Title: Inhibition of G protein-gated K^+ channels by tertiapin-Q rescues sinus node dysfunction and atrioventricular conduction in mouse models of primary bradycardia

Running title: Pharmacological inhibition of I_{KACh} rescued sinus node dysfunction

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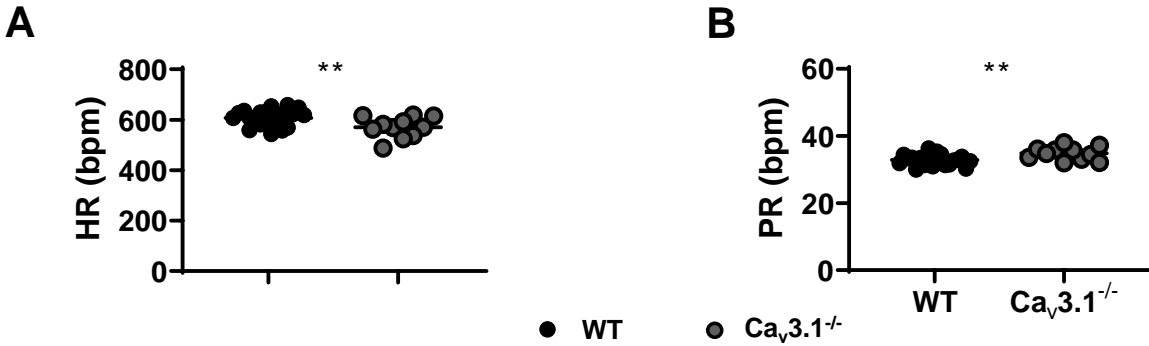
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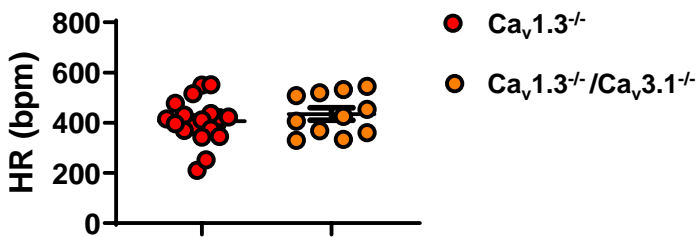* These authors contributed equally to this work

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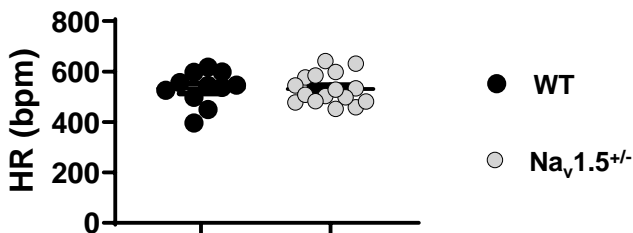Email: Pietro.Mesirca@igf.cnrs.fr

A

B

** (Panel A)
** (Panel B)

● WT   ● Ca$_v$3.1$^{-/-}$

Supplementary figure 1. Heart rate and atrioventricular conduction time in Ca$_v$3.1$^{-/-}$ mice in basal condition.
24h heart rate (A) and PR Interval (B) recorded in WT (black circle, n=22) and Ca$_v$3.1$^{-/-}$ mice (gray circle, n =11). Statistics: unpaired t test. **$p < 0.01$. Error bars define the s.e.m.
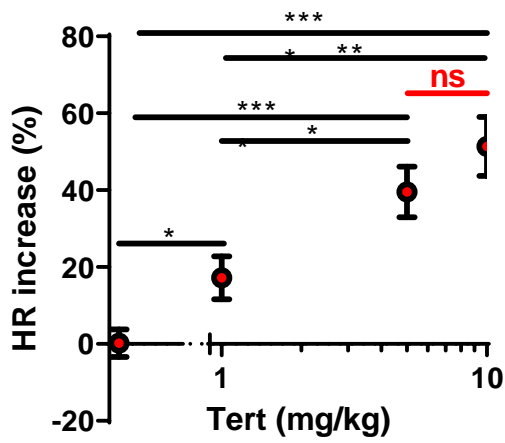
SUPPL FIGURE 1

● Ca$_v$1.3$^{-/-}$
● Ca$_v$1.3$^{-/-}$/Ca$_v$3.1$^{-/-}$

Supplementary figure 2. Heart rate in Ca$_v$3.1$^{-/-}$ and Ca$_v$1.3$^{-/-}$/Ca$_v$3.1$^{-/-}$ mice in basal condition. Heart rate recorded in Ca$_v$1.3$^{-/-}$ (red circle, n=18) and Ca$_v$1.3$^{-/-}$/Ca$_v$3.1$^{-/-}$ (orange circle, n=11). Statistics: unpaired t test. Error bars define the s.e.m.
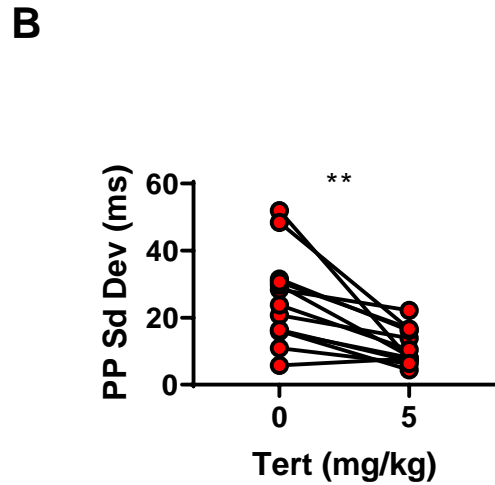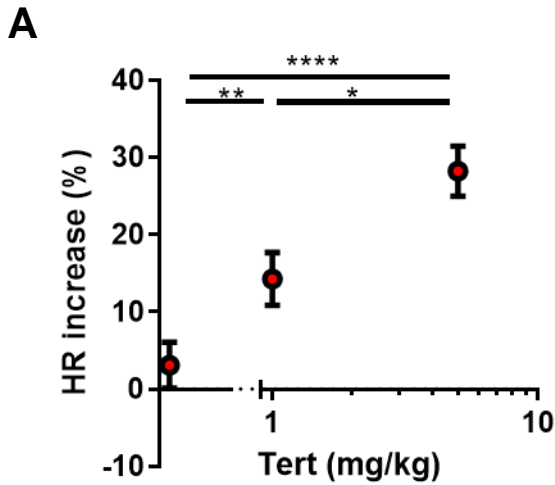
SUPPL FIGURE 2

● WT
○ Na$_v$1.5$^{+/-}$

Supplementary figure 3. Heart rate Na$_v$1.5$^{+/-}$ animals in basal condition.
24h heart rate recorded in WT (black circle, n=11) and Na$_v$1.5$^{+/-}$ mice (gray circle, n=16). Statistics: unpaired t test. Statistics: unpaired t test. Error bars define the s.e.m.
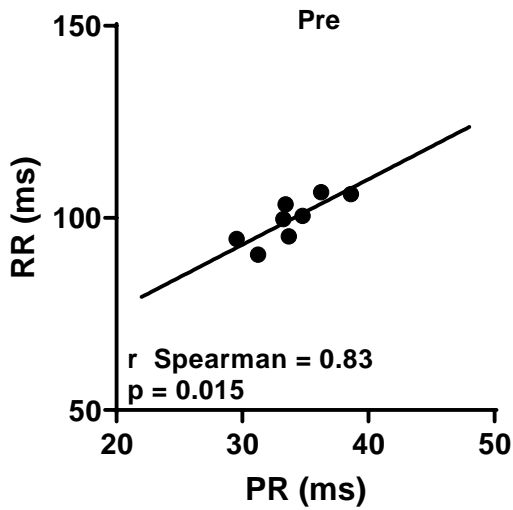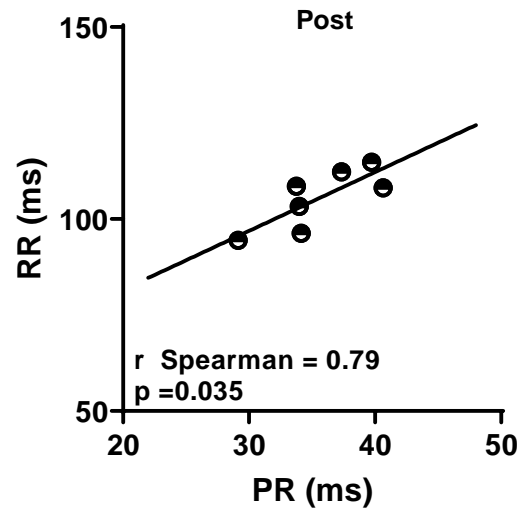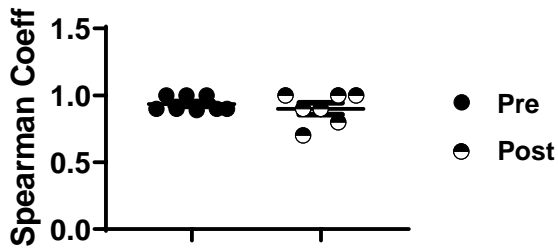
SUPPL FIGURE 3

Supplementary figure 4. Dose response curve of heart rate in response to tertiapin-Q in Ca$_v$1.3$^{+/-}$ animals.
Percentage of heart rate increasing in mutant Ca$_v$1.3$^{+/-}$ animals after injection of different doses of tertiapin-Q (n=11 at 0 mg/kg, n=11 at 1mg/kg, n=8 at 5mg/kg and n=6 at 10mg/kg); Statistics: analysis of variance (ANOVA) followed by Holm-Sidak multiple comparisons test. *p < 0.05, **p < 0.01, ****p < 0.0001. Error bars define the s.e.m.

SUPPL FIGURE 4

A

B

Supplementary figure 5. **A.** percentage of increase in the heart rate in response to injection of different doses of tertiapin-Q (n=19 at 0 mg/kg, n=24 at 1 mg/kg and n=23 at 5mg/kg) in Ca$_v$1.3$^{-/-}$ animals. Statistics: analysis of variance (ANOVA) followed by Holm-Sidak multiple comparisons test. **B.** PP interval variability before and after injection of 5 mg/kg tertiapin-Q (n=13). Statistics: paired-test. *p < 0.05, **p < 0.01, ****p < 0.0001. Error bars define the s.e.m..
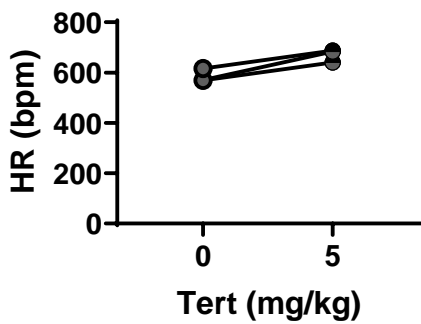
SUPPL FIGURE 5

Supplementary figure 6. Effect of tertiapin-Q on RR-PR intervals correlation in WT animals.
Dot-plots of RR versus PR interval and relative linear regression lines in control condition (A) and in 5mg/kg tertiapin-Q (B) measured in WT mice (n=8). C: r-Spearman correlation coefficients calculated in control condition (full black circle) and after injection (horizontally black-striped circle) of 5mg/kg tertiapin-Q. Statistics: Mann-Whitney test. Error bars define the s.e.m.
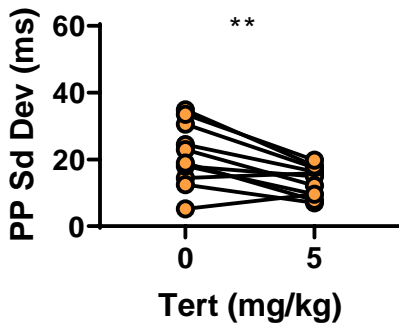
SUPPL FIGURE 6

Supplementary figure 7. Tertiapin-Q effect on heart rate in Ca$_v$3.1$^{-/-}$ mice.
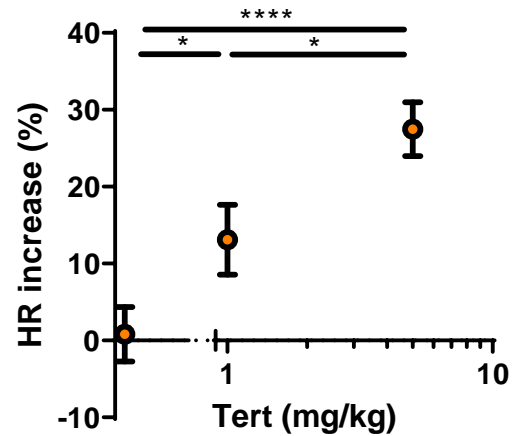Heart rate measured before (full gray circle) and after (horizontally gray-striped circle) injection of 5mg/kg tertiapin-Q in Ca$_v$3.1$^{-/-}$ animals (n=3).
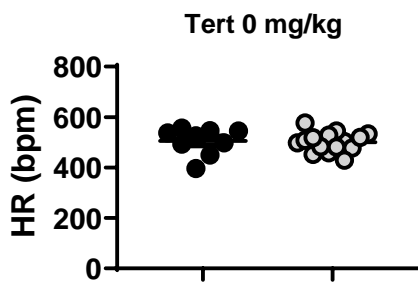
SUPPL FIGURE 7

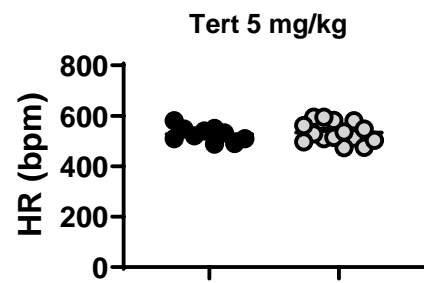**Supplementary figure 8. A.** PP variability before and after 5mg/kg tertiapin-Q injection in Ca$_v$1.3$^{-/-}$/Ca$_v$3.1$^{-/-}$ mice (n=11). Statistics: paired-t-test. B. percentage of increase in the heart rate in response to injection of different doses of tertiapin-Q (n=11 at 0 mg/kg, n=10 at 1 mg/kg and n=11 at 5mg/kg) in double-mutant animals. Statistics: analysis of variance (ANOVA) followed by Holm-Sidak multiple comparisons test. *p < 0.05, **p < 0.01, ****p < 0.0001. Error bars define the s.e.m..
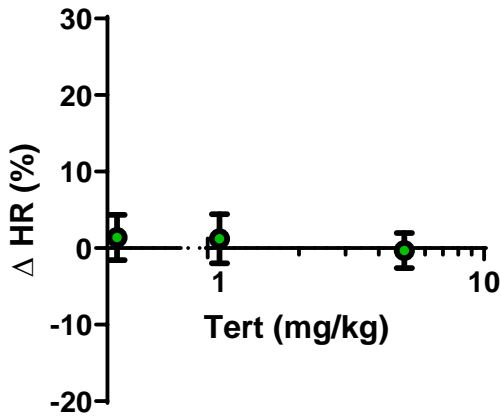
SUPPL FIGURE 8

Supplementary figure 9. Tertiapin-Q effect on heart rate in Na$_v$1.5$^{+/-}$ mice.
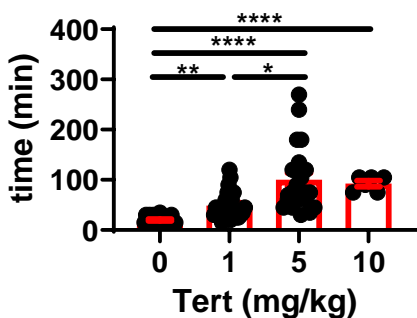Heart rate measured in 5mg/kg tertiapin-Q and control (NaCl) conditions in Na$_v$1.5 homozygous (black circle, n=9) and heterozygous (gray circle, n=15) animals. Statistics: unpaired t test. Error bars define the s.e.m.

SUPPL FIGURE 9

Supplementary figure 10. Dose response relationship of heart rate in response to tertiapin-Q injection in Girk4^{-/-} animals. Percentage of heart rate increasing in mutant Girk4^{-/-} animals after injection of different doses (n=6 in control condition, n=6 at 1 mg/kg and n=10 at 5 mg/kg) of tertiapin-Q; Statistics: analysis of variance (ANOVA) followed by Holm-Sidak multiple comparisons test. Error bars define the s.e.m.

SUPPL FIGURE 10

Supplementary figure 11. Dose response curve of the duration of the 'rescuing' effect on heart rate in response to tertaipin-Q injection in Ca$_v$1.3[-/-] animals. Duration of effect on the heart rate after injection of different doses of tertiapin-Q in Ca$_v$1.3[-/-] mice (n=19 at 0 mg/kg, n=24 at 1 mg/kg, n=23 at 5 mg/kg and n=6 at 10 mg/kg). Statistics: Kruskal-Wallis test followed by multiple comparisons test. *p < 0.05, **p < 0.01, ****p < 0.0001. Error bars define the s.e.m.

SUPPL FIGURE 11