Abnormal cortical and spinal inhibition in paroxysmal kinesigenic dyskinesia

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SUMMARY
Paroxysmal kinesigenic dyskinesia (PKD) is characterized by brief episodes of choreic/dystonic movements precipitated by sudden movement. The condition responds to antiepileptic medication, particularly carbemazepine. Autosomal dominant inheritance is often seen, and a locus in the pericentromeric region of chromosome 16 has been identified in some families. Little is known of the pathophysiology of PKD, although an ion channel abnormality is thought likely. We assessed a number of electrophysiological parameters in 11 patients with idiopathic PKD, a proportion of them on and off treatment. We identified reduced short intracortical inhibition (SICI), reduced early phase of transcallosal inhibition, and a reduced first phase of spinal reciprocal inhibition (RI) in subjects with PKD. The cortical silent period, the startle response and the second and third phases of RI were normal. Treatment with carbamazepine normalized the abnormalities in transcallosal inhibition, but had no effect on other parameters. Patients with PKD show a discrete set of abnormalities in cortical and spinal inhibitory circuits that differ from those seen in primary dystonia and epilepsy, and which may provide clues to the underlying pathophysiology of the disorder.

KEYWORDS: PKD; pathophysiology; transcranial magnetic stimulation

ABBREVIATIONS: EDC = extensor digitorum communis; EMG = electromyography; FCR = flexor carpi radialis; FDI = first dorsal interosseous; ICF = intracortical facilitation; ISI = interstimulus interval; MEP = motor evoked potential; PKD = paroxysmal kinesigenic dyskinesia; RI = reciprocal inhibition; SICI = short intracortical inhibition; SP = cortical silent period; SR = startle reflex; TI = transcallosal inhibition; TMS = transcranial magnetic stimulation


INTRODUCTION
Paroxysmal dyskinesias are a rare group of hyperkinetic movement disorders that recur in an episodic fashion (Bhatia, 2001). When sudden movements provoke the attacks, the term paroxysmal kinesigenic dyskinesia (PKD) has been used (Demirkiran and Jankovic, 1995). The typical clinical picture in such cases is of brief (seconds to minutes) attacks of chorea/dystonia affecting a limb, precipitated by sudden movement (Houser et al., 1999). In most patients, one limb or side of the body is more frequently affected than the other, and attacks are typically unilateral, although generalized attacks are occasionally seen. The condition is usually exquisitely responsive to small doses of carbamazepine (Houser et al., 1999).

PKD is often familial with an autosomal dominant inheritance. In some families with autosomal dominant PKD, a locus has been mapped to the pericentromeric region of chromosome 16, 16p11.2–q12.1 (Tomita et al., 1999; Bennett et al., 2000). Interestingly, loci for other paroxysmal neurological disorders have been mapped to the same pericentromeric region including autosomal dominant infantile convulsions and choreathetosis (ICCA syndrome) in six families (Swoboda et al., 2001), and Rolandic epilepsy, writer’s cramp and paroxysmal exercise-induced dyskinesias in one family (Guerrini et al., 1999). Whether these families represent variable expression of the same underlying genetic
disorder is unknown. A separate, non-pericentromeric, locus on chromosome 16 has been reported in a family with PKD and epilepsy: 16q13–q22.1 (Valente et al., 2000), while some PKD families do not link to chromosome 16 at all, suggesting further genetic heterogeneity (Spacey et al., 2002).

The pathophysiology of PKD is unclear at the present time. Ion channel abnormalities have been identified in other paroxysmal movement disorders including episodic ataxia type 1 (KCNA1) and type 2 (CANCA1) (Browne et al., 1994; Litt et al., 1994; Vahedi et al., 1995), and in paroxysmal neurological disorders without associated movement disorder including familial hemiplegic migraine (Joutel et al., 1994; Ophoff et al., 1994, 1996) and some forms of familial epilepsy (Charlier et al., 1998; Singh et al., 1998; Wallace et al., 1998). Thus it is hypothesized that PKD is also an ion channel disorder. It has been suggested that the primary pathophysiological process is of (ion channel-mediated) epilepsy perhaps at a subcortical level, given the paroxysmal character of attacks, the possible presence of prodromic aura-like symptoms, the short duration of the attacks and their response to antiepileptic drugs (Hudgins and Corbin, 1966; Stevens, 1966). In support of this hypothesis are several reports of families in which some individuals presented with either or both PKD and epilepsy, with different age-related expression (Guerrini et al., 1999; Singh et al., 1999). On the other hand, the occurrence of dystonia in 70–80% of PKD episodes might indicate a pathophysiological process similar to primary dystonia, where deficits in cortical, brainstem and spinal inhibitory circuits, due to disordered basal ganglia modulation of cortical motor output, have been detected. Evidence to support the role of the basal ganglia in the pathophysiology of PKD is the observation of secondary PKD in association with focal basal ganglia lesions (Blakeley and Jankovic, 2002). It is possible, given the co-occurrence of epilepsy and PKD, that a common, genetically determined, pathophysiological abnormality is variably expressed in the cerebral cortex and in basal ganglia (Guerrini et al., 2002).

Few studies to date have investigated the pathophysiology of paroxysmal dyskinesias. Franssen et al. (1983) investigated the contingent negative variation (CNV) in one patient with PKD. The slow negative wave component of the CNV was more pronounced when compared with control subjects (the opposite to the pattern observed in primary dystonia), but this was normalized after phenytoin treatment. Lee et al. (1999) studied forearm reciprocal inhibition in 10 patients with PKD and found a paradoxical facilitation of H reflex size in the first phase of reciprocal inhibition (a pattern not routinely observed in primary dystonia). Later phases of reciprocal inhibition were not studied.

Invasive long-term electrode monitoring of a patient with secondary PKD was reported to show consistent ictal discharge recorded from the ipsilateral caudate nucleus with a concomitant discharge recorded from the supplementary sensory motor cortex, without significant spread to other areas (Lombroso, 1995). Invasive monitoring has also been performed in a child with severe, paroxysmal non-kinesigenic dyskinesia (PNKD) which recorded an ictal discharge from the caudate nuclei with no cortical correlate (Lombroso and Fischman, 1999), [18F]DOPA and [11C]raclopride PET scans in the same patient revealed a marked reduction in the density of presynaptic dopa decarboxylase activity in the striatum, together with an increased density of postsynaptic dopamine D2 receptors (Lombroso and Fischman, 1999).

The aim of the present study was to investigate the physiopathology of PKD using electrophysiological techniques, and in addition to study the effect of medication on these parameters. We assessed intracortical inhibition and facilitation, silent period (SP), transcallosal inhibition (TI), startle reflex (SR) and spinal reciprocal inhibition (RI) in 11 PKD patients, a proportion of them both on and off treatment, and compared them with age-matched control subjects.

Methods

Subjects

We recruited 11 patients (nine men, two women) with idiopathic PKD, 10 from the movement disorder clinics at the National Hospital for Neurology and Neurosurgery, UK and one from the Department of Neurological Sciences, University of Rome La Sapienza, Italy. Seven patients were studied both on and off treatment. Two patients were studied on treatment only, and the remaining two patients were studied off treatment only. Clinical details of these patients are given in Table 1. All 11 patients invariably had dystonia as the main feature of their PKD attacks. Exclusion criteria for the study were evidence of secondary causes for PKD, other serious neurological or medical disease and features precluding the use of transcranial magnetic stimulation (TMS) (e.g. implanted electromagnetic devices). Thirteen healthy controls (nine men, four women) were recruited from a departmental register of volunteers. The average age of those in the PKD group was 27 years (SD 8) and in the control group was 33 years (SD 8). The study was approved by the Joint Research Ethics Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology, and the ethics committee of the University of Rome La Sapienza. Subjects gave their written informed consent to participate.

Study design

Assessments of short intracortical inhibition (SICI) and intracortical facilitation (ICF), cortical SP, TI, RI and SR were attempted in all subjects. One subject found the TMS studies uncomfortable, and therefore SICI/ICF, SP and TI were not possible in this individual. SICI/ICF were not able to be assessed in a further patient due to high motor thresholds. RI was not able to be assessed in one patient as he had no H reflex.

Intracortical inhibition and facilitation

This technique measures the influence of a subthreshold conditioning pulse given over the hand motor area on a subsequent suprathreshold ‘test’ pulse given over the same area. Experiments in normal subjects have shown that at short interstimulus intervals (ISIs 0–4 ms), there is a reduction in the size of the motor evoked potential (MEP) elicited from the contralateral first dorsal interosseous (FDI) (Kujirai et al., 1993). This is known as SICI. At ISIs of between 7 and 15 ms, there
Table 1 Clinical characteristics of the PKD patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Age of onset (years)</th>
<th>Family history</th>
<th>Type of dyskinesia</th>
<th>Treatment, dose per day</th>
<th>Response</th>
<th>Drug state studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>27</td>
<td>10</td>
<td>No</td>
<td>D</td>
<td>Carbamazepine in the past</td>
<td>Complete</td>
<td>Off</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>41</td>
<td>9</td>
<td>No</td>
<td>D, C</td>
<td>Carbamazepine, 800 mg; diazepam 13 mg</td>
<td>Complete</td>
<td>On</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>36</td>
<td>14</td>
<td>No</td>
<td>D</td>
<td>Carbamazepine, 200 mg</td>
<td>Complete</td>
<td>On/off</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>18</td>
<td>12</td>
<td>No</td>
<td>D</td>
<td>Carbamazepine, 200 mg</td>
<td>Complete</td>
<td>On/off</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>26</td>
<td>16</td>
<td>NK</td>
<td>D</td>
<td>Carbamazepine in the past</td>
<td>Complete</td>
<td>Off</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>38</td>
<td>6</td>
<td>No</td>
<td>D</td>
<td>Phenytoin, 150 mg</td>
<td>Complete</td>
<td>On</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>22</td>
<td>13</td>
<td>NK</td>
<td>D</td>
<td>Carbamazepine, 200 mg</td>
<td>Complete</td>
<td>On/off</td>
</tr>
<tr>
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<td>M</td>
<td>18</td>
<td>15</td>
<td>No</td>
<td>D</td>
<td>Carbamazepine, 600 mg</td>
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<td>On/off</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>19</td>
<td>NK</td>
<td>No</td>
<td>D</td>
<td>Carbamazepine, 100 mg</td>
<td>Complete</td>
<td>On/off</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>27</td>
<td>14</td>
<td>Yes</td>
<td>D</td>
<td>Carbamazepine, 200 mg</td>
<td>Complete</td>
<td>On/off</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>22</td>
<td>21</td>
<td>No</td>
<td>D</td>
<td>Phenytoin, 200 mg</td>
<td>Complete</td>
<td>On/off</td>
</tr>
</tbody>
</table>

D = dystonia; CD = chorea; NK = not known.

Silent period (SP)

The SP is a period of EMG silence that occurs in a voluntarily contracted muscle following a suprathreshold magnetic stimulation given over the contralateral representative motor area. For this experiment, EMGs were recorded as described above. A single magnetic stimulation unit (Magstim Company, Whithland, Dyfed, UK) was used to deliver the magnetic pulse through a standard figure-of-eight coil. Motor thresholds were obtained as described above. Subjects were asked to squeeze a 2.5 cm block between their thumb and index finger. Visual feedback on the intensity of muscle contraction was provided to the subjects, and they were instructed to maintain a constant muscle contraction at ~20% of maximum. Magnetic stimulation was applied over the contralateral hand motor area at the same intensity used for test stimuli in the SICI/ICF experiment. Fifteen stimuli were recorded for each subject. The SP was calculated by measuring the time from the end of the MEP to the reappearance of continuous EMG activity in excess of 20 μV. Those trials where voluntary muscle activation exceeded or was less than 20% of maximum were rejected on-line, and the stimulus was given again.

Reciprocal inhibition (RI)

RI assesses the interaction between stimulation of the radial nerve supplying the extensor muscles of the forearm and the H reflex.
produced by stimulation of the median nerve. At particular ISIs, a reduction in the size of the H reflex occurs in normal subjects (Day et al., 1984). Electrical median and radial nerve stimulation was performed through surface electrodes. Electric pulses were supplied by two constant current generators (Digitimer, Welwyn Garden City, UK). One electrical stimulator was used to stimulate the median nerve in the antecubital fossa. Stimulation duration was 500 μs, and the intensity used was that which produced the maximum size of the H reflex with minimum M response. The second electrical stimulator was used to stimulate the radial nerve above the elbow. The duration of the stimulus was 500 μs, and the intensity used was that which produced an EMG response of ~50 mV from extensor digitorum communis (EDC). The study was performed in the upper limb of the side more frequently affected by the attacks in PKD patients, and in the dominant limb for control subjects. EMG recordings were collected through surface electrodes from flexor carpi radialis (FCR) and EDC. The EMG signal was amplified (Digitimer D360), bandpassed (3 Hz to 1 kHz), and analysed off-line on a personal computer using NUCUSOR. We recorded H reflex size during stimulation of the median nerve alone, and for ISIs of −1, 0, 3, 5, 10, 20, 30, 50, 70, 100, 300, 500 and 750 ms. Stimuli were given in a random order with a total of 10 trials per stimulus condition. The amplitude of the H reflex was measured peak to peak. Any trials where EMG movement artefact occurred were rejected on-line, and were repeated.

**Startle response (SR)**

A loud sound obtained by discharging the magnetic coil of a magnetic stimulator over a metallic platform (111 dB measured at a distance of 1 m from the source) was used to induce the SR. We obtained a minimum of eight trials in each subject. Subjects were seated comfortably in an armchair and were instructed to keep their eyes open. EMG recordings were collected bilaterally through surface Ag–AgCl electrodes from orbicularis oculi, sternocleidomastoïd, biceps, FCR, EDC, FDI, tibialis anterior and gastrocnemius. The EMG signal was amplified (Digitimer D360), bandpass filtered (3 Hz to 1 kHz), and analysed off-line on a personal computer using dedicated software (Spike2, Cambridge Electronic Design Ltd, Cambridge, UK). The startle measures examined were: (i) onset latency, i.e. the time interval between onset of acoustic stimulus and the onset of the EMG response recorded at the orbicularis oculi muscle; (ii) degree of spread, i.e. the number of muscles in each trial in which there was a discernible startle EMG response; and (iii) rate of habituation, i.e. number of muscles activated in each of the eight trials.

**Statistical analysis**

Repeated measures analysis of variance (ANOVA) was used to analyse group factors. When necessary, t tests were used to compare individual effects. For each parameter tested, we first assessed whether there was any significant difference between the seven subjects who were studied both on and off medication. If there was no difference, then an average of the data for each subject on and off medication was taken, and combined with the data from those subjects studied only on or only off medication. If a statistically significant difference was found in data of the seven patients who were studied both on and off medication, then the data of those seven patients when off medication were combined with that of the two patients who were studied off medication only, while the data of those seven subjects when on medication were combined with that of the two patients studied on medication only. Statistical analysis was performed using SPSS for Windows 10.0. The pre-set level for statistical significance was P < 0.05.

**Results**

**Intracortical inhibition and facilitation**

SICI/ICF was compared in nine PKD patients, six of them both on and off treatment, two off treatment only, one on treatment only, and in 13 control subjects. The complete time course at all ISIs is shown in Fig. 1A, with grouped data [inhibitory (2–4 ms), intermediate (5–6 ms) and facilitatory (7–15 ms) ISIs] in Fig. 1B. Repeated measures...
ANOVA was performed with drug (on and off) and ISI (2, 3, 4, 5, 6, 7, 10 and 15 ms) as main factors, showing no significant interaction between drug and ISI \( F(7,35) = 0.26, \text{NS} \). Therefore, the data for subjects on and off treatment were combined (Fig. 1C) and compared with controls using repeated measures ANOVA, with group (PKD and controls) and ISI (inhibitory, intermediate and facilitatory) as main factors. As expected, ANOVA showed a highly significant effect of ISI \( F(7,147) = 31.15, P < 0.001 \), but there was also a significant interaction between group and ISI \( F(7,147) = 2.07, P < 0.05 \). Post hoc analysis showed that there was significantly less inhibition in PKD subjects compared with controls in the inhibitory interval \( F(1,20) = 5.23, P < 0.05 \). No significant differences were found between controls and PKD subjects at the intermediate or facilitatory intervals.

**Transcallosal inhibition**

TI was compared in 10 PKD patients, six of them both on and off treatment, two on treatment only, two off treatment only, and in 10 control subjects. The complete time course at all ISIs is shown in Fig. 2A, with grouped data (ISI 7 and 10 ms, ISI 45 and 75 ms) in Fig. 2B. Repeated measures ANOVA was performed with drug (on and off) and phase (early and late) as main factors, showing a significant difference regarding drug \( F(1,5) = 7.91, P < 0.05 \). There was also a significant interaction between patient (PKC and control) and ISI when the medication was on \( F(4,38, P < 0.05) \) or off \( F(5.65, P < 0.01) \). We compared the two phases separately with a \( t \) test. The early phase of TI showed a significant difference between PKD patients on and off using a paired \( t \) test \( t = -3.43, P < 0.05 \) and between off and control \( t = 2.17, P < 0.05 \) using an independent \( t \) test. In contrast, when patients were on medication, there was no difference found between patients and controls in any phase of TI.

**Silent period**

SP was assessed in 10 PKD patients, six of them both on and off treatment, two on treatment only, two off treatment only, and in 13 control subjects. The durations of the SP for all subjects are shown in Fig. 3. ANOVA was performed with drug (on and off) and length of the SP as main factors, showing no significant interaction between drug and length of the SP \( t = 0.99, \text{NS} \). Therefore, the data for PKD subjects on and off treatment were combined and averaged, and were compared with control subjects using independent sample \( t \) tests. This showed no significant difference between the durations of SP in controls and PKD subjects.

**Reciprocal inhibition**

RI was assessed in 10 PKD patients, six of them both on and off treatment, two on treatment only, two off treatment only, and in 13 control subjects. The complete time course of RI at all ISIs is shown in Fig. 4A, with grouped data (first phase, ISI 0 ms; second phase, ISI 10 and 20 ms; third phase, ISI 70–500 ms) in Fig. 4B. A two-way ANOVA with drug (on/off) and phase of RI revealed no significant difference between patients with and without medication. Therefore, the data for PKD subjects both on and off treatment were merged and compared with controls using repeated measures ANOVA, with group (PKD and controls) and phase as main factors.

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**Fig. 2** Transcallosal inhibition for PKD patients and control subjects. (A) The size of MEP as a percentage of the unconditioned size at all ISIs. (B) The mean size of MEP as a percentage of the unconditioned size at ISI 7 and 10 ms, ISI 40 ms and ISI 75 ms.

**Fig. 3** SP duration for PKD patients on and off medication, and control subjects.
A significant interaction between group and ISI was found \[ F(2,40) = 4.07, P < 0.05 \]. Post hoc analysis on grouped data showed that there was significantly less inhibition in PKD subjects compared with controls in the first inhibitory phase \( t = –2.58, P < 0.05 \). No significant differences were found between controls and PKD subjects in the second \( t = –0.38 \) and third inhibitory phases \( t = 0.12 \).

**Startle response**

SR was assessed in 10 PKD patients, six of them both on and off treatment, two on treatment only, two off treatment only, and in 11 control subjects. Table 2 shows the onset latency, degree of spread and rate of habituation following the startle stimulus for all subjects. No significant differences were found in any of these parameters between PKD patients on or off treatment or between PKD patients and control subjects.

**Discussion**

We have shown for the first time that PKD patients have a discrete pattern of abnormalities in cortical and spinal inhibitory pathways with abnormal SICI, early phase of TI and first phase of RI, but a normal SP, SR and later phases of RI.

**Cortical inhibition in PKD**

SICI is thought to be mediated by GABA-A, circuits and has been found to be abnormal in patients with various movement disorders, including primary dystonia (Berardelli et al., 1998), and also in some patients with epilepsy (Werhahn et al., 2000). Although our patients with PKD were symptom free when studied, it is not unexpected that abnormalities in SICI could be still detected, as this is similar to what has been noted for example in non-manifesting carriers of mutation of the \textit{DYT1} gene (Edwards et al., 2003) and also interictally in patients with epilepsy (Cantello et al., 2000). What is a more surprising finding in PKD patients is that SP was normal, despite the abnormality in SICI. Although SP is thought to be mediated by a mechanism (GABA-B) different from SICI, abnormalities in both pathways typically occur together in patients with movement disorders, in particular those with primary dystonia (Berardelli et al., 1998). A different, and more variable, pattern of abnormalities in SICI and SP has

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**Table 2** (A) Mean latencies in ms (SD) to startle onset in sampled muscles in PKD patients and normal subjects; (B) mean (SD) number of muscles activated in each of the eight trials

<table>
<thead>
<tr>
<th>(A) Muscles</th>
<th>On</th>
<th>Off</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orbicularis oculi</td>
<td>51.0 (7.8)</td>
<td>49.8 (6.0)</td>
<td>49.2 (3.4)</td>
</tr>
<tr>
<td>Sternocleidomastoid</td>
<td>80.2 (9.2)</td>
<td>75.3 (10.8)</td>
<td>90.4 (28.4)</td>
</tr>
<tr>
<td>Biceps brachii</td>
<td>102.7 (26.4)</td>
<td>116.9 (38.2)</td>
<td>111.8 (36.9)</td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>122.7 (28.0)</td>
<td>106.9 (25.1)</td>
<td>123.0 (38.7)</td>
</tr>
<tr>
<td>Extensor digitorum communis</td>
<td>94.5</td>
<td>123.0</td>
<td>140.8 (62.4)</td>
</tr>
<tr>
<td>First dorsal interosseous</td>
<td>114.9</td>
<td>103.6 (2.3)</td>
<td>113.0</td>
</tr>
<tr>
<td>Tibialis anterior</td>
<td>131.6 (17.5)</td>
<td>168.1 (18.7)</td>
<td>173.4 (8.2)</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>178.3</td>
<td>173.4</td>
<td>173.4 (8.2)</td>
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<table>
<thead>
<tr>
<th>(B) Trials</th>
<th>1</th>
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<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<td></td>
<td>2.1 (1.9)</td>
<td>2.6 (2.7)</td>
<td>2.5 (2.2)</td>
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*Where no SD is given, only one patient had muscle activation.*
been reported for patients with different forms of epilepsy (Delvaux et al., 2001; Macdonell et al., 2001) and, even where there is a reduction in SICI, a shortening of SP is rarely seen. Thus, with respect to SICI and SP, patients with PKD appear to show a different pattern of abnormalities from those with primary dystonia and other movement disorders, and resemble the pattern observed in some, but by no means all, patients with epilepsy.

We were particularly interested in the integrity of TI given the clinical observation of occasional generalization of PKD attacks following the usual unilateral onset. The physiology of the circuit probed by paired pulse TI is uncertain at the present time. In vivo animal studies have demonstrated a reduction in TI using a paired pulse paradigm following the administration of GABA-B, but not GABA-A antagonists (Chowdhury et al., 1995, 1996; Chowdhury and Matsunami, 2002). In these experiments, inhibition was assessed at an ISI of 200 ms only. Our results in patients with PKD suggest that ‘early’ TI (at ISIs of 7 and 10 ms) can be affected independently of ‘late’ TI (at ISIs of 45 and 70 ms). A difference in mechanism between these two phases has also been noted by others (Chen et al., 2003; Gilio et al., 2003). The abnormality we detected in early TI may predispose patients with PKD to occasional generalization of attacks. Given the abnormalities observed in SICI and SP in these patients, and given the data from animal studies, it is tempting to speculate that early TI may be mediated by GABA-A mechanisms (which are impaired in PKD) and that the late phase is mediated by GABA-B (which is intact in PKD). This abnormality in the early phase of TI was the only parameter measured in which patients were different depending on whether they were on or off medication with carbamazepine. The abnormality in early TI resolved with medication, although, given the uncertainty that surrounds the mechanism of TI at the present time, it is difficult to speculate further on the nature of this effect.

In our studies of cortical inhibition, we chose to assess inhibition in the dominant hemisphere in all control subjects and in the hemisphere contralateral to the side where most attacks occurred in the PKD patients. In fact, this led to the assessment of the dominant hemisphere in eight out of 11 of the PKD patients. There is some evidence for an asymmetry in the degree of cortical inhibition in normal subjects when non-dominant and dominant hemispheres are compared, with less inhibition present in the non-dominant hemisphere (Hammond et al., 2004). Despite this, we do not feel that the differences we observed between PKD patients and controls with respect to cortical inhibition are sufficiently explained by dominant/non-dominant hemisphere effects, particularly as the non-dominant hemisphere was only studied in three out of 11 subjects.

**Spinal inhibition and the startle response**

RI in patients with PKD was abnormal only in the first phase (ISI 0 ms), with normal inhibition in the second and third phases. The first phase of RI is due to activity in a disynaptic inhibitory pathway that was once thought to be analogous to the disynaptic glycinergic Ia reciprocal inhibitory pathway described in the cat hindlimb (Hultborn, 1976). However, since it does not receive recurrent inhibition from forearm motoneurons, it has been suggested that evolution may have modified the connectivity of reciprocal inhibition to complement the increased circumduction movements that are possible at the human wrist (Aymard et al., 1995). The second phase of inhibition is thought to be due to presynaptic inhibition of the terminals of Ia afferents responsible for the H reflex (Berardelli et al., 1987). The origin of the third phase is less clear. It has been proposed that it is due to continued presynaptic inhibition, and that the division between second and third phases is caused by superimposition of a short period of facilitation at ~50 ms (Berardelli et al., 1987). An alternative hypothesis is that, due to its long latency, it may involve long loop inhibitory connections from radial nerve to brainstem (spino-bulbo-spinal connections) or even cerebral cortex (transcortical connections) and thence back to the H reflex pathway in the spinal cord. This hypothesis has been supported by the recent finding that the third phase of RI is capable of modification (independent of the second phase) by 1 Hz premotor rTMS in patients with DYT1 dystonia (Huang et al., 2004).

In a previous study in patients with PKD, an abnormal first phase of RI was identified, but no assessment was made of the second and third phases (Lee et al., 1999). In this current study, we have confirmed the presence of an abnormality in the first phase of RI, and also demonstrated that both second and third phases were normal. These new findings raise some interesting points regarding the pathogenesis of PKD. In line with the findings from SICI and SP, patients with PKD demonstrate a different pattern of abnormality with respect to RI compared with patients with primary dystonia, who typically show abnormalities in the second and third phases. Interestingly, the discrete abnormalities in the first phase of RI found in PKD resemble the pattern observed in patients with hereditary hyperekplexia, an inherited disorder of the glycine receptor gene (GLRA1), characterized clinically by continuous muscle stiffness in the first year of life, and later an exaggerated SR (Shiang et al., 1993). In such patients the first phase of RI is absent, and there may even be some facilitation of the H reflex, but later phases of inhibition are intact (Floeter et al., 1996; Brown, 2002). In our PKD subjects, the first phase of RI was reduced, but not absent as seen in hyperekplexia. This would be compatible with reduced, but not absent, glycinergic inhibition in patients with PKD. Certainly the symptoms in hyperekplexia and PKD are different, and we found no evidence for an exaggerated SR in PKD patients. As well as the different degree of deficit in glycinergic inhibition in the two conditions, there is evidence of normal cortical GABAergic inhibition in hyperekplexia (Nielsen et al., 2002) in contrast to PKD patients, perhaps further modifying the phenotypic expression of impaired glycinergic inhibition.
Patients with PKD are typically exquisitely responsive to small doses of carbamazepine. We only detected modulation of the abnormality in the early phase of TI when patients with PKD were withdrawn from medication, with no effect on SICI or RI. Given the current uncertainty regarding the mechanism of TI, this finding does not shed much light on how carbamazepine might have its remarkable effect on symptoms in PKD. The main mode of action of carbamazepine is as an antagonist of voltage-gated sodium channels, most probably leading to a subsequent reduction in glutamate release (Davies, 1995). This, in itself, might be responsible for a sufficient reduction in cortical excitability to abolish attacks in those with PKD.

In conclusion, we have presented evidence of impaired cortical and spinal inhibition in patients with PKD. The pattern of impairment in PKD patients is different from those previously described in primary dystonia and epilepsy. Based on the current state of knowledge regarding the mechanisms of SICI, SP, TI and RI, our results would suggest abnormal glycineric and GABA-Aergic inhibition in PKD. It is of interest that glycine and GABA-A receptors form part of the ligand-gated ion channel superfamily (LGIC) (Jentsch et al., 2002), members of which have a common structure in which five subunits form an ion channel, and which are thought to have evolved from a common receptor subunit (Jentsch et al., 2002). Binding of ligands to both glycine and GABA-A receptors opens a central pore that leads, in the adult CNS, to chloride influx, hyperpolarizing the neuron and inhibiting neuronal activity (Jentsch et al., 2002). This structural and functional link between glycine and GABA-A receptors coupled with the data we have presented may be of interest in the future investigation of the pathophysiology of PKD.

References


