patients. Initial large studies grouping all genotypes together showed no relevant difference between types of betablockers \(^{76}\) yet later investigations highlighted that similarly to CPVT, not all betablockers are equally effective—non-selective betablockers like nadolol (1–1.5 mg/kg/day) and propranolol were more effective than metoprolol \(^{77,78}\) (see Supplementary material online, Table S3).

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#### 3.2.2 Interventional neuromodulation

CSD increases the ventricular fibrillation threshold \(^{79}\) and ventricular refractory period. \(^{80}\) It has been repeatedly demonstrated and highlighted as an efficient anti-arrhythmic therapy to reduce syncope and ICD shocks in LQTS \(^{81–83}\). Anti-adrenergic therapy is particularly effective in LQT1 and more individualized and refined patient selection incorporating clinical and genetic features have been proposed to maximize procedural success. \(^{84}\)

Early consideration of device and surgical therapies has been suggested in high-risk patients with malignant LQT5 genotypes but also in case of betablocker intolerance or non-compliance. \(^{85}\) The use of renal denervation has been described as a successful neuromodulation strategy in LQT animal models. \(^{86,87}\) Experience in humans is currently limited to isolated case reports. \(^{88,89}\) There is an ongoing debate as to whether renal sympathetic denervation is indirectly beneficial by modulating sympathetic inputs or directly shortening the QTc. \(^{90}\)

### 3.3 Long QT syndrome 3

Unlike the above, in LQT3 cardiac events have been associated with increased vagal tone. At lower heart rates, the action potential duration prolongs due to a more pronounced late sodium current at low stimulation rates. In turn, during tachycardia, there appears to be a protective role of elevated intracellular Ca\(^{2+}\), which suppresses the late sodium current. \(^{91}\)

#### 3.3.1 Pharmacological modulation

Betablockers have been discussed controversially for long QT 3 patients due to the association with bradycardia, conduction disturbances as well as increased cardiac events at rest. \(^{92}\) Yet, there is evidence that indeed betablockers were not proarrhythmic but protective in females and neutral in males. \(^{93}\) Propranolol may theoretically be preferred due to its additional use dependent peak and late sodium channel blocking properties, \(^{94}\) which may in selected cases contribute to QT interval shortening. Functional heterogeneity of the underlying mutation may play an important role on the therapeutic effect of sodium channel blockers such as mexiletine that is a second line therapy (see Supplementary material online, Table S3).

#### 3.3.2 Interventional therapy

A limited number of LQT3 patients have been included in studies of CSD and found to benefit from the reduction in sympatho-excitation.

### 3.4 Brugada syndrome

A large body of literature has been published about the possible underlying mechanism of BrS. \(^{95,96}\) On a cellular level, two principal hypotheses have been proposed: the repolarization hypothesis and the depolarization hypothesis, which are likely not exclusive and a combination of de- and repolarization abnormalities has been described. \(^{97}\) The original repolarization hypothesis \(^{98}\) suggests that an outward shift in the balance of currents in the right ventricular epicardium (via reduction in inward sodium and accentuation of outward currents) can result in repolarization abnormalities and facilitate the development of phase 2 re-entry generating closely coupled premature beats that can precipitate VF. The depolarization hypothesis \(^{99}\) suggests that the ST elevation is caused by slow conduction/delay in the RVOT that in turn creates a potential difference and thereby facilitates VAs. Autonomic influences play an important but complex role in arrhythmogenesis of BrS. \(^{100,101}\) There is a recognized association of cardiac events with proarrhythmic vagal influences and/or decreased sympathetic input supported by circumstantial evidence of cardiac events. \(^{102,103}\) Findings in Holter ECG \(^{104}\) and nuclear imaging (MIBG SPECT \(^{105–109}\) and PET CT \(^{110}\)). The mechanism of vagally driven arrhythmias may be caused by a reduction in I\(_{\text{Na,L}}\) during the action potential plateau and indirectly via a decrease in heart rate that in turn decreases intracellular calcium, reduces myofilament calcium sensitivity, and is associated with elevated ST-segments. \(^{111}\) In turn, β-adrenergic activation with isoproterenol is effective in suppressing arrhythmias by enhancing inward calcium current.

However, in a small subset of Brugada patients, malignant arrhythmias were observed under increased adrenergic stress. The latter has been associated with a specific SCNSA mutation involving the C-terminal portion of the sodium channel that augments slow inactivation and delays recovery of sodium channel availability. \(^{111,112}\)

#### 3.4.1 Pharmacological neuromodulation

In case of acute electrical instability and/or recurrent ICD discharges, intravenous isoproterenol is considered the first-line treatment to suppress VAs. The anti-arrhythmic effect of isoproterenol is thought to be secondary to its augmentation of L-type calcium channel current that contribute to restoring the action potential dome and thereby prevention of phase 2 re-entry. \(^{112}\) The requirement for intravenous access precludes its use in the long-term. Options for oral anti-arrhythmic treatment are sparse and essentially limited to quinidine. Quinidine acts as a transient outward potassium current (I\(_{\text{Ko}}\)) inhibitor with additional anti-cholinergic properties contributing to its anti-arrhythmic effect in Brugada patients. \(^{114}\) Its benefits are off set by the frequent adverse effects leading to poor patient compliance as well as often restricted availability. Alternative oral drugs targeting proarrhythmic vagal autonomic influences have been explored although only anecdotal evidence is available for their beneficial effects. Among these are orciprenaline \(^{115}\) and denopamine, acting as oral beta-adrenergic agonists, as well as bepridil, a calcium channel block with I\(_{\text{Ko}}\) inhibiting properties. \(^{116}\) Yet, more evidence is needed to define their role in the clinical management of Brugada patients.

#### 3.4.2 Interventional treatments

In case of recurrent ventricular arrhythmias and ICD shocks, ablation of both VF triggers and epicardial abnormal electrograms was found to prevent arrhythmic recurrences. \(^{117}\) There are no clinical recommendations for interventional neuromodulation to reduce VAs in BrS. Investigational approaches to reduce cardiac vagal influences via central or peripheral neuromodulation are described below and may provide possible therapeutic options to minimize the proarrhythmic vagal influences associated with arrhythmic events.

### 3.5 Early repolarization pattern/syndrome (ERS)

The electrical substrate of early repolarization pattern/syndrome (ERS) is thought to arise from the current imbalances between the epicardial layers, predominantly in the infero(lateral) wall. The accentuation of the phase 1 action potential notch results in steep transmural action potential duration and repolarization gradients. \(^{118}\) The loss of the action potential dome predisposes to phase 2 re-entry and VF. \(^{119}\) Both, the more
prominent early repolarization pattern and cardiac events have been associated with periods of high vagal tone.\textsuperscript{10–12} In experimental settings, acetylcholine caused loss of epicardial dome at some sites but not others resulting in epicardial dispersion and precipitating repeated episodes of phase 2 re-entry and polymorphic VT/VF, whereas quinidine and isoproterenol restored epicardial AP dome and suppressed VT/VF.\textsuperscript{126}

### 3.5.1 Pharmacological modulation

Similar to the above BrS, intravenous isoproterenol has been found to be effective in acute suppression of VAs and ICD discharges. The augmentation of inward calcium current counterbalances the excess net outward potassium current and restores the epicardial action potential dome explaining the anti-arrrhythmic properties in ERS.\textsuperscript{126} So does the transient outward potassium current inhibition by quinidine, which reduced the magnitude of the J wave and remains the only available oral drug therapy. Alternative drugs, including betablockers, lidocaine, mexiteline, and verapamil, have not been found to be beneficial.\textsuperscript{127} Case reports of oral Phosphodiesterase III inhibitors Cilostazol have been described to reduce the occurrence of phase 2 re-entry in ERS. The latter is thought to be secondary to an increase in $I_{CaL}$ and reduction in $I_{Ko}$ currents.\textsuperscript{128} No larger studies are available to support their use.

### 3.5.2 Interventional treatment

In case of recurrent ventricular arrhythmias triggered by a consistent PVC morphology, ablation of such trigger should be attempted. Targeted interventional autonomic modulation has not been reported for ERS.

### 4. Emerging therapeutic targets and novel concepts for precision neuromodulation

Available neuromodulation strategies are comparatively blunt with only limited consideration of the pathophysiological specificities and anatomical distribution of functionally critical areas of the underlying channelopathy pathology. Yet, the improved molecular understanding of cardiac channelopathies and cellular autonomic signalling have allowed to identify more precise targets for autonomic therapies. These include receptors mediating adrenergic and parasympathetic inputs to the heart, encompassing the large group of G-protein coupled receptors and the still sparsely investigated sigma-1 receptors, as well as neurotransmitters, neural chemorepellents and attractants, and metabolic ligands like adiponectin.

#### 4.1 Precision medicine in cardiac neuromodulation: molecular and central nervous system targets

##### 4.1.1 Modulation of G-protein coupled receptors

These mediate important cardiac transmembrane and intracellular signalling pathways. They are divided into three main categories: stimulatory ($G_s$) and inhibitory subunits ($G_i/o$) affecting cAMP (adenosine monophosphate) and $G_{q/11}$ involved in the phospholipase C-$\beta$ and inositol-1,4,5-triphosphate ($IP_3$) and 2-diacylglycerol (DAG) signalling pathway. Adrenergic receptors, including $\beta_1$, primarily signal through heterotrimeric $G_s$ proteins.\textsuperscript{11} In turn, binding of acetylcholine to the muscarinic M2 receptors leads to activation and dissociation of inhibitory G-protein ($G_i/o$) heterotrimers. In pacemaker cells, this directly activates the inward rectifying potassium (GIRK) channel causing hyperpolarization and slowing sinus rate.\textsuperscript{129} $G_{q/11}$ also has an important impact on electrophysiological signalling and is involved in impulse generation and propagation by modulating myocytes Ca$^{2+}$ handling and intercellular communication.\textsuperscript{130,131} As such, G-protein coupled receptors have been identified as promising targets for autonomic precision medicine to modulate their activity and intracellular downstream effectors.

Preclinical in vivo studies associated loss of $G_s$ with sinus tachycardia and loss of high frequency power in heart rate variability (HRV) assessment.\textsuperscript{132} This could represent a possible target for vagally induced VA e.g. BrS or LQT3 by increasing baseline heart rate and reduce vagal inputs. Alternatively, in Brugada patients, $\text{IC-PET-CT}$ studies demonstrated increased norepinephrine recycling with no change in post-synaptic beta-adrenoreceptor density. The latter may suggest a possible altered signal transduction by $G_s$-proteins and resulting lower cAMP and PKA activity and calcium current. Targeting and enhancing beta-adrenergic $G_s$-coupled receptors may therefore represent another approach to mitigate proarrhythmic autonomic influences. Lastly, $G_q$ mediates the response to hormonal (angiotensin-II and endothelin-1) and neural (noradrenaline/ adrenaline over alpha-adrenergic receptors) inputs. It has been associated with proarrhythmogenic properties via contributing over multiple pathways to intracellular calcium overload associated with delayed afterdepolarizations, as well as reducing conduction velocity by PKC mediated phosphorylation of $\text{CX43}$.\textsuperscript{133} Selective cardiac inhibition of the $G_q$ pathway could represent a target to suppress VAs e.g. in CPVT.

##### 4.1.2 Neuropeptides

Neurotransmitter-mediated autonomic modulation other than by noradrenaline and acetylcholine are complementary promising targets for neuromodulation to address sympathetic hyperactivity.\textsuperscript{134} Neuropeptide Y, galanin, and dopamine have been investigated in this regard:

- Neuropeptide Y is released by sympathetic nerves and known for its proarrhythmic properties,\textsuperscript{135} stimulating calcium release in myocytes and cardiac sympathetic electrical modulation including shortening of action potential duration in the context of betablocker therapy.\textsuperscript{136} High levels of neuropeptide Y in the coronary circulation have been associated with increased adverse events in heart failure and higher recurrent ventricular arrhythmias after percutaneous coronary angioplasty. NPY1 receptor antagonist has been found to mitigate and reduce sympathetic effects and may complement existing anti-adrenergic therapies.\textsuperscript{137,138}
- Galanin, a slowly diffusing sympathetic co-transmitter, reduces vagal acetylcholine release via a receptor-mediated protein kinase dependent pathway. It may contribute to regeneration of sympathetic nerves following myocardial infarction and contribute to VAs.\textsuperscript{139} In preclinical studies, galanin receptor antagonists abolished the effect of galanin on vagal bradycardia as did protein kinase C inhibitors.\textsuperscript{140}
- Dopamine is well known and in clinical use for its inotropic and natriuretic effect. It has also been associated with VAs secondary to overexpression of cardiac D1 receptors.\textsuperscript{141} It is thought that this is associated with hyperactivation of $\text{RyR2}$ receptors that in turn represent a driver for dysregulated calcium handling.\textsuperscript{142} Whether dopamine and dopamine receptors could represent possible targets for anti-arrrhythmic therapies remains to be investigated.

Most neuropeptide research relates to heart failure or myocardial infarction, with a distinct lack of data in autonomic mediated arrhythmias in channelopathies. Yet, they may offer important additional treatment options. For example CPVT or LQT1 and 2 with breakthrough cardiac events during betablocker therapy may possibly benefit from complementary NPY receptor antagonists.

##### 4.1.3 Sigma-1 receptors ($S1R$)

These ligand-regulated chaperone proteins are sensitive to a wide number of ligands including neuroactive steroids. Their role and interaction is complex and many aspects still controversial. They are thought to be involved in modulation of cardiac contractility, voltage gated potassium, sodium and calcium ionic channels in cardiomocytes but also sympathetic and parasympathetic neurons.\textsuperscript{143} In preclinical studies, sigma 1-receptor activation reversibly inhibited voltage gated sodium currents,\textsuperscript{144} depresses neuronal excitability of intracardiac neurons,\textsuperscript{145} and reduced Ca$^{2+}$ leakage into the cytosol via modulating calcium channels.\textsuperscript{146} Chronic activation of $S1R$
was shown to beneficially influence ventricular remodelling and decreases susceptibility to VAs after myocardial infarction in animal studies. With a better understanding, targeting specific sigma-1 receptor ligands may achieve precise ion channel modulation to oppose disease-specific gain- or loss of function mutations in channelopathies. Nuclear imaging with SPECT (I-125iodophenyl-piperidino-cyclopentanol, 125I-0I5V) may be used to guide and titrate neuromodulating therapies.  

4.1.4 Semaphorines

Semaphorines are a family of secreted and membrane anchored glycoproteins that are important during neuro-embryogenesis and reinnervation of peripheral organs following neural injury. Sema3a in particular acts as a potent neural chemorepellent, inhibiting neural growth and thereby regulating axon growth and neuronal migration. Dysfunction, over- or underexpression of Sema3a may, among others, result in pathological innervation patterns of sympathetic nerves. In preclinical studies, overexpression of Sema3a in the heart and the left stellate ganglion was associated with a reduced inducibility of VAs associated with sympathetic hyperinnervation e.g. in the post-infarction remodelling. The anti-arrhythmic effect of Sema3a is thought to be secondary to the combination of decreased sympathetic hyperinnervation, decrease in norepinephrine content and restoration of dephosphorylated CX43 in the infarct border zone. In clinical studies, certain polymorphisms of Sema3a have been associated with suspected abnormal sympathetic innervation pattern with otherwise unexplained ventricular fibrillation. Tailored stimulation or inhibition of Sema3A and/or nerve growth factors could potentially allow to modulate innervation pattern on a tissue-based level to counterbalance pathological proarrhythmogenic autonomic influences.

4.1.5 Adiponectin

Adiponectin is secreted by adipocytes and known for a multitude of metabolic effects including prevention of inflammation, oxidative stress, regulating energy metabolism, and improving insulin sensitive. Yet, it has also important regulatory effects on the ANS. It is involved in the regulation of neuronal excitability of the paraventricular nucleus in the hypothalamus, reduce peripheral sympathetic tone via signalling in the locus coeruleus, and inhibit excessive activation in the GP of the heart thereby preventing atrial fibrillation. Injection in the adipose tissue surrounding the left stellate ganglion using a chemogenetic approach has been shown to decrease neural activity and cardiac effective refractory period. In turn, this has been associated with a reduction in VAs in a preclinical infarct model. Adiponectin is not the only promising target with other metabolic targets involved in connexin and gap junction signalling already highlighted. Yet, overall, the highly complex metabolic-immunological-autonomic cardiac interactions and their contribution to ventricular arrhythmogenesis are still poorly understood.

4.1.6 Central cardiac autonomic centres

Genetic neuronal targeting and functional neuroanatomical mapping has allowed to identify several key centres involved in central cardiac autonomic regulation (see Figure 6). Their complex interaction has been reviewed. The improved understanding of the effect on electrophysiological properties of each of these central structures in combination with the technological advances in invasive and non-invasive brain stimulation plus molecular-based therapies opens new possibilities for central cardiac neuromodulation. In brief, central targets on the vagal side include the preganglionic parasympathetic neurons of the nucleus ambiguous and vagal dorsal motor nucleus, which have been reported to have preferential control over pacemaker and ventricular tissue. The cardio vagal neurons of the nucleus ambiguous innervate the cardiac nodal tissues, activate cholinergic cardiac ganglion neurons, and inhibit the automaticity of the sinus (and AV) node with beat-to-beat modification by the baroreflex. They are also modulated by respiration with a rhythmic respiratory related pattern of discharge (inspiration inhibiting and expiration stimulating the cardio vagal neurons) causing the respiratory associated sinus arrhythmia. In turn, ventricular contractility is affected by the tonic inhibitory muscarinic influence via the preganglionic neurons of the caudal regions of dorsal motor nucleus. Silencing of the neurons of the dorsal motor nucleus has been found to increase left ventricular contractility. Yet, any form of intervention targeting the central and/or peripheral extra cardiac nervous system with the aim to modulate electrophysiological properties specifically at a distinct cardiac site only, will need to take the complex interconnectivity of the intrinsic cardiac nervous system into account. The latter likely mitigates the lateralization of the extrinsic cardiac nervous system to a substantial degree.

Sympathetic tone is largely mediated by the discharge of the sympatho-excitatory glutamatergic neurons in the RVLM oblongata. Silencing the RVLM neurons has been shown to eliminate the central sympathetic outflow. Yet, there remains an ongoing debate about the functional organization of the RVLM neurons. Some evidence suggests that pre-sympathetic neurons are organized organotrophic in that distinct populations regulate defined peripheral targets, for example the heart. This has been supported by micro-stimulation of specific sites in the RVLM activating specific sympathetic nerves e.g. in the heart. In turn, other studies found that pre-sympathetic neurons in the RVLM may serve multiple organs to allow the brain to recruit a molecularly defined subset of RVLM neurons to produce a suitable autonomic outflow for a particular stimulus. Clarification of the functional organization and molecular features of these pre-sympathetic neurons will be key to allow tailored cardio selective neuromodulation without inadvertent non-cardiac side effects. Furthermore, the PAG in the midbrain has been identified as an important contributor to central autonomic regulation with efferent pathways to cardiac-related sympathetic premotor neurons as well as projecting to vagal preganglionic neurons. The improved regulation including in cardiovascular disease.
4.2 The future of neuromodulation: deep brain stimulation, chemogenetics, optogenetics?

Several promising therapeutic approaches (see Figure 7) have been suggested in addition to the existing autonomic therapies outlined in Figure 4. Broadly, these potential candidates for cardiac neuromodulation can be divided in two categories: physical stimulation technologies take advantage of the in vivo synaptic plasticity, which allows to adapt the strength of synaptic signalling in the neural network following a defined stimulatory or inhibitory stimulus. This allows to provoke long-term effects beyond the duration of the stimulus (long-term ‘potentiation’ or ‘depression’). The exact underlying molecular mechanism of such long-term potentiation and depression is a major area of interest in modern neuroscience and the complex processes suggested to be involved have been reviewed.

In turn, molecular precision medicine approaches like chemo- and optogenetics have raised hopes to target very precisely inter- and intracellular signalling pathways based on the underlying aetiology while minimizing inadvertent side effects.

4.2.1 Physical central and peripheral neuronal stimulation technologies

4.2.1.1 Deep brain stimulation (DBS)

Deep brain stimulation (DBS) is an established neurosurgical procedure for selected neurological conditions (e.g. movement disorders, essential tremor, dystonia, and chronic pain). It involves implantation of a device (‘neurostimulator’) connecting a lead positioned in the specific area of the brain to a generator placed under the collarbone or abdomen. Via delivery of electrical impulses of modifiable frequency, intensity, and location, the activity of the neural circuits can be modulated. DBS of the brainstem has been employed as well and found to elicit autonomic (cardiovascular and cardiorespiratory) effects.

Emerging neuromodulation approaches in cardiac ion channelopathies

Figure 6 Overview novel molecular and central nervous system targets. Left: central autonomic nervous system centres, key targets for cardiac neuromodulation highlighted in green (vagal) or orange (sympathetic) (adapted from Benarroch et al.158). Right: overview of novel molecular targets including (A) inhibitory and excitatory G-protein coupled receptors including the cardiac receptors of norepinephrine, acetylcholine, and other neuropeptides. (B) Metabolic targets including adiponectin released from adipocytes. (C) Sigma-1 receptors, ligand specific cellular signalling pathways are still under investigation, inhibition of sodium channel currents, and reduction in calcium leakages have been described as possible anti-arrhythmic mechanism via sigma-1 receptors. (D) Chemorepellents/attractants, e.g. Semaphorin3A suppressing sympathetic nerve sprouting in the heart.
this approach will require a very strong level of evidence for efficacy and safety for the treatment of VAs, particular if less invasive options (outlined below) are available.

4.2.1.2 Transcranial electromagnetic stimulation (TMS)
Transcranial electromagnetic stimulation (TMS) is a non-invasive neurologic therapy modality that applies a changing magnetic field to induce an electric current at specific areas of the brain through electromagnetic induction. This results in depolarization or hyperpolarization of the neurons in the target area and may be delivered up to several centimetres deep into the brain tissue. A variety of stimulation methods have been reported. Effects can be modified by adjusting frequency and intensity of the magnetic impulse, number of repetitions and length of treatment causing long-term potentiation or depression in synaptic efficacy. Cardiac rhythm and HRV have been observed during TMS for neurological diseases. Small clinical feasibility studies investigating the effect on cardiac rhythm indeed demonstrated that significant changes in heart rate and heart rate variability parameters (including LF/HF ratio) can be achieved by repetitive TMS. Improved neurofunctional imaging and understanding of target areas may open possibilities of non-invasively targeting central cardiac autonomic areas to modify pathological autonomic remodelling and responses by tailored stimulation or inhibition of synaptic efficacy via TMS.

4.2.1.3 (Left) stellate ganglion transcutaneous magnetic stimulation (TcMS)
A peripheral application via transcutaneous magnetic stimulation (TcMS) of the (left) stellate ganglion has already been employed in clinical studies. A small feasibility study demonstrated an impressive reduction of ventricular...
arrhythmia burden (99 to 5 episodes within 48 h) in a small case series of five patients with low frequency stimulation of the left stellate ganglion (LSG). A subsequent double-blind sham controlled RCT including 26 patients with VT storm further confirmed the beneficial use of TcMS to suppress VAs safely and non-invasively with a single session, including in patients with cardiac devices. Further research will need to focus on refining stimulation sequences and pattern and exploring the long-term effect.

A similar concept employing low intensity (1–2 W) ultrasound stimulation as opposed to magnetic stimulation has been proposed. In a sham controlled animal study, this successfully modified sympathetic neural activity in the LSG and reduced VAs in a canine infarct model.

4.2.1.4 Selective fascicular vagal nerve stimulation for organ specific neuromodulation

It is recognized that there are closed loop vagal reflexes in the brainstem and peripherally that modulate sympathetic activity and vice versa. Vagal up-regulation could counterbalance sympathetic overdrive but may need to be targeted to specific fascicles supplying certain cardiac sites and ganglia. This requires detailed knowledge of functional anatomical organization of the nerve as well as sophisticated lead designs and cuffs to be applied. Precision medicine with spatially selective stimulation of specific fibres is currently under active investigation to maximize therapeutic benefit while mitigating the traditional wide ranging side effects of non-selective vagal nerve stimulation.

One important example of vagal neuromodulation is the auricular nerve stimulation. Afferent auricular vagus nerve (aVN) stimulation recruits sensory afferent vagus nerve (aVN) fibres and thus mimics/proj.ects sensory input to the brainstem in terms of neuromodulation, forming the so-called auriculo-vagal afferent pathway. Since aural vagus nerve stimulation (aVNS) projects directly to nucleus tractus solitarius, both the peripheral and central nervous systems can be modulated by aVNS stimulation. Selective targeting of specific fibres of the aVN may allow precise modulation of systemic parameters of cardiovascular and respiratory functions by a sympatho-inhibitory effect. Clinical research has been so far focused on employing aVNS for atrial arrhythmias and blood pressure management, but preclinical studies indicate a protective anti-fibrillatory effect also in VAs.

4.2.2 Molecular precision medicine

4.2.2.1 Chemogenetics

One of the most exciting advances in recent years has been the progress in using a combined genetic and chemical approach to generate exogenous ‘designer receptors’ that respond to a specific synthetic ligand to modify cellular signalling and activity.

Types of chemogenetics

Initial chemogenetic receptors were termed ‘RASSLs’ (receptors activated solely by synthetic ligands) but were found to exhibit off-target effects and high levels of constitutive activity. Further improvements let to the development of the current two main types of chemogenetic receptors as follows:

(1) DREADD (‘designer receptors exclusively activated by designer drugs’), which are monomeric proteins with low constitutive activity and few off-target effects. They have become the most widely employed type of chemogenetic receptors to target G-protein coupled receptor signalling to replicate the signalling output of the naturally occurring receptors. They are classified in excitatory and inhibitory types: Gs, DREADDDS signal through the Gs111 protein, Gs, and Gs, DREADD activate respectively inhibit neuronal signalling by increasing intracellular cAMP concentrations. Detailed reviews about their use in neuronal research have been published.

(2) PSAM (pharmacologically selective actuator modules) are modified ligand binding domains, which respond to specific small molecules termed PSEM (‘pharmacologically selective effector molecules’). PSAMs may be coupled to an ion pore domain (forming a chimeric protein) to form ligand gated ion channels that can directly excite or inhibit neuronal signalling. Initial challenges of PSEM have been short clearance times and low micromolar potency preventing in vivo use, though ultrapotent chemogens have been developed to overcome these limitations.

Delivery

To achieve in vivo expression in the target cells, chemogenetic receptors are traditionally delivered through viral injections, most commonly using a replicant deficient adeno-associated virus. Cell specificity, e.g. selectively targeting cardiomyocytes, can be achieved by choosing AAV serotypes with cardio-tropism and adding cell type specific promoters in the chemo
genetic plasmids that may be complemented by enhancers. This has allowed to achieve highly precise spatiotemporal targeting of cardiomyocyte and cardiac autonomic specific effects.

Examples of chemogenetics for autonomic modulation of cardiac electrophysiology

In a transgenic mouse model with Gs coupled DREADD, Gs, in vivo activation over designer ligands caused a measurable increase in generation of cAMP and transient positive inotropy. This was likely by activation of the ryanodine receptors and increase in cellular Ca2+ as well as PKC activation and phosphorylation of calcium-handling proteins. Secondly, changes in impulse propagation in the AV node as well as spatiotemporal dispersion of ventricular excitation were observed and thought to be secondary to a direct effect on connexin assembly, function, and ion conductivity. These findings suggest that with further refinement of chemogenetic engineering very specific G-protein cascades at the level of the sinus node, AV node, Purkinje or working myocardium may be targeted to allow highly precise modulation of impulse propagation and contractility.

In BrS, chemogenetic targeting of the protein trafficking regulator MOG1 (a chaperone that binds to the voltage gated sodium channel and traffics it to the cell surface) has allowed an increase cell surface expression of NaV1.5 and ventricular Ica and thereby normalize action potential abnormalities and abolished J waves. Chemogenetic modulation of central autonomic neuronal circuit activity has also been shown to be feasible. Silencing the dorsal motor nucleus of the vagus nerve achieved successful modulation of ventricular excitability by abbreviating the ventricular ERP and elevating the threshold for VT induction.

Challenges

Whereas the initial concerns in regards to the effect of high levels of engineered protein expression in the absence of chemical activation and constitutive activity may have been overcome, questions of desensitization and down-regulation remain. Also, protein interactions need to be considered as they dictate the degree of viral spread within the injected tissue and may impact gene expression. Lastly, agonists may activate more than one downstream effector pathway inducing effects other than just silencing or enhancing neural activity. Further research is required to confirm safety and absence of inadvertent side effects. Lastly durability of chemogenetic modulating effects is still an open question.

4.2.2.2 Optogenetics

Genetic information coding for light sensitive proteins (‘opsins’, ion channels or pumps) is introduced into cellular DNA of the target cells. Once the target protein is expressed, exposure to a defined activation wavelength allows for reversible modulation of its activity via the opsins, which may then result in depolarization or hyperpolarization of the cell membrane causing cellular excitation or silencing
Types of opsins and delivery

The original opsin used was channelrhodopsin-2, a membrane channel that opens in response to blue light and allows cation flow to depolarize the cell. Subsequent variants have been engineered to increase the spectral and kinetic properties and improve expression and membrane targeting in the cells. The use of different activation wavelength also allowed to combine multiple opsins to be expressed on the same cell. The light sensitive opsins are induce by e.g. using a viral vector injected in the area of interest and activated via photo stimulation devices ('photo switch'). This offers not only high spatial but also temporal reversible control of protein activity.

Examples of optogenetics for autonomic modulation of cardiac electrophysiology

Optogenetic approaches have been successfully employed to modulate cardiac autonomies in preclinical studies. In animal infarct model, an inhibitory light sensitive opsin was introduced to the left stellate ganglion and reversible neural silencing achieved via neuronal hyperpolarization during transient light emitting diode illumination. The optogenetic inhibitions significantly but reversibly suppressed LSG neural activity, sympathetic heart rate variability indices and ischaemia induced arrhythmias. It let to prolonged left ventricular effective refractory periods and action potential duration with all values turning back to baseline within 2 h after illumination was turned off. Long-term optogenetic neuromodulation of the LSG over a self-powered optogenetic system in an infarct model equally reported successful suppression of LSG hyperactivity and prolongation of effective refractory period, action potential duration and reduction in VA inducibility. The findings highlight the potential of optogenetic neuromodulation to suppress adrenergically driven ventricular arrhythmias, not only in ICM but also potentially CPVT and LQTS.

In turn, optogenetics have also been successfully employed to modulate pacemaker activity of cardiomyocytes via Gs signalling as well as stimulate the dorsal brainstem vagal preganglionic neurons associated with improvement in left ventricular function in an animal infarct model.

Challenges

The most challenging consideration for the use of opsins as well as preservation of gene expression are the practicality of delivery (the opsin needs to be expressed and the area then sufficiently illuminated), which requires an invasive approach. Yet, novel developments of wireless self-powered optogenetic systems may overcome this limitation and also allow to study the anti-arrhythmic effect in awake and moving subjects over longer time.

In canine studies, a wireless LED lead was placed over the LSG and connected to a power receiver under the skin. An external wireless charging module was then applied to the chest wall of the dog to harvest the mechanical energy from the body motion and convert into electricity and achieve optical illumination off the LSG.

4.2.2.3 Sonogenetics

To overcome the challenges of optogenetics for in vivo application, the related concept of sonogenetics has been proposed. This may allow to maintain the benefits—cell type selective stimulation—but facilitate non-invasive application and stimulation. Analogue to optogenetics, sonogenetics utilizes genetically encoded, ultrasound responsive mediators for non-invasive and selective control of neural activity via the mechanical wave. Feasibility of activating specific regions and cell types in the brain by sensitizing them to ultrasound using such mechanosensitive ion channels has been demonstrated in animal studies. Spatial resolution is defined by the spatial resolution of ultrasound focusing as well as the spatial distribution of sonogenetic mediators and has been reported as high as 0.59 mm. The majority of published research has been focused around its application in brain tissue, whereas its benefit and use as anti-arrhythmic treatment have only been reported in an open-access in silico experiment.

Overall, sonogenetics is another promising modality, although substantially under investigated in cardiovascular diseases. More generally, it has also been highlighted that many in vivo performance metrics, including in vivo spatiotemporal resolution, selectivity and specificity as well as safety are still under investigation and important challenges for translating it into clinically efficient and safe therapy options remain.

5. Conclusion

Contemporary diagnostic and therapeutic means to efficiently and safely address proarrhythmic autonomic inputs to the heart remain unsatisfactory. Improving methods to assess autonomic influences on the cardiac substrate to refined patient selection and delivery of neuromodulating techniques as well as better definition of acute and longer therapeutic effects of each modality are required. Also, uncertainties of long-term tolerance to stimulation and/or inhibitions, dynamic changes in the responses of autonomic targets as well as inadvertent side effects caused by the complex autonomic interactions remain and need further addressing.

Yet, multiple new molecular and central nervous system targets involved in proarrhythmogenic autonomic signalling pathways in cardiac channelopathies have been identified. Complemented by a number of promising emerging neuromodulating technologies, this may open a new era in the treatment and prevention of VAs. Non-invasive electromagnetic stimulation, deep brain stimulation, as well as the exciting field of chemo-, opto-, or sonogenetics all may contribute to fill that important gap in contemporary anti-arrhythmic therapies. These new developments could address the heterogeneous pathophysiology in patients with cardiac channelopathies and VAs, by offering precise, individualized and, if desired, reversible cardiac neuromodulation to successfully prevent SCD.

Supplementary material

Supplementary material is available at Cardiovascular Research online.

Conflict of interest: none declared.

Data availability

No new data were generated or analysed in support of this manuscript.

References

hypothalamic as a potential link between emotional stress and cardiac arrhythmias. Auton Neurosci 2011;170:22–27.


The role of inhibitory G proteins and regulators of G protein signaling in the in vivo control of heart rate and predisposition to cardiac arrhythmias. Front Physiol 2012;3:176.


