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Short communication

Quinpirole treatment increases renal sympathetic nerve activity and baroreflex gain in conscious rabbits: a spectral study

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Abstract

Intravenous administration of 0.3 mg/kg of quinpirole to conscious rabbits that had been pretreated with domperidone caused a marked increase in blood pressure and renal sympathetic nerve activity with a peak at 5–10 min after injection (25% and 3-fold increase, respectively). Spectral analysis of the blood pressure–renal sympathetic nerve activity relationship in the 0.2–0.4 Hz domain showed that baroreflex gain was markedly increased at 5–10 min (4-fold) and at 20–25 min after injection (3.7-fold). These results show that administration of the dopamine D_2/D_3 receptor agonist quinpirole causes profound and long-lasting changes in the central integration of the sympathetic baroreceptor–vasomotor reflex.

Keywords: Quinpirole; Baroreflex; Renal sympathetic nerve activity; Rabbit, conscious

1. Introduction

The administration of quinpirole and other dopamine D_2 and mixed D_2/D_3 receptor agonists causes a rapid and pronounced increase in blood pressure in conscious animals (Nagahama et al., 1986; Van den Buuse, 1992; Van den Buuse et al., 1996) and man (McNay et al., 1987). The site of action of quinpirole on blood pressure has been suggested to be the nucleus tractus solitarii (Yang et al., 1990), the primary relay station for baroreceptor afferent input. In rats, the pressor response is associated with little change in heart rate and a small reduction of the upper plateau of the baroreceptor–heart rate reflex (Van den Buuse, 1997b). The administration of quinpirole in conscious rabbits induced a marked rise in blood pressure and renal sympathetic nerve activity (Van den Buuse et al., 1998); however, it is unclear to what extent this effect is associated with changes in the baroreceptor–vasomotor reflex, making it difficult to understand its functional implications. The present study was undertaken to address this question. We used spectral analysis of blood pressure and renal sympathetic nerve activity before and after administration of quinpirole to conscious rabbits.

2. Material and methods

Eight male or female cross bred rabbits weighing between 2.5 and 3 kg were obtained from the Baker Medical Research Institute breeding stock and housed as previously described (Van den Buuse and Malpas, 1997). All experiments and procedures were in accordance with the *Australian code of practice for the care and use of animals for scientific purposes (1990)* and were approved by the Animal Experimentation Committee of the Alfred Hospital/Baker Medical Research Institute. The procedures for instrumenting the rabbits with a coil renal nerve electrode and for obtaining blood pressure and renal nerve activity recordings have been described in detail previously (Dorward et al., 1985; Malpas et al., 1996; Van den Buuse et al., 1998). In all experiments, the rabbits were intravenously pretreated with 1 mg/kg of the peripherally acting dopamine D_2 receptor antagonist domperidone (Research Biochemicals, Natick, MA, USA) (Laduron and Leysen, 1979) to block systemic effects of quinpirole (Nagahama et al., 1986; Van den Buuse, 1992). Baseline values were then recorded and 10 min after domperidone injection, 0.3 mg/kg of quinpirole (Research Biochemi-

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cals) was administered intravenously. Blood pressure and nerve activity were recorded continuously and 30 min later another quinpirole injection was given (Van den Buuse et al., 1998). Renal sympathetic nerve activity was recorded in microvolts and baseline activity before quinpirole treatment was normalised to 100 units.

Mean arterial pressure and renal sympathetic nerve activity were digitised at 500 Hz using a National Instruments (Austin, TX, USA) data acquisition card (ATMI016 or PC plus) and a data acquisition program written in the Labview graphical programming language (National Instruments, Austin TX, USA). The beat to beat signals corresponding to four 5-min periods were analysed for spectral analysis using a program developed at the Baker Institute and written in Labview. Data were obtained before quinpirole treatment, 5–10 min after quinpirole injection ('peak' effect), 20–25 min after quinpirole injection ('late' effect), and 5–10 min after a second quinpirole injection (Van den Buuse et al., 1998). Beat to beat data was displayed on screen and artefacts eliminated. The data

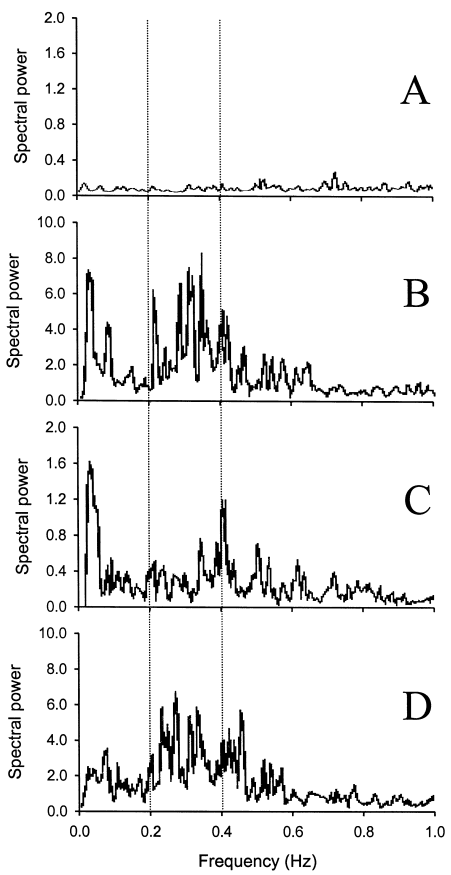

Fig. 1. Typical example of spectral analysis of renal sympathetic nerve activity in a conscious rabbit treated with quinpirole. Top panel (A): control measurement before administration of 0.3 mg/kg of quinpirole; (B) 5–10 min after quinpirole injection; (C) 20–25 min after quinpirole injection; (D) 5–10 min after a second quinpirole injection. Note difference in vertical scale between panels A and C versus panels B and D. Stippled lines border the mid-frequency range which was used for further analysis.

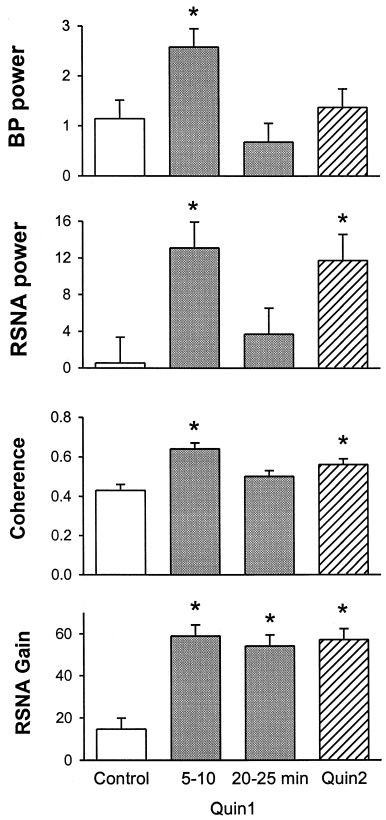

Fig. 2. The effect of 0.3 mg/kg of quinpirole on mean arterial pressure, renal sympathetic nerve activity (RSNA) and baroreflex gain in eight conscious rabbits. Blood pressure and nerve activity are expressed as power (area under the curve) from the spectral analysis in $mmHg^2$ Hz and normalised $units^2$ Hz/1000. RSNA gain is expressed as normalised units per mmHg. $^*P < 0.05$ for difference with baseline values.

was then re-sampled at 5.12 Hz and partitioned into segments of 100-s (512 points) length overlapping by 50%. The auto- and cross-power spectra were calculated for each segment using Fast Fourier transform and phase and coherence of the transfer function between blood pressure and heart rate were calculated using mathematical methods available in the Labview programming language. Coherence can have a value between 0 and 1 and is a frequency domain estimate of correlation coefficient indicating the degree that variance in one variable can be explained by a linear operation of the variance in the other. Only periods of data where the coherence was more than 0.5 were used in estimation of the baroreflex gain. Baroreflex gain itself was calculated as the square root of the ratio of blood pressure and renal sympathetic nerve activity at each frequency point and averaged over the mid-frequency range (0.2–0.4 Hz), which is the relevant autonomic band (Robbe et al., 1987). Values were expressed as mean ± standard error of the mean (S.E.M.). Spectral parameters were analysed by two or three-way analysis of variance where the between animal variance was removed from the residual. Significant effects were taken at the level of $P < 0.05$.

3. Results

Intravenous injection of 0.3 mg/kg of quinpirole caused a rapid rise in blood pressure and renal sympathetic nerve activity associated with a marked rise in spectral power of renal sympathetic nerve activity in the 2–4 Hz frequency domain (Fig. 1). When expressed as spectral power (area under the curve) of this frequency band, there was a significant rise in blood pressure at 5–10 min after treatment but not 20–25 min after treatment. A second injection of quinpirole caused little further pressor response (Fig. 2). Total spectral power of blood pressure, including all frequency bands from 0 to 2 Hz, was not significantly altered at any of the time-points (data not shown). Renal sympathetic nerve activity power in the 0.2–0.4 Hz frequency band had significantly risen 5–10 min after quinpirole injection but had returned to baseline 20–25 min after treatment. A second injection of quinpirole again caused a significant rise in renal nerve activity power (Fig. 2). Spectral analysis showed a marked and highly significant 4-fold increase in renal sympathetic nerve activity baroreflex gain 5–10 min after quinpirole treatment. This effect was maintained 20–25 min after injection and a second treatment did not cause a further increase in gain (Fig. 2). Spectral coherence was generally between 0.4 and 0.6 units.

4. Discussion

The marked rise in blood pressure and renal sympathetic nerve activity in the present study was similar to that described before (Van den Buuse et al., 1998). The present study shows for the first time that baroreflex gain of the relationship between mean arterial pressure and renal sympathetic nerve activity is markedly increased by quinpirole treatment. Unlike blood pressure or sympathetic activity, this increase in baroreflex gain is maintained and is not enhanced further by a second quinpirole treatment.

Given the previously observed effects of quinpirole on blood pressure and renal sympathetic nerve activity (Van den Buuse et al., 1998), vasomotor reflex gain could have changed in three ways. It is well known that the relationship between mean arterial pressure and renal sympathetic nerve activity is best described by a sigmoidal curve with plateaus of nerve activity at blood pressure extremes (Dorward et al., 1985; Malpas et al., 1996). It could have been possible that the curve simply followed the pressor response and shifted to the right with the increased nerve activity ending up on the upper plateau and resulting in a markedly diminished baroreflex gain. Alternatively, the entire sigmoidal baroreflex curve could have been reset rightward and upward so that the reflex operated from a higher set point and the gain essentially remained the same. A third possibility could have been that the increase in blood pressure and nerve activity resulted in a marked change in curve parameters, resulting in an increased gain and upper plateau, similar to the effects of hypoxia (Malpas et al., 1996). The present results show that the third possibility is most likely, although it should be noted that spectral analysis does not provide estimates of the renal nerve activity's plateau. Another indication that baroreflex gain is not passively following changes in blood pressure and nerve activity is that at 20–25 min after quinpirole injection, when both of these parameters have returned towards baseline, gain is virtually unchanged as compared to 5–10 min after injection, when both blood pressure and nerve activity are increased. This suggests an additional site of action of quinpirole in the blood pressure–renal sympathetic nerve activity arc and expands the complexity of the action of this drug on central integration of the circulatory system.

The functional implications of the marked and prolonged rise in renal sympathetic baroreflex gain in quinpirole-treated rabbits remains to be elucidated. It could be expected that blood pressure levels are very tightly regulated by such a marked increase in gain. However, we did not observe a significant reduction in total spectral power of blood pressure (data not shown), arguing against such a systemic effect. Given the role of central dopaminergic mechanisms in the control of locomotor behaviour and stress mechanisms (Van den Buuse, 1997a, 1998), it could be that renal sympathetic baroreflex gain is enhanced as part of a 'defence' type response, tightly controlling renal blood flow in the face of threatening or stressful environmental stimuli. Quinpirole treatment then mimics endogenous dopaminergic activation without the actual stress stimulus. Alternatively, as discussed previously, there are similarities between cardiovascular responses induced by quinpirole and those induced by hypoxia (Van den Buuse et al., 1998). Dopamine is released in the nucleus tractus solitarii upon hypoxic stimulation (Goiny et al., 1991) and dopamine receptors have been observed in this nucleus by receptor autoradiography (Lawrence et al., 1995). Administration of quinpirole could then mimic endogenous dopaminergic mechanisms usually triggered by hypoxia, but without the actual hypoxic stimulus. It would be important to study the effect of quinpirole in other species, since rabbits, as herbivores, show a relatively large hypoxia-induced vasodilatation in the gut which makes a renal nerve activity increase necessary to keep blood pressure stable.

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