Facilitation and Inhibition of Tibialis Anterior Responses to Corticospinal Stimulation After Maximal Voluntary Contractions

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We hypothesized that despite the different functional roles of the elbow flexor and ankle dorsiflexor muscles, corticospinal connections to the two muscles would show the same activity-dependent changes in the motor pathway and may be muscle specific.

INTRODUCTION

The corticospinal tract is the major pathway controlling voluntary movements in humans (e.g., Lemon and Griffith 2005; Lemon et al. 2004). It links the motor cortex and motoneurons and includes direct monosynaptic connections, which are strongest for distal upper limb muscles (De Noordhout et al. 1999; Palmer and Ashby 1992; Porter and Lemon 1993). Changes in corticospinal transmission can be assessed by transcranial magnetic stimulation (TMS) over the motor cortex. Responses to TMS depend on both motor cortical and motoneuron pool excitability. Therefore corticospinal responses evoked at a subcortical level provide a more direct assessment of the efficacy of input to motoneurons (Taylor 2006). For upper limbs, this can be achieved by stimulation of the corticospinal tract at the cervicomedullary junction. It elicits a single descending volley that activates motoneurons and produces electromyographic (EMG) responses (Taylor and Gandevia 2004). There is a large monosynaptic component to the responses in the elbow flexor muscles (Petersen et al. 2002; Taylor et al. 2002), so that the size of the responses depends on the number of activated descending axons, the efficacy of their synapses, and the excitability of the motoneuron pool.

After a strong contraction lasting 10 s to 2 min, responses to cervicomedullary stimulation (CMEPs) in elbow flexors muscles are immediately reduced in size (Gandevia et al. 1999) and this lasts ~90 s (Petersen et al. 2003). As corticospinal fibers are not subject to classical presynaptic inhibition (Jackson et al. 2006; Nielsen and Petersen 1994; Rudomin and Schmidt 1999), depression of the CMEPs presumably reflects activity-dependent changes at the cortico-motoneuronal synapse (Petersen et al. 2003). This postcontraction depression affects not only the response evoked by a single corticospinal volley but also EMG and force during voluntary contractions. Because it can occur after short (10-s) contractions at only 50% maximal force (Petersen et al. 2003), the depression of motoneuron output may occur commonly with voluntary movements. Thus far, this depression has only been demonstrated in elbow flexor muscles. It is unknown whether it is a general feature of all motoneuron pools or is peculiar to antigravity muscles of the arm.

Therefore in the current study, we examined whether corticospinal responses evoked in tibialis anterior (TA) by descending tract stimulation were also depressed after strong contractions. TA dorsiflexes the ankle and acts concentrically in the swing phase and eccentrically during ground contact in locomotion. It has a high percentage of type I fibers compared with most limb muscles (Johnson et al. 1973). Motor cortical stimulation elicits responses in lower limb muscles including TA (e.g., Capaday et al. 1999; Petersen et al. 1998; Rothwell et al. 1991; Schubert et al. 1997), and responses include a monosynaptic component (Brouwer and Ashby 1992; De Noordhout et al. 1999; Zidar et al. 1987). Electrical stimulation over the thoracic spine can activate corticospinal axons and thus allow assessment of the cortico-motoneuronal projections to muscles in the leg (Martin et al. 2008; Ugawa et al. 1995).

We hypothesized that despite the different functional roles of the elbow flexor and ankle dorsiflexor muscles, corticospinal connections to the two muscles would show the same activity-dependent behavior after strong voluntary contractions.

METHODS

Responses in a lower leg muscle (TA) elicited by stimulation of the corticospinal tract were examined after a 10-s and a 1-min maximal voluntary contraction (MVC). Additional studies explored the effect of ongoing voluntary contraction and tested the H reflex in this...
muscle. A total of 41 healthy subjects (23 males; 28 ± 8 yr) volunteered and gave written consent to participate in the experiments. Of these subjects, 12 volunteers were excluded due to a lack of response to corticospinal stimulation at the thoracic spine (Martin et al. 2008). Ten of the remaining participants completed multiple sets of studies. The Human Research Ethics Committee at the University of New South Wales approved the procedures and the studies were conducted according to the Declaration of Helsinki.

Experimental set up

Subjects were seated in an immobile chair with both knees and ankles flexed to 90°. The right foot was strapped into a rigid myo-graph, which measured dorsiflexion torque (Todd et al., 2004). A strap over the dorsum of the foot held it to a footplate. In all studies subjects received visual feedback of the torque of ankle dorsiflexion via a light-emitting diode (LED) display.

EMG recording

After preparation of the skin, surface EMG activity was recorded via self-adhesive Ag-AgCl electrodes (1 cm diam). To record responses from TA, one electrode was placed over the mid belly of the muscle and the other over the distal tendon. The EMG signal was amplified (100–3,000 times) and filtered (16–1,000 Hz; CED 1902 amplifier). EMG and torque were sampled to computer (2 kHz) using a CED 1401 interface (Cambridge Electronic Design, Cambridge, UK).

Stimulation

Three forms of stimulation were used. These included stimulation of the common peroneal nerve to evoke maximal M-waves (Mmax), stimulation of the common peroneal nerve to evoke H-reflexes, and stimulation of the corticospinal tract at the upper thoracic spine.

Common peroneal nerve stimulation

To evoke Mmax in TA, the peripheral nerve was stimulated electrically (100 µs pulse, Digitimer DST7AH, constant-current stimulator, Digitimer, Welwyn Garden City, UK) using a surface cathode over the common peroneal nerve (Ag-AgCl, 1 cm diam). The anode was placed proximally, lateral to the popliteal fossa. To identify the best site for the cathode, stimulation was initially carried out with a hand-held electrode. Stimulus intensity (42–132 mA) was set above that required to evoke Mmax by 20% (for the 10-s MVC) or 40% (for the 1-min MVC).

H-reflex stimulation

The common peroneal nerve was also electrically stimulated to evoke the H-reflex in TA. Here 1-ms pulses (1.6–12.7 mA) were delivered during steady weak dorsiflexion contractions.

Corticospinal tract stimulation at upper thoracic spine

The corticospinal tract was stimulated with a high-voltage electrical pulse (Digitimer D180, maximum output: 750 V, constant voltage) between two surface electrodes fixed over the thoracic spine to evoke motor responses in TA (thoracic motor evoked potentials, TMEPs). The cathode was between the spinal processes of T5 and T4 vertebrae and the anode ~10 cm above. This stimulation activates corticospinal axons to lower limb muscles (Martin et al. 2008). With TA at rest, stimulus intensity ranged from 43 to 99.9% of stimulator output (median: 99%). During weak voluntary contraction, intensities were between 37 and 99.9% stimulator output (median: 99%). Although the electrical stimulation over the upper thoracic spine was perceived as an unpleasant event, all subjects tolerated the sets of single stimuli well.

Protocol

STUDY 1: TA RESPONSES TO CORTICOSPINAL STIMULATION AFTER A 10-S MVC. Initially, control responses to electrical stimulation of the corticospinal tract and the peripheral nerve were collected in two sets (Fig. 1A). In each set, five corticospinal stimuli (TMEPs) and three common peroneal nerve stimuli (Mmax) were evoked from the relaxed TA muscle with ~10 s between stimuli and ~1 min between sets. Subjects (n = 10) then performed an isometric MVC lasting for 10 s. Subjects were verbally encouraged to maintain maximal torque throughout the contraction. Immediately after relaxation, at 2 and 5 s after the contraction, corticospinal tract stimuli were delivered, followed by common peroneal nerve stimulation at 10 s after the MVC. Over the following 10 min, the TMEP and Mmax were elicited in pairs separated by intervals of 10 s. TMEPs were elicited at 2, 5, 30, 50, 70, 100, 130, 190, 250, 370, 490, and 610 s after the MVC.

STUDY 2: TA RESPONSES TO CORTICOSPINAL STIMULATION AFTER A 1-MIN MVC. Six of the subjects who participated in study 1 plus an additional four subjects took part in study 2 (n = 10). The protocol was identical to study 1 except that the duration of MVC was increased to 1 min (Fig. 1A).

STUDY 3: TA RESPONSES TO CORTICOSPINAL STIMULATION AFTER A 10-S MVC RECORDED DURING WEAK CONTRACTION (5% MVC). Seven subjects who participated in the first protocol and an additional three
subjects took part in study 3. Individuals \((n = 10)\) performed a 10-s conditioning maximal ankle dorsiflexion contraction. TMEPs and Mmax were elicited in the TA muscle before and after this maximal contraction, while subjects maintained a weak voluntary contraction \((5\% \text{ MVC})\) of the ankle dorsiflexors (Fig. 1B). The weak contraction was held for \(\sim 60 \text{ s}\) during each control set of stimuli and for \(\sim 120 \text{ s}\) after the MVC. Subsequently subjects resumed the contraction 5–10 s prior to the corticospinal tract stimulation for each pair of stimuli, which evoked a TMEP and Mmax. Pair of stimuli were 10 s apart and continued at intervals until 30 min after the MVC. To ensure the same level of excitability of the motoneuron pool before and after the MVC, subjects received visual feedback of rectified integrated EMG from TA and maintained this target EMG level of 5% maximum throughout the protocol.

**Study 4: H-reflex recorded from the TA after a 10-s MVC.** Initially, control H-reflex responses to stimulation of the common peroneal nerve were collected in two sets. Each set consisted of 12 H-reflexes evoked from the TA muscle during a weak voluntary contraction \((5\% \text{ MVC})\) with \(\sim 5 \text{ s}\) between stimuli and \(\sim 1 \text{ min}\) between the sets. Subjects \((n = 7)\) then performed a 10-s ankle dorsiflexor MVC. Starting at 2 s after the MVC, 11 H-reflexes were evoked at intervals of 5 s in the weakly contracting muscle. Subsequently, sets of seven H-reflexes \((5\text{-s intervals})\) were evoked during weak contractions lasting \(\sim 30 \text{ s}\) and starting at 90, 150, 210, 270, 360, 450, 540, 630, 720, 810, and 900 s after the MVC. Again, subjects received feedback of the rectified integrated EMG recorded from TA and maintained a target EMG level of 5% MVC.

**Data analysis**

Area and peak-to-peak amplitude of TMEPs and M-waves elicited in TA were measured for all potentials in all subjects between cursors set to encompass a region from the initial deflection from baseline to the third crossing of the horizontal axis. Area of TMEPs was normalized to Mmax measured at close to the same time and then to the mean control value for each subject. In addition, to focus on the early events within the motoneuron pool, we measured also the area of each potential for 5 ms from onset of the potential. Mmax and H-reflex values were normalized to their respective control values. Background EMG was sampled 50 ms prior to each stimulus. Group data are presented as means \(\pm \text{SD}\) of the amplitude and area in the text and as means \(\pm \text{SE}\) in the figures. For each set of data, 95% confidence intervals were calculated for the means of the control values. For the TMEPs and Mmax, the group mean of individual responses was determined. For the H-reflex, within each subject, every five to seven consecutive responses were averaged. Means were then taken across the group. Subsequent values were considered to be significantly different from the control values if they fell outside the 95% confidence intervals. Paired t-tests were also used to compare torques at the beginning and end of each MVC. A paired Student’s t-test was used to compare the level of changes in TMEPs after the short \((\text{study 1})\) and prolonged \((\text{study 2, 1 min})\) MVC. Because the two protocols were not completed by the same subjects, group means for data collected at each of the postcontraction times were compared.

**Results**

**Study 1**

TMEPs and Mmax were evoked in the relaxed TA before and after a 10-s MVC. TMEP areas were first normalized to the areas of Mmax evoked at a similar time and then expressed relative to control values obtained before the MVC. Prior to the contraction, the area of the TMEPs was an average of 2.6 \(\pm 3.2 \mu\text{V} \cdot \text{s}\) \((\text{area range}: 1.8–7.0 \mu\text{V} \cdot \text{s}; \text{amplitude}: 0.5 \pm 0.5 \mu\text{V})\) and Mmax area was 55 \(\pm 2 \mu\text{V} \cdot \text{s}\) \((\text{amplitude Mmax}: 10.9 \pm 5.3 \mu\text{V})\). During the contraction, the torque values of voluntary dorsiflexion fell by an average of 4.7 \(\pm 2.7 \text{ Nm}\) from 36.7 \(\pm 11.5 \text{ Nm}\) \((P < 0.001)\). Following the 10-s MVC, there was an immediate large, but variable, increase in size of the TMEPs to 349 \(\pm 335\%\) of control values \((\text{Figs. 2 and 3A})\). This increase was no longer significant at 30 s. By 50 s after the contraction the TMEPs had decreased to 38 \(\pm 28\%\) of control. The reduction lasted until testing finished 10 min after the end of the contraction. TMEP area measured over the initial 5-ms period of all potentials showed an initial significant increase for \(\sim 30 \text{ s}\) to 233 \(\pm 333\%\) of control, followed by a significant long-lasting depression to 55 \(\pm 73\%\) of control. Responses elicited by peripheral nerve stimulation \((\text{Mmax})\) revealed significant changes only immediately following the MVC with a very small increase to 102 \(\pm 14\%\) of control values \((\text{Fig. 3A})\). Background EMG showed no significant change throughout the experiment.

**Study 2**

TMEPs and Mmax were again evoked in the relaxed muscle before and after a sustained MVC, but the duration of the MVC was increased to 1 min. This was a fatiguing contraction in which torque dropped from an average of 29.6 \(\pm 5.5\) to 12.5 \(\pm 2.6 \text{ Nm}\) \((P < 0.001)\). TMEPs prior to the MVC were similar in size to those in study 1 \((\text{area}: 4.4 \pm 8.3 \mu\text{V} \cdot \text{s}; \text{area range}: 3.2 \text{ to } 8.3 \mu\text{V} \cdot \text{s})\).
In the resting TA after the MVC, the area of the TMEPs was again facilitated in the first 30 s to 191 ± 133% of the control values (Fig. 3B). This increase was followed by a reduction in size to 46 ± 27% of control values. The responses were still significantly depressed at 10 min after the MVC. The deepest depression (18 ± 23% control) occurred at 8 min after the MVC. Again, TMEP area measured over the initial 5-ms period showed facilitation (146 ± 108% control) and a subsequent depression (55 ± 56% control) after the MVC. Mmax showed small but significant changes for a short period after the MVC. It decreased to 95 ± 9% of control values but returned ∼2 min after the MVC. The background EMG was well maintained throughout the testing.

Study 3

TMEPs and Mmax were examined during a steady voluntary contraction of ankle dorsiflexion (5% MVC) before and after a 10-s MVC. Testing after the MVC was extended to 30 min. Prior to the MVC, TMEP area was 8.3 ± 4.3 μV·s (area range: 3.4–13.3 μV·s; amplitude: 1.8 ± 1.0 mV). Torque decreased by 6.1 ± 3.0 Nm from 41.8 ± 15.4 Nm (P < 0.001). After the MVC, the area of the TMEPs was facilitated to 131 ± 41% of control (136 ± 50% of control for area measured for 5-ms period). This was followed by a depression to 58 ± 22% of control values (Fig. 4A; 70 ± 40% of control for area measured for 5-ms period). The depression was significant at ∼1, 1.5, 3, 4, and 8 min after the MVC. As in study 2, Mmax values showed a small initial reduction for only a short time after the MVC. The background EMG was well maintained at 5% MVC levels throughout the testing.

Study 4

To compare the responses of the motoneuron pool to corticospinal and reflex inputs following a maximal effort, H-reflexes were evoked in the TA muscle during weak voluntary contraction (5% MVC) before and after a 10-s MVC. Prior to the MVC, the area of H-reflexes was 3.9 ± 2.2 μV·s (amplitude: 0.7 ± 0.5 mV). After the MVC, there was initially a significant decrease in H-reflex area to 86 ± 26% of control (Fig. 4B). This recovered to control values in ∼30 s. The background EMG was well maintained throughout the experiment.

DISCUSSION

Counter to our hypothesis, a preceding strong voluntary contraction had quite different effects on responses to cortico-
spinal stimulation recorded from TA compared with those reported for responses in biceps brachii. Electrical stimulation of the corticospinal tract over the thoracic spine evokes responses (TMEPs) in the TA. Based on collision studies (Martin et al. 2008), this method allows the assessment of transmission in the corticospinal pathway to lower limb muscles (Martin et al. 2008). After a 10-s MVC, TMEPs recorded from the relaxed TA were immediately facilitated. This facilitation lasted for ~30 s and was followed by a depression which lasted for >10 min. A longer 1-min voluntary contraction resulted in similar behavior of TMEPs. Although a 10-s maximal contraction also caused facilitation and depression of TMEPs recorded from the weakly contracting TA muscle (5% MVC), changes were less pronounced than with the muscle at rest. In contrast to the changes in TMEPs, H-reflexes in the same motoneuron pool during weak contraction showed only an initial short-lasting depression after a 10-s MVC.

These changes in leg muscle responses to corticospinal stimulation after a strong voluntary contraction contrast with previous findings in upper limb muscles. A prolonged 2-min MVC immediately depressed CMEPs in the elbow flexor muscles, biceps brachii and brachioradialis (Gandevia et al. 1999). The responses recovered to control values after ~90 s. Shorter MVCs of 5 or 10 s also evoked a postcontraction depression of CMEPs in these muscles, but activation of motoneurons antidromically through peripheral nerve stimulation did not (Gandevia et al. 1999; Petersen et al. 2003). These findings suggest that voluntary activity causes a short-lasting depression of corticospinal transmission to the upper limb muscles and this probably occurs at a premotoneuronal site.

Depression of transmission at the cortico-motoneuronal synapse was proposed (Gandevia et al. 1999). The current studies of the ankle dorsiflexor, TA, reveal a different pattern of responses, with an initial facilitation and subsequent longer-lasting depression. We discuss in the following text some technical and other factors, which may contribute to the complex activity-dependent changes in corticospinal transmission to the TA motoneuron pool.

Electrical stimuli were delivered over the thoracic spine. Stimulation at the cervicomedullary junction is believed to evoke a single descending volley in corticospinal axons (Ugawa et al. 1991) and collision studies have shown that activation of corticospinal axons contributes to CMEPs evoked in the biceps brachii and first dorsal interosseous muscles (Gandevia et al. 1999; Taylor et al. 2002; Ugawa et al. 1999). Similarly, collision of orthodromic descending action potentials evoked by cortical stimulation with antidromic volleys evoked by stimulation of the thoracic spine reduces the size of motor-evoked potentials in leg muscles (Martin et al. 2008). Thus thoracic stimulation also activates populations of corticospinal axons.

In studies of responses of single motor units to motor cortical stimulation, it has been shown that corticospinal projections to biceps brachii have a large monosynaptic component in humans (Palmer and Ashby 1992). Stimulation of corticospinal axons at the cervicomedullary junction shows that CMEPs in this muscle also have a dominant monosynaptic component (Petersen et al. 2002). It is likely that motor potentials evoked by stimulation at the thoracic spine also have a monosynaptic component, as the responses of single motor
units in TA to cortical stimulation show short-latency peaks with similar size to those in biceps (Brouwer and Ashby 1992; De Noordhout et al. 1999). In addition, we found that the area of the first 5 ms of the TMEPs behave in a similar way to the main measures (amplitude and area). While our results are consistent with the changes occurring in the monosynaptic component of the corticospinal projections to TA, it is possible that the size of the TMEPs is also influenced through oligosynaptic interneuronal pathways acting on the motoneuron pool.

TMEPs recorded from TA could be influenced by activity-dependent changes in the muscle fiber action potential (e.g., Cupido et al. 1996; McFadden and McComas 1996; Nielsen and De Paoli 2007). However, there were only small changes in maximal M-waves so that the large facilitation and depression of the TMEP cannot be caused by changes in the muscle. Thus the present findings imply that changes in TMEPs after a contraction occur distal to the descending tracts in the thoracic spine and proximal to the peripheral motor axons. Possible mechanisms include altered excitability of the descending axons at the point of TMEP stimulation, altered efficacy of synaptic transmission, and altered excitability of the motoneurons or interneurons.

Our results rule out some possibilities. Hyperpolarization of human motor axons can be produced by natural activity but depends highly on the strength and duration of the voluntary contraction (e.g., Vagg et al. 1998). Thus a longer MVC leads to bigger, longer-lasting decreases in excitability. In our study, both facilitation and inhibition of the TMEPs were similar after a 1-min and a 10-s MVC. Therefore it is unlikely that the changes in the TMEP reflect activity-dependent changes in the excitability of the descending corticospinal axons. This is consistent with findings in the elbow flexors following brief and prolonged voluntary contractions (Gandevia et al. 1999; Petersen et al. 2003).

TMEPs evoked while subjects maintained a weak voluntary contraction showed qualitatively similar behavior to those in the relaxed condition. By maintaining a constant level of EMG, subjects held steady the level of motoneuron pool excitability. This suggests that changes in the excitability of the motoneuron pool are not solely responsible for the postcontraction facilitation then inhibition of the TMEPs. This again corresponds with studies in the upper limb (Petersen et al. 2003). In addition, the H-reflex, evoked in TA by electrical stimulation of its Ia afferents, did not show the same changes as the TMEP after a conditioning MVC. When the TMEP was facilitated, the H-reflex showed a short-lasting depression that rapidly returned to baseline. This stability of the H-reflexes makes it unlikely that changes in TMEPs after maximal voluntary efforts reflected an alteration in reciprocal inhibition. Given that TMEPs are elicited through stimulation of corticospinal axons, it is likely that they recruit a population of low-threshold motoneurons that overlap with those recruited in H-reflexes (Bawa and Lemon 1993; Gandevia and Rothwell 1987; cf. Nielsen et al. 1999). Thus the comparison of the H-reflex and TMEP strongly argues that neither the facilitation nor inhibition of the TMEPs can be accounted for by changes in excitability at the motoneuron pool.

Hence by exclusion, we hypothesize that the activity-dependen
t changes seen in the TMEPs originate at a premotoneuronal site. This could occur through altered excitability of inter-neurons or altered efficacy at cortico-motoneuronal or inter-neuronal synapses. Repetitive activation can cause synapses to increase their efficacy in the short-term through several processes, including facilitation, augmentation, and post-tetanic potentiation (Fishet al. 1997; Zucker and Regehr 2002). Post-tetanic potentiation decays over tens of seconds after trains of conditioning stimuli (Fisher et al. 1997; Zucker and Regehr 2002). The immediate facilitation of the TMEP is consistent with this time course. It has been suggested that a maintained elevation of Ca++ ions in the presynaptic terminals following the conditioning stimuli contributes to these processes. This is known as the residual calcium hypothesis (Erulkar and Rahamimoff 1978; Rosenthal 1969; Weinreich 1971; Zucker and Regehr 2002).

Conversely, during repeated stimulation, synapses can also decrease their efficacy. At many synapses, facilitatory and inhibitory processes occur concurrently. Short-term depression can occur through depletion of the readily-releasable pool of synaptic vesicles (Zucker and Regehr 2002). However, the time course of this effect is short. Although it is compatible with the time course for depression in the upper limb, it is unlikely to account for the ~10-min depression of TMEPs in TA. Longer-term decreases in synaptic strength can be caused by decreased release of transmitters from the presynaptic terminal through actions on presynaptic receptors (Dong and Feldman 1999; Giacomo and Hasselmo 2006; Wu and Saggau 1997). While corticospinal terminals are thought not to show classical afferent-mediated presynaptic inhibition (Jackson et al. 2006; Nielsen and Petersen 1994; Rudomin and Schmidt 1999), homosynaptic modulation is possible. For example, output from respiratory motoneurons can be depressed for minutes through actions on presynaptic metabotropic glutamate receptors (Dong and Feldman 1999). Hence it is possible that synaptic responses to repetitive activation could underlie both the immediate facilitation and longer-lasting depression of TMEPs seen in the present study.

Irrespective of the exact physiological mechanisms that generate the facilitation and depression, our current results for the lower leg muscle, TA, show major differences compared with activity-dependent changes in the upper limb muscles. Synapses can be specialized by their use to the extent that even different terminals of the same neuron can respond differently to activity (Parnas et al. 1982). TA is most commonly recruited in repetitive rhythmic contractions during locomotion, whereas the elbow flexors are used for maintaining hand position against gravity and carrying. Thus the different patterns of use of our limb muscles might contribute to different patterns of responses to corticospinal tract stimulation after maximal voluntary efforts. The facilitation of responses in TA immediately after a contraction suggests that this muscle should be easily rerecruited by voluntary drive. This is apt for a muscle that performs repetitive contractions and suggests that voluntary drive and effort associated with locomotor activity could be minimized if such properties are shared by other leg muscles. Our results show activity-dependent changes in the lower limb muscle at a premotoneuronal site and would imply that corticospinal connections to different muscles differ not just in the strength of the connection but that they differ qualitatively in their dynamic changes with activity. This potent phenomenon needs further study to elucidate the precise physiological mechanisms.
REFERENCES


