Deep brain stimulation can regulate arterial blood pressure in awake humans

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*Conflict of interest: A.L. Green, D.J. Paterson, J.F. Stein and T.Z. Aziz have applied for a US patent – Method and Apparatus for Regulating Blood Pressure.

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The periaqueductal grey matter is known to play a role in cardiovascular control in animals. Cardiovascular responses to electrical stimulation of the periventricular/periaqueductal grey matter were measured in 15 awake human study participants following implantation of deep brain stimulating electrodes for treatment of chronic pain. We found that stimulation of the ventral periventricular/periaqueductal grey matter caused a mean reduction in systolic blood pressure of 14.2 ± 3.6 mmHg in seven patients and stimulation of the dorsal periventricular/periaqueductal grey matter caused a mean increase of 16.7 ± 5.9 mmHg in six patients. A comparison between ventral and dorsal electrodes demonstrated significant differences ($P < 0.05$). These changes were accompanied by analogous changes in diastolic blood pressure, pulse pressure, maximum dP/dt but not in the time interval between each R wave on the electrocardiogram. *NeuroReport* 16:1741–1745

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Introduction

Control of arterial blood pressure (ABP) is a complex process that is influenced by both hormonal and neural pathways from the forebrain down to each individual cardiac and vascular myocyte. In the midbrain, the periaqueductal grey matter (PAG) is organized into functionally distinct and functionally opposite columns [1]. These columns receive afferents from the sympathetic chain [2], the rostral raphe [3], anterior hypothalamus [4], thalamus [5] and cortex [6]. In turn, the PAG projects to sympathetic premotor neurons in the hypothalamus, pons and medulla. These projections influence sympathetic outflow that alters cardiovascular output [2] and are commonly thought to be the link between forebrain emotional processing and motor pathways involved in the defence reaction. The PAG also projects to vagal preganglionic neurons [7]. Thus, the neurocircuitry of the PAG plays a pivotal role in cardiovascular control, probably via the medulla.

The periventricular grey matter (PVG) is rostral and continuous with the PAG. This rostral PVG/PAG area that we stimulated, however, is not included in the aforementioned columns. In this study, we show, in awake humans, that deep brain stimulation of this area can increase or decrease ABP. This effect is dependent on the ventral/dorsal location of the electrode, and highlights a potential neurotherapeutic target to regulate ABP.

Materials and methods

Fifteen patients (12 men, 3 women) were referred for deep brain stimulation for neuropathic pain of varying aetiology. Mean age was 51.3 years (range 30–74). Four patients acted as their own controls as they had both PVG/PAG and thalamic stimulators. Two controls were patients with non-pain conditions – one with a thalamic stimulator, the other with a spinal cord stimulator. Informed consent for participation in the study was obtained from each patient, and the study was approved by the local ethics committee.

Surgical technique

Details of our surgical technique have been described previously [8].

Postoperative localization of electrodes

Electrode positions were plotted on a brain atlas [9] using the postoperative magnetic resonance imaging and a manipulation program (MRIcro version 1.38, Chris Rorden). First, the scan was rotated such that the anterior and posterior commissures were on the same slice. The mid-commissural point was then calculated, followed by the relative position of the electrode contacts in all three planes. The centre of each contact was taken as the position of the electrode and this corresponds to the centre of the contacts

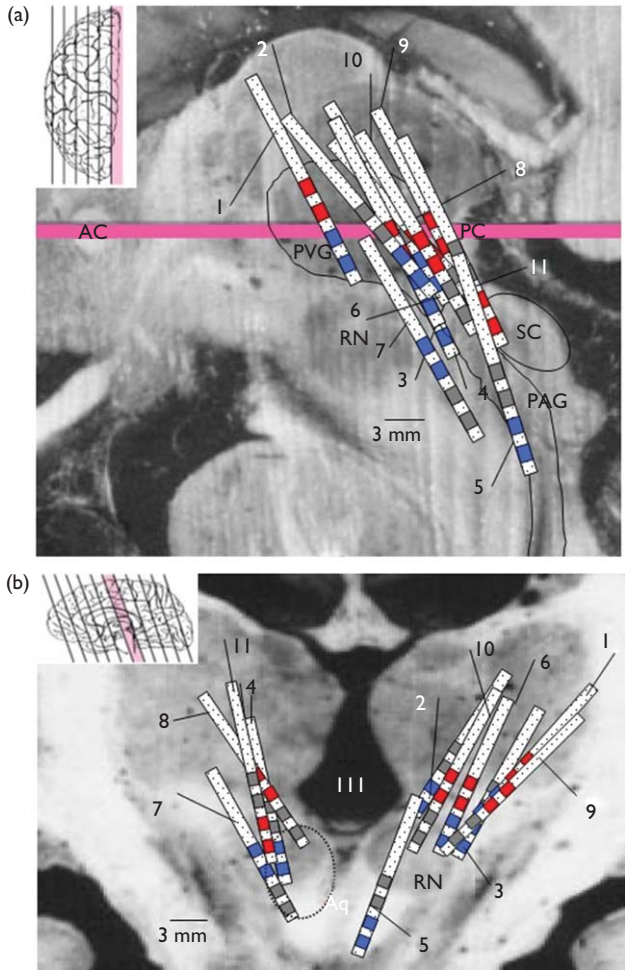

Fig. 1 (a) Sagittal positions of the electrodes in patients in whom there were changes in BP. (b) Coronal positions. For clarity, patients with no changes are not shown. Note that patients #1–7 all had reduction in BP (blue contacts) at the most ventral electrodes. Conversely, patients #8–11 and the upper two contacts of patients #1 and #6 had a rise in BP (red contacts). Grey contacts are those that, when stimulated, had no effect on BP. BP, blood pressure; AC, anterior commissure; PC, posterior commissure; PVG, periventricular grey; PAG, periaqueductal grey; SC, superior colliculus [the level of which is depicted by the dotted circle in (b)]; RN, red nucleus; III, third ventricle; Aq, aqueduct. Inset of (a) shows the AC–PC plane; inset of (b) shows the slice position. Background reprinted from [9], with permission from Elsevier.

in Fig. 1. In this reconstructed diagram, the angle of the electrodes in both the sagittal and coronal plane, the distance to the superior colliculus and the relative positions between electrodes were compared with the original scans for verification.

Measurements

During lab-based recordings, non-invasive continuous finger arterial pressure was measured with an Ohmeda Finapres 2300 (BOC Healthcare, Murray Hill, New Jersey, USA). The blood pressure (BP) was calibrated using a sphygmomanometer and the pressure transducer and finger cuff were positioned at heart level. A lead II electrocardiogram was recorded using disposable adhesive Ag/AgCl electrodes (H27P, Kendall-LTP, Mansfield, Massachusetts, USA) and amplified $\times 1000$ (CED 1902, Cambridge Electronic Design, Cambridge, UK). The finger pressure and electrocardiogram were digitized at 4 kHz with 16-bit resolution (CED 1401 Mark II, Cambridge Electronic Design) using Spike II software (version 5.0, Cambridge Electronic Design).

To validate the lab-based (Finapres, Amsterdam, The Netherlands) recordings, in one patient (#8), intra-arterial pressure was measured during general anaesthesia. The dorsal PVG was stimulated at 10 Hz at 4.0 V (pulse width 120 μs) for 3 min. This was repeated three times with 5 min rest inbetween to confirm the effect.

Study design

Experiments were performed more than 2 h after any meal and room temperature was kept constant at 22°C. Patients delayed opioid or antihypertensive medication (two patients) until after the experiment. They also abstained from caffeine. The deep brain stimulator was initially turned off for at least 10 min prior to experiments.

Experiments were started with the patient sitting for 5 min. The first session consisted of a 12-min rest period with the stimulator turned off. This was repeated with the stimulator turned on. During most sessions, stimulation lasted for 5 min, followed by a 3-min recovery period. In sessions with no change in BP, stimulation was continued for 12 min to confirm no effect. A 9-min rest period followed with the stimulation off inbetween each session. This rest period was extended if BP had not yet returned to the baseline value. The Medtronic 3387 electrode (Minneapolis, Minnesota, USA) consists of four circumferential contacts. During each 'on' session, bipolar stimulation was used between the two deepest or the two most proximal contacts, at 10 Hz. The pulse width was 120 μs and amplitude was increased to the maximum tolerated by the patient without side effects (including nausea, sweating or increased pain – see Discussion), up to 3 V. This was repeated three times for each pair of contacts tested with rest periods inbetween. Pain was quantified with a visual analogue score at the beginning and end of each session.

Signal processing and statistical analysis

To avoid change of BP caused by pain, the data segment was excluded when visual analogue score changed. A one-way analysis of variance of BP with time was performed on all raw data segments for each session to determine significant change ($P<0.05$). For each stimulation setting, data segments were divided into three groups depending on whether BP increased, decreased or did not change. For each session, data were averaged every 30 s and the mean values were taken to give the average across sessions in each patient. The average data from all patients were plotted sequentially to provide the overall changes over time. The BP changing rate, dP/dt, was derived by differentiating the BP. The maximum dP/dt (maximum slope of the BP curve) was then extracted. All results are expressed with ± 1 standard error of the mean.

In order to test whether changes in BP are related to stimulation location, we analysed the BP changes over time for the eight most ventral and nine most dorsal stimulation sites using ANOVA, taking the three stimulation sessions from both the bottom and top two contacts that were stimulated (i.e. six sessions per patient) (data were averaged within each patient prior to ANOVA). This analysis

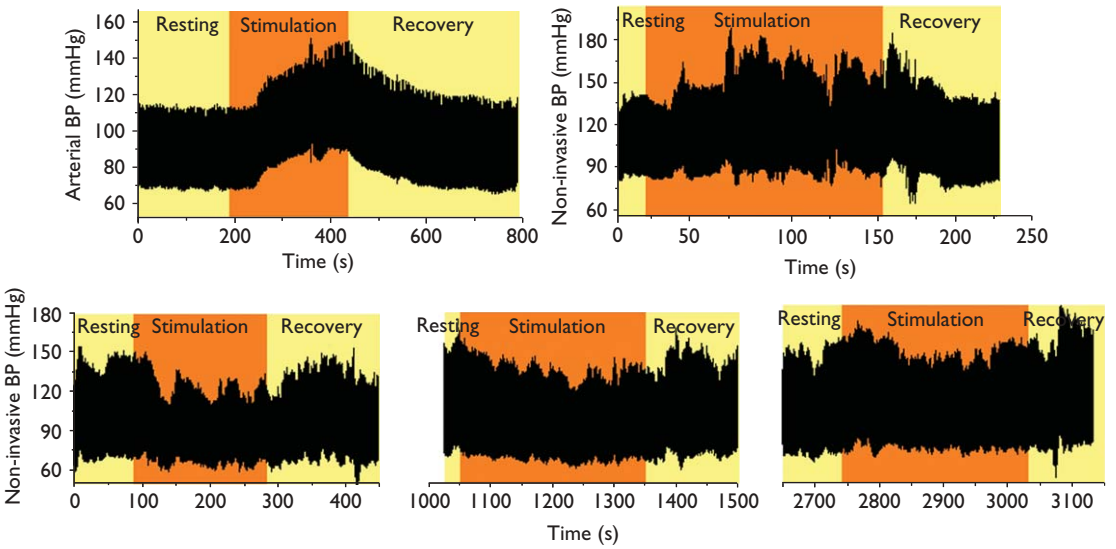

Fig. 2 Raw data traces of BP recordings. Top left shows intra-arterial BP recording of patient #8 demonstrating a sustained rise in both systolic and diastolic BP when stimulation was turned on at 10 Hz, 120 μs, 4.0V. Top right shows the finger arterial pressure measurements (Finapres) at similar parameters (10 Hz, 120 μs, 3.0 V) in the same patient in the laboratory. Raw Finapres data from patient #6 is also shown (bottom three graphs). In this patient, BP dropped when the ventral periventricular grey was stimulated at 10 Hz, 3.0 V and 120 μs pulse width. The traces were recorded on three separate occasions over 2 days. BP, blood pressure.

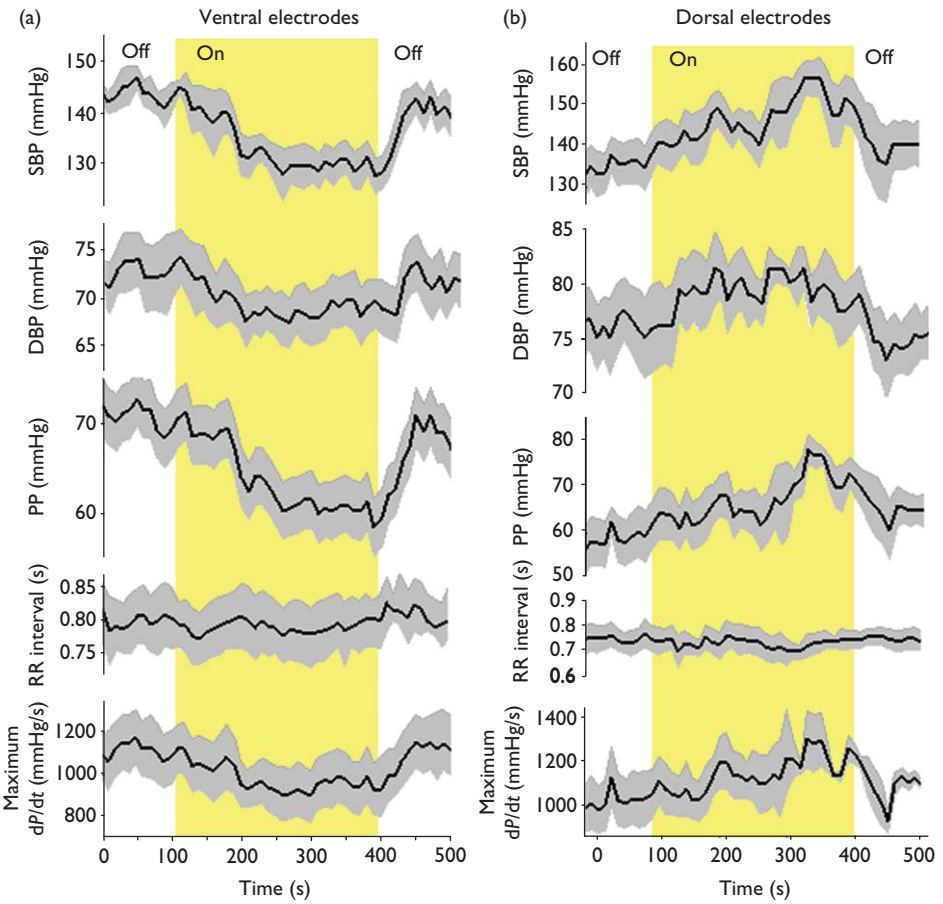

Fig. 3 (a) Mean changes in SBP, DBP, PP, RR interval and maximum d*P*/d*t* for the seven patients who had a reduction in blood pressure during stimulation (yellow area) of ventral PVG. Stimulation was started at 100 s and stopped at 400 s. The grey area denotes ± one standard error of the mean. (b) The same mean changes for the six patients with an increase in SBP on stimulation of dorsal PVG. SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; PVG, periventricular grey.

included those with no discernable change, in whom we also took six sessions.

Signal processing was performed in Matlab (version 6.1, MathWorks Inc., Natick, Massachusetts, USA) and statistical analysis was performed in SPSS (version 11, SPSS Inc., Chicago, Illinois, USA).

Results

Of 15 patients with PVG/PAG electrodes (two bilateral), five had episodes of significant decreases in BP (five electrodes), four had significantly increased BP (four electrodes) and two had episodes of both (two electrodes). Stimulation of the four remaining PVG patients (six electrodes) and six control electrodes caused no significant changes.

Intra-arterial and non-invasive blood pressure recordings

To verify the non-invasive ABP measurements, we showed under general anaesthesia in one patient that stimulation of the dorsal PVG caused an increase of 30 mmHg in ABP when measured via an arterial line while the postoperative non-invasive recordings showed an increase of 43 mmHg (Fig. 2, top).

Repeatability of response of BP to stimulation was demonstrated by the consistency of responses on three occasions in each patient (Fig. 2, bottom, shows an example). Although the magnitude of the decrease varied, the direction of the response and the approximate time course did not.

Reduction of arterial blood pressure with stimulation of ventral periventricular grey

Figure 3a shows the composite data from all seven patients in whom systolic blood pressure (SBP) dropped significantly after the onset of stimulation, without significant changes in pain severity (#1–7, lower two contacts only in #1 and #6). It is striking that the contacts that reduced BP were the most ventral electrodes (the contacts in blue, Fig. 1). Thus, it appears that stimulation of the ventral PVG/PAG is required to reduce BP. Considerable variation occurs in the lateral location of electrode placement but there is no relation to decreased BP.

The average reduction in SBP was 14.2 ± 3.6 mmHg (range 7–25 mmHg), or 13.9%, after a 300-s stimulation. The mean latency (i.e. the time from initiation of stimulation to the maximum fall in SBP) was 160 ± 29 s (range 34–214 s). When stimulation was turned off, the latency was much shorter (48 ± 23 s).

The drop in SBP is accompanied by a fall in diastolic blood pressure (DBP) of 4.9 ± 2.9 mmHg (range 1.5–9.3), or 6%. As the SBP drops more than the DBP, there is a mean decrease of 9.3 ± 3.16 mmHg in pulse pressure. The change of SBP with time (maximum dP/dt, i.e. the slope of the BP curve) reduced by 222 ± 126 mmHg/s (19.8%). This implies that the contractility of the myocardium was reduced. On the other hand, RR interval (time between each R wave on the electrocardiogram) did not change throughout the stimulation period; that is, there was no change in heart rate (mean change$=0.01 \pm 0.04$ s, range 0–0.08 s).

Increase in arterial blood pressure with stimulation of dorsal periventricular grey

Six patients (#8–11 and the upper two contacts in patients #1 and #6) had episodes of a sustained increase in BP shortly after the onset of stimulation (Fig. 3b). One of these patients (#10) was hypertensive. Two patients (#1, #6) also had episodes of decreased BP when the lower contacts were stimulated – see above). Analysis of the image data (Fig. 1) showed that the electrodes in this group were placed dorsally.

The mean rise in SBP was 16.73 ± 5.9 mmHg (range 16–31 mmHg), or 16.4% after 300 s stimulation (however, the maximum rise of 22.23 mmHg occurred just before this). The mean latency was 230 ± 44 s (range 48–289 s). As with BP reduction, increases were accompanied by a smaller rise in DBP of 4.9 ± 2.8 mmHg or 6.4% (range 2.4–12.1 mmHg). An increase in mean pulse pressure of 11.83 ± 5.4 mmHg or 14.5% was also observed and, again, the maximum rise of 17.33 mmHg occurred just before 300 s. Maximum dP/dt increased by 212 ± 97 mmHg/s. As with reduction in BP, there was no change in RR interval and therefore no change in heart rate. Thus, it appears that increasing BP is accompanied by a mirror of the changes that occur during reduction in BP.

Statistical comparison between ventral and dorsal areas

The responses of BP to stimulation were further analysed for the two groups of ventral ($n=8$) and dorsal ($n=9$) areas from all patients. Significant decrease and increase in BP, pulse pressure and dP/dt were found for the ventral and dorsal groups, respectively ($P<0.05$, ANOVA). No significant difference of RR interval was found over time and between the two groups ($P=0.13$, ANOVA).

Controls and electrodes that had no effect

Six control patients were investigated (six thalamic electrodes, one spinal cord stimulator). BP did not change significantly in any of these patients. In addition, four patients with PVG electrodes (six electrodes) had no effect. Four of the five electrodes plotted (one had no postoperative scan) were dorsal to the group that raised BP and were therefore probably outside the PVG/PAG.

Discussion

We have shown for the first time in awake humans that electrical stimulation of the PVG/PAG can influence ABP in a predictable way. Ventral stimulation at 10 Hz can have a consistent depressor response, whereas dorsal stimulation can have a pressor response. In addition to changes in SBP, we found analogous changes in DBP, pulse pressure and maximum dP/dt, but no change in RR interval and therefore in heart rate. This suggests that the changes are elicited by a mixture of altered myocardial contractility (change in dP/dt) and a change in total peripheral resistance (changes in pulse pressure). In turn, this implies that the changes are due to altered sympathetic activity, with little or no change in parasympathetic activity.

As early as 1935, Kabat *et al.* [10] showed that PAG stimulation influenced BP in the cat. It later emerged that the PAG is organized into four longitudinal columns [1]. The cardiovascular changes are but one component of an integrated response involved in the 'defence' reaction. For example, activation of the dorsomedial and dorsolateral columns evokes active 'fight or flight' responses such as hypertension and tachycardia [11–13], and non-opioid-mediated analgesia [14] whereas stimulation of the lateral and ventrolateral columns produces passive coping

responses such as hypotension and bradycardia [15,16], opioid-mediated analgesia [17] and freezing behaviour [18]. These responses are associated with emotional changes such as fear [19]. In this study, two patients experienced feelings of nausea and sweating, associated with dorsal PVG/PAG stimulation. This was associated with anxiety in both cases and with an increase in BP. These findings are similar to those of Nashold *et al.* [19] and Young and Rinaldi [20] who found that dorsal PVG stimulation evoked feelings of doom, fear, anxiety and agitation. Pain ratings remained unaffected by stimulation but this is probably because we were using a single frequency (10 Hz) and pain relief with DBS responds to different frequencies in different patients.

Anatomical substrates for efferent PAG pathways involved in cardiovascular control include descending serotonergic and adrenergic sympathetic pathways to the rostroventromedial medulla (raphe magnus, gigantocellular nucleus) [2,4], the rostroventrolateral medulla, locus coeruleus [21] and pontobulbar reticular formation [22], among others. PAG neurons also project to cardiac vagal preganglionic neurons in the nucleus ambiguus, dorsal motor vagal nucleus and the nucleus of the tractus solitarius [21]. Also, cardiovascular reactions of the PAG can be altered by attenuation of these areas [23].

Important differences between our findings and those in animals include much longer latency between stimulus and peak response [10,24]. One possible reason is that we have activated a hormonal mechanism such as that shown by Bamshad and Albers [25] in which PAG stimulation caused a release in arginine vasopressin via a rostral projection to the hypothalamus. A second difference is that we found no significant change in RR interval with stimulation. This may be indicative of the higher vagal tone in humans.

Conclusion

In summary, we have shown that electrical stimulation of different regions of the human PVG/PAG can selectively modulate BP, almost certainly via a sympathetic effect. In the future, perhaps hypertension or indeed postural hypotension may be controlled by manipulation of this area.

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