Editorial

Forebrain lateralization and the cardiovascular correlates of epilepsy

Two papers in this issue of *Brain* remind us that autonomic dysregulation and cardiac arrhythmias are not uncommon correlates of seizures (Druschky *et al*., 2001; Tinuper *et al*., 2001). These phenomena are important as mechanistic pointers towards the cause of sudden unexpected death in epilepsy (SUDEP). This condition has a frequency of ~0.5% and is independent of the type and severity of the convulsion (Leestma *et al*., 1984). In a reported case of a patient who died unexpectedly whilst undergoing cardiac monitoring, a non-resuscitable malignant ventricular arrhythmia occurred, indicating the likely arrhythmogenic cause of SUDEP (Dasheiff and Dickinson, 1986). To what extent medication may be involved is unclear: many SUDEP patients have infrequent seizures and subclinical anticonvulsant levels. It has been suggested, therefore, that seizures originating from or spreading to forebrain areas of cardiovascular regulation (such as the insular cortex) desynchronize sympathovagal cardiac neural firing, which affects a heart destabilized by declining levels of anticonvulsant medication with potentially lethal consequences.

Druschky and colleagues, using [123I]metaiodobenzylguanidine single photon emission computed tomography (MIBG SPECT) and heart rate variability analysis, indicate a reduction in cardiac sympathetic innervation in patients with chronic temporal lobe epilepsy (Druschky *et al*., 2001). Whether this represents true denervation (secondary to transynaptic degeneration of forebrain cardiovascular pathways) or a functional effect (secondary to sympathetic upregulation decreasing vesicular accumulation of MIBG) is unknown. Although possibly independent of carbamazepine treatment, the contribution of other medications towards these observations cannot be discounted. There was, however, some disagreement in their heart rate variability data: frequency domain analysis showed no abnormalities and time domain analysis indicated parasympathetic predominance. Consequently, Druschky *et al*. recommend carbamazepine for treatment of partial seizures on the basis of its reported parasympatholytic effects.

Tinuper and colleagues, on the other hand, report on ictal bradycardia, and outline the frequency of this arrhythmia in patients with partial seizures originating from frontotemporal regions (Tinuper *et al*., 2001). An association with left-sided origin was indicated. Carbamazepine, they suggest, possibly might be deleterious because of reported association with QTc prolongation, heart block and asystole.

The true incidence of ictal bradyarrhythmias is unclear. In a systematic report of temporal lobe epilepsy patients undergoing simultaneous EEG and ECG monitoring, sinus tachycardia was the most common finding, occurring in 92% of recordings (Blumhardt *et al*., 1986). Bradycardia was seen in only one patient (4%). Cardiac arrhythmias, taking the form of relapsing–remitting interval variations, occurred in 42% of patients. Ventricular ectopy was identified in 12%. Whether these arrhythmias are primary or secondary to other phenomena, including respiratory changes, is unknown. Contrasting with Tinuper *et al*.’s study, respiration was not recorded. Differences in respiration, definition of bradycardia, blood pressure and demographics might account for disparities in bradycardia frequency between these studies.

Nonetheless, mechanisms have been identified that could illuminate this controversy. ECG-triggered phasic microstimulation of the rat rostral posterior left insular cortex results in bradyarrhythmia, complete heart block and asystolic death (Oppenheimer *et al*., 1991). These parasympathetic arrhythmias were accompanied by increased sympathetic tone and myocytolysis, a form of cardiac damage of sympathetic neural origin. This dual activation, and the differential sensitivity of methods used to detect cardiac vagal and sympathetic tone, might account for the contradictory findings of Druschky *et al*.

There are other lateralization effects. In the human, rat and monkey, considerable evidence implicates the left insular cortex in regulating the vagal cardiac parasympathetic neuronal pool, and the right insular cortex in regulating sympathetic neurones regulating vascular resistance. In the human, stimulation of the right anterior insular cortex elevates diastolic blood pressure and heart rate; stimulation of the left anterior insula decreases heart rate (Oppenheimer *et al*., 1992). Left anterior insular ablation by stroke is associated with significant tachyarrhythmias in some patients, and in the rat with reduction in baroreflex sensitivity (and hence parasympathetic tone) (Oppenheimer *et al*., 1996; Zhang *et al*., 1998). Deactivation of the rat right anterior insula is associated with increased heart rate and blood pressure (Zhang *et al*., 1998). Evidence exists for both inhibitory and excitatory pathways from the insula to segregated neuronal
pools in the lateral hypothalamic area with differential projection pathways, which may explain these phenomena (Oppenheimer and Zhang, 1999). In the anaesthetized rat, inhibition prevails and removal of insulofugal fibres from the right insular cortex upregulates cardiovascular sympathetic control. In the awake, behaving animal, the balance between these pathways is more complex. Activation of the right insular cortex in these circumstances might then upregulate cardiovascular sympathetic effects as noted during human insular stimulation. Such a circumstance may also occur during the non-iatrogenic effects of right insular activation by seizure discharge.

The clinical expression of activation of forebrain structures involved in cardiovascular regulation is likely, therefore, to be complex. The seemingly contradictory findings related to cardiovascular sympathovagal balance in Druschky et al.’s study might depend on the distribution and spread of seizures, with confounding effects of medication and the chronic effects of lateralization and differential activation of descending inhibitory and excitatory pathways on postganglionic cardiac neurone synaptic plasticity and activity.

Post-ictal neuronal hyperpolarization resulting in inhibition may also be important in the generation of cardiac arrhythmias, by contributing a relative imbalance between the two cortices, thereby disrupting the normal smooth regulation of cardiac sympathovagal balance. In this regard, non-myelinated transcallosal interhemispheric pathways (both inhibitory and excitatory) have recently been described linking the cardiovascular regions of the two insulae (Zhang and Oppenheimer, 2000). While these pathways might contribute to interhemispheric cardiovascular integration, they may also afford a means of rapid spread of ictal discharge between cardiovascular sites, each with different effects on the heart and vasculature.

On balance, the prevailing data do point to the left hemisphere (and so far, primarily the insula) in the generation of parasympathetic cardiac effects (chronotropic, dromotropic, inotropic), and the right hemisphere in the regulation of cardiac function (inotropic, chronotropic) and in the control of vascular resistance and blood pressure. In practical terms, clinicians should therefore be vigilant about the cause of cardiac arrhythmias, especially in the absence of overt cardiac abnormalities and, in these cases, investigations pointed at a possible cerebral and/or ictal source might be warranted. In addition, physicians concerned for the welfare of their seizure patients might be particularly interested in seizures involving either insular cortex. These patients might benefit from combined ECG/EEG monitoring to assess their potential for cardiac arrhythmias and SUDEP.

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References