Migraine can be induced by sildenafil without changes in middle cerebral artery diameter

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Summary

Migraine is considered a neurovascular disease involving dilatation of cerebral arteries. Nitric oxide (NO) donors induce dilatation of cerebral and extracranial arteries and migraine, but NO has several mechanisms of action in addition to its cyclic guanosine monophosphate (cGMP)-mediated vasodilatation. We examined whether sildenafil (Viagra®), a selective inhibitor of cGMP-hydrolysing phosphodiesterase 5 (PDE5), which acts exclusively by increasing cGMP, can induce migraine and dilatation of cerebral arteries. We included 12 patients with migraine without aura in this double-blind, placebo-controlled crossover study, in which placebo or sildenafil 100 mg was administered orally on two separate days. Blood flow velocity in the middle cerebral artery (Vmca) was recorded by transcranial Doppler ultrasonography and regional cerebral blood flow in the territory of the middle cerebral artery (rCBFmca) was measured using SPECT (single photon emission computed tomography) and xenon 133 inhalation. Radial and temporal artery diameters were studied using high-frequency ultrasonography. Headache response, tenderness of pericranial muscles, blood pressure and heart rate were measured repeatedly. We found that migraine attack was induced by sildenafil in 10 of 12 migraine patients and by placebo in two of 12 patients (P = 0.01). Vmca (P = 0.1) and rCBFmca (P = 0.93) remained unchanged after sildenafil. Temporal (P = 0.47) and radial (P = 0.87) artery diameter and pericranial tenderness (P = 0.16) were unaffected by sildenafil. Systolic and diastolic blood pressures were unchanged but heart rate increased from a mean of 62 ± 2 to 74 ± 3 beats/min (P = 0.01) after sildenafil. Our results demonstrate that migraine may be induced via a cGMP-dependent mechanism, and we show for the first time that this occurs without initial dilatation of the middle cerebral artery. We propose that triggering mechanisms may reside within the perivascular sensory nerve terminals or the brainstem. However, other sites of action may also be possible and future studies are needed to elucidate this. In the clinical use of sildenafil, patients who have migraine should be informed about the risk of migraine attacks.

Keywords: migraine; cerebral blood flow; cerebral arteries; phosphodiesterases; sildenafil

Abbreviations: CGRP = calcitonin gene-related peptide; gCBF = global cerebral blood flow; GTN = glyceryl trinitrate; NO = nitric oxide; PDE5 = phosphodiesterase 5; rCBF = regional cerebral blood flow; TCD = transcranial Doppler ultrasonography

Introduction

The search for new causative mechanisms involved in migraine depends on studies performed in patients since no validated animal model exists. However, the study of spontaneous attacks is difficult and can most often only be performed hours after onset. This complicates the interpretation of the causative role of abnormal findings. The study of experimental migraine induction, on the other hand, may reveal important mechanisms involved in the initiation of the attack.

Glyceryl trinitrate (GTN), a prodrug for nitric oxide (NO), induces migraine attacks indistinguishable from spontaneous attacks in ~80% of migraine sufferers (Thomsen et al., 1994). Treatment of spontaneous migraine attacks with an inhibitor of nitric oxide synthases, the enzymes that catalyse the production of NO, is effective in 60% of patients (Lassen et al., 1997). In animal experiments, infusion of GTN is associated with inflammatory changes in the meninges and it potentiates expression of the immediate early gene c-fos in
the nucleus caudalis of the trigeminal nerve in the brainstem (Jones et al., 2001; Reuter et al., 2001). Thus, NO may not only initiate the migraine attack but may also be involved in propagating pain throughout the attack.

Also, there is evidence of crosstalk between NO and the neurotransmitter calcitonin gene-related peptide (CGRP), which has been found to be released during migraine attacks (Goadsby et al., 1990) at the level of cyclic nucleotides, and the vasodilating effects of NO and CGRP are suggested to interact at this level (Gray and Marshall, 1992; Wei et al., 1992; Pelligrino and Wang, 1998). However, these links are still being discussed and investigated, and their role in migraine induction is not fully clarified.

The main effect of NO is to activate intracellular soluble guanylate cyclase and thus catalyse the formation of cyclic guanosine monophosphate (cGMP). However, NO has a variety of other actions, such as binding to ion channels, activating phosphokinases, and possibly activating nociceptive nerve fibres directly via the formation of free radicals such as hydroxyl ions (Garthwaite and Boulton, 1995). It remains to be shown which of these mechanisms are most important in migraine.

In order to answer this question we conducted a double-blind crossover trial comparing the effect of placebo with that of sildenafil (Viagra®), a highly selective inhibitor of phosphodiesterase 5 (PDE5), which is the major enzyme responsible for the breakdown of cGMP. Inhibition of this enzyme results in accumulation of cGMP, and the effect of sildenafil therefore mimics one of the effects of NO (activation of soluble guanylate cyclase and increased cGMP formation) but not its other effects. Our study gave a clear answer to this question and also, unexpectedly, altered our view of the significance of the initial dilatation of the middle cerebral artery in migraine.

Methods

Patients and study design

This was a double-blind, randomized, placebo-controlled crossover study in which migraine patients received on two occasions at least 1 week apart a dose of either sildenafil (Viagra, Pfizer A/S, Ballerup, Denmark) 100 mg or placebo in a non-transparent gelatine capsule. A nurse not otherwise involved in the study organized the randomization, in which half of the patients were to receive sildenafil and the other half placebo on the first day. The study was approved by the ethics committee of Copenhagen County and the Danish health authorities and was conducted according to the Helsinki II declaration. All patients were recruited from The Danish Headache Centre and gave informed consent before inclusion. We aimed to include 12 patients suffering from migraine without aura. They had an attack frequency ranging between one and three every 6 weeks and no more than 6 days of tension-type headache a month. They were otherwise healthy, had a body weight between 60 and 90 kg and had no daily intake of medication except contraceptives. A total of 17 patients were eligible but five patients dropped out the first study day (two men and three women) and were replaced, leaving 12 patients completing the study (12 women). They had a mean age of 37.3 ± SEM, 3.2 years and a mean body weight of 69 ± 2.8 kg. Three of the dropouts did not wish to continue, because of induction of a severe migraine attack on the first study day, two after sildenafil and one after placebo. One suffered from fear of needles and could not complete the first study day (placebo) because of hyperventilation, and one had an attack of mild syncope after placebo at the end of the first examination day and did not wish to return.

On the days of examination we measured baseline values after 30 min of rest and the subject was kept for observation and measurements in the supine position in quiet surroundings for a period of 180 min. SPECT (single photon emission computed tomography) acquisitions were performed at baseline and at 60 and 120 min. The following measurements were taken at baseline and every 15 min for 180 min: transcranial Doppler ultrasonography (TCD), radial and temporal artery diameter; blood pressure; heart rate; and headache score. In one patient it was not possible to measure cerebral blood flow (CBF) and temporal artery diameter on both study days because of technical problems.

Headache recordings

Headache intensity was scored on a verbal scale from 0 to 10, where 1 represents a very mild headache (including a feeling of pressing or throbbing), 5 a headache of moderate intensity and 10 the worst possible headache (Iversen et al., 1989). Headache characteristics, location, side-effects and intake of medication were recorded and all subjects continued these recordings every hour at home until 13 h after drug administration.

Transcranial Doppler ultrasonography

A time-averaged mean of the maximal blood velocity in the middle cerebral artery (V_mca) was recorded bilaterally by TCD (2 MHz, Multidop X Doppler; DWL, Sipplingen, Germany) with simultaneous end-tidal CO₂ (PETCO₂) measurements. The average of four measurements, comprising approximately four cardiac cycles each over an interval of 30 s, was used. A fixed point for measurement of V_mca was chosen along the middle cerebral artery, and was used throughout the study in each individual (Kruuse et al., 2000). The middle cerebral artery was chosen for measurement because of better reproducibility than measurements in the posterior or anterior cerebral arteries, as shown in previous methodological studies (Thomsen and Iversen, 1993) and because the timeframe for the measurements only allowed measurements in one set of arteries during the study. There are no available techniques for measurement of the diameter of the pial arteries. Only patients suffering from migraine...
without aura were studied, and thus the posterior cerebral artery was not of major interest in the present study, in view of poorer reproducibility of measurement.

**SPECT**

Measurements of CBF were performed by means of xenon 133 inhalation and single photon emission computed tomography (SPECT), using a brain-dedicated camera (Ceraspect; DSI, Waltham, MA, USA) with a stationary annular NaI crystal and a fast-rotating collimator system, and a dynamic protocol of \(^{133}\)Xe inhalation using the Kanno–Lassen algorithm (Kanno and Lassen, 1979; Kruuse et al., 2000). We used a Datex Normocap 200 (Dameca, Rødovre, Denmark) for \(P_{\text{ETCO}_2}\) measurements and a Ceretronic (Xenon Administration System XAS SM 32C; Randers, Denmark) for \(^{133}\)Xe administration. Mean regional CBF (rCBF) in the perfusion area of the middle cerebral artery (rCBF\(_{\text{mca}}\)) for each side was calculated. Since there were no changes when the two sides were analysed separately, the mean of left and right rCBF\(_{\text{mca}}\) was used. Global CBF (gCBF) was also calculated.

**Diameters of temporal and radial arteries**

We measured the diameter of the frontal branch of the superficial temporal artery and the diameter of the radial artery proximal to the distal volar wrist crease using a high-resolution ultrasound unit (Dermascan C; Cortex Technology, Hadsund, Denmark) (20 MHz, bandwidth 15 MHz) (Nielsen et al., 1993). Marks were drawn on the skin to ensure that the repeated measurements were performed in the same place and to ensure reproducibility in measurements from day to day.

**Tenderness score**

The tenderness of pericranial muscles was recorded by bilateral palpation of eight pairs of muscle and tendon insertions (masseter, temporal, frontal, sternocleidomastoid and trapezius muscles, coronoid and mastoid processes, and neck muscle insertions) according to the Total Tenderness Scoring system on a four-point scale (0–3) (Langemark and Olesen, 1987).

**Statistics**

All values are presented as mean ± standard error of the mean (SEM), and \(P < 0.05\) was considered significant.

Sample size was chosen on the basis of results from similar previous studies performed by our group showing induction of migraine in eight of 10 patients after administration of NO donors and in one of 10 after placebo and changes in cerebral haemodynamic parameters of at least 5–10% (Thomsen et al., 1994). Primary outcome measures were the induction of migraine similar to a usual migraine attack, analysed using the McNemar test.

The total tenderness and headache scores were plotted against time, and the area under the curve and the peak responses were compared using the Wilcoxon rank sum test.

The calculated area under the curve was chosen as the summary measure when analysing difference in response (\(V_{\text{mca}}, \text{CBF}, \text{rCBF}_{\text{mca}}, \text{artery diameters}, \text{blood pressure, heart rate, } P_{\text{ETCO}_2}\)) between treatments, and values were compared using the paired \(t\) test. Changes over time for each variable on each treatment day were analysed by two-way analysis of variance with the factors time and subject, and the analysis was repeated for each single variable (Statgraphics 3.3, Manogistics Inc, Rockville, MD, USA).

On the placebo day one patient experienced migraine during examination and had to take rescue medication at 90 min. Data following this time-point on the placebo day were excluded from further analysis.

**Results**

A dose of 100 mg sildenafil induced symptoms similar to the patient’s usual migraine attacks in 10 out of 12 patients suffering from migraine without aura. Nine of these patients fulfilled the criteria for migraine without aura of the International Headache Society, and one patient took migraine medication before complete fulfilment of these criteria (Table 1). After placebo, migraine without aura was induced in two of 12 patients. Thus, sildenafil induced significantly more migraine attacks than placebo (\(P = 0.01\)). All patients indicated that the symptoms were similar to those of their usual migraine attack. One patient reported mild transient headache on both days and one reported no headache on either day. The median time to peak headache score was 4.5 h after administration of sildenafil. Headache intensity progressed slowly over time. Median peak headache score during the first 3 h was 0 (range 0–8) after placebo and 1 (range 0–9) after sildenafil (\(P = 0.61\)). For the total observation period of 13 h after sildenafil administration, the median peak headache score was 0 (range 0–9) for placebo and 6.5 for sildenafil (range 0–10) (\(P = 0.02\)) (Fig. 1B). The area under the headache curve differed significantly between placebo and sildenafil treatments (\(P < 0.005\)).

Nine patients took medication to treat their migraine attack and one tried to sleep through the attack. All patients except one responded well to their usual migraine treatment, which was mostly a triptan (Table 1). After sildenafil, one patient reported very short-lasting palpitation, four patients complained of nasal congestion, nine felt warm in the face or body and all patients showed objective flushing. After placebo, eight patients had objective flushing and six reported a feeling of warmth; none had nasal congestion or palpitations.

\(g\text{CBF} (P = 1.0)\) and \(\text{rCBF}_{\text{mca}} (P = 0.93)\) did not differ between sildenafil and placebo. Baseline \(\text{rCBF}_{\text{mca}}\) was 49.1 ± 2.1 ml/100 g brain tissue/min on the day of placebo and
Table 1  Headache characteristics after sildenafil administration

<table>
<thead>
<tr>
<th>Subject</th>
<th>Headache (location/peak intensity/quality)</th>
<th>Time to peak (h)</th>
<th>Aggravated</th>
<th>Accompanying symptoms</th>
<th>Similar to usual migraine</th>
<th>Treatment/time to treatment after sildenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right/4/pressing</td>
<td>6</td>
<td>No</td>
<td>No/no/no</td>
<td>Yes</td>
<td>Sumatriptan/6 h</td>
</tr>
<tr>
<td>2</td>
<td>Bilateral/9/throbbing</td>
<td>3</td>
<td>Yes</td>
<td>Minor/severe/minor</td>
<td>Yes</td>
<td>Zolmitriptan/3 h</td>
</tr>
<tr>
<td>3</td>
<td>Right/10/throbbing</td>
<td>9</td>
<td>Yes</td>
<td>Severe/severe/no</td>
<td>Yes</td>
<td>Zolmitriptan/8 h</td>
</tr>
<tr>
<td>4</td>
<td>Left/8/throbbing</td>
<td>6</td>
<td>Yes</td>
<td>Moderate/no/no</td>
<td>Yes</td>
<td>Rizatriptan/6 h</td>
</tr>
<tr>
<td>5</td>
<td>Right/8/pressing</td>
<td>5</td>
<td>Yes</td>
<td>Severe/minor/minor</td>
<td>Yes</td>
<td>Rizatriptan/5 h</td>
</tr>
<tr>
<td>6</td>
<td>Left/9/throbbing</td>
<td>8</td>
<td>Yes</td>
<td>Severe/moderate/no</td>
<td>Yes</td>
<td>Sumatriptan/4 and 8 h</td>
</tr>
<tr>
<td>7</td>
<td>Bilateral/7/throbbing</td>
<td>3</td>
<td>Yes</td>
<td>Severe/minor/minor</td>
<td>Yes</td>
<td>Rizatriptan + plain analgesics and metoclopramide/3 h</td>
</tr>
<tr>
<td>8</td>
<td>No headache</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>Right/4/throbbing</td>
<td>2</td>
<td>Yes</td>
<td>Minor/minor/no</td>
<td>Yes</td>
<td>Plain analgesics/6 h</td>
</tr>
<tr>
<td>10</td>
<td>Left/3/pressing</td>
<td>4</td>
<td>Yes</td>
<td>Minor/minor/minor</td>
<td>Yes</td>
<td>Plain analgesics/12 h</td>
</tr>
<tr>
<td>11</td>
<td>Bilateral/6/throbbing</td>
<td>6</td>
<td>Yes</td>
<td>Severe/severe/severe</td>
<td>Yes</td>
<td>Slept</td>
</tr>
<tr>
<td>12</td>
<td>Right/1/pressing</td>
<td>2</td>
<td>No</td>
<td>No/no/no</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>

*Headache pain was scored on a verbal scale of 0–10; †accompanying symptoms were graded none, minor, moderate, severe; ‡patients were allowed to treat the headache with their usual migraine treatment (Patient 1 treated her headache before the migraine criterion concerning accompanying symptoms was fulfilled; this patient also experienced migraine fulfilling all criteria on the day of placebo and had to receive rescue medication after 90 min); §similar in characteristics to the known migraine, but usually with more severe headache.

49.4 ± 1.7 ml/100 g brain tissue/min on the day of sildenafil. \( P_{ECO2} = 0.18 \) and \( V_{mca} = 0.1 \) did not differ between placebo and sildenafil and was unchanged compared with baseline \( \Delta P = 0.4 \) on both days for \( P_{ECO2} = 0.57 \) and \( P = 0.82 \) for \( V_{mca} \) (Fig. 2). In five patients migraine criteria were fulfilled within the 3 h period in the laboratory. Four of these patients reported an initial unilateral headache, one of which changed into a bilateral headache within 45 min. \( V_{mca} \) and cCBF showed no systematic change on the headache side compared with the non-headache side before or during migraine.

No significant change in radial \( P = 0.87 \) or temporal \( P = 0.47 \) artery diameter was seen after sildenafil when compared with placebo.

Systolic and diastolic blood pressures were unchanged but heart rate increased from a mean of 62 ± 2 to 74 ± 3 beats/min within the first hour after sildenafil \( P = 0.01 \).

There was no difference in tenderness score on either side or in total tenderness score between placebo and sildenafil \( P = 0.16 \). Median total tenderness score was 0 (range 0–17) at baseline on the day of placebo and 2 (range 0–24) at baseline on the sildenafil day. Only two of the five patients experiencing a migraine attack during the 3 h observation period showed an increase in total tenderness score; this was not seen on the day of placebo \( P = 0.5 \).

**Discussion**

For more than a decade we have explored methods of experimentally inducing migraine in order to understand the basic biology of the disease and develop new targets for drug development for this disabling condition (Iversen, 1995; Humphrey et al., 2001). The NO donor GTN induces headache in normal volunteers and migraine in migraine suffers (Olesen et al., 1995). In migraine patients a temporary mild headache occurs during the infusion, concomitant with dilatation of the middle cerebral and temporal arteries, and this headache usually returns to baseline shortly after the infusion. However, at a median of 5 h after GTN, patients get increasing headache and accompanying symptoms that are similar to those of their usual spontaneous migraine attacks. These migraine attacks are relieved by sumatriptan to the same extent as spontaneous migraine attacks. The marked cerebral artery dilatation disappears shortly after the infusion and long before the migraine attack develops.

A similar immediate dilatation of the middle cerebral artery has been seen after treatment with other migraine-inducing substances, such as histamine, CGRP and dipyrnadamole, and has therefore been considered to play a causative role in the induction of migraine attacks (Olesen et al., 1995). However, the present study clearly shows that migraine can be induced without a similar initial dilatation of the middle cerebral artery. The median time to peak headache is almost equal to that seen after GTN, suggesting that similar pathways are activated despite the lack of significant artery dilatation. The present study thus indicates that the cGMP-elevating action of NO seems to play a significant role in migraine induction. First, sildenafil has no other actions than inhibiting the breakdown of cGMP; secondly, it was at least as effective as GTN in causing migraine. It was more effective than CGRP and probably also more effective than histamine (Lassen et al., 1996, 2002). It must be noted, however, that the present findings do not exclude the possibility that NO is involved in migraine induction by other mechanisms also, but further studies investigating other mechanisms of action separately are needed to elucidate this.

Sildenafil is a very selective inhibitor of the cGMP-degrading enzyme PDE5 (Wallis, 1999). PDE5 is located at
several different sites throughout the body, including the vascular smooth muscle of the penis. This latter location underlies the use of sildenafil as a remedy for male impotence. There are not yet any published studies showing the effects of sildenafil on cerebral artery dilatation in general or on the specific role of PDE5 in the regulation of human cerebral artery tone. This is partly the result of difficulty in obtaining enough human tissue for enzyme analysis and the limited availability of selective PDE5 inhibitors. However, the awakening interest in the role of cGMP-related phosphodiesterases in the brain and cerebral circulation will most likely shed light on this aspect in near future.

In preliminary studies we found the presence of both PDE5A mRNA and PDE5A protein in human middle cerebral, basilar and meningeal arteries obtained from post-mortem examinations (unpublished). This is consistent with the finding that PDE5A protein is present and active in the guinea-pig basilar artery (Kruuse et al., 2001). PDE5 has also recently been reported to be present in brain tissue, mostly cerebellum and hippocampus, and in the superior cervical ganglion (Giorgi et al., 1994; Loughney et al., 1998; Giordano et al., 2001), and sildenafil has been suspected to have central effects in humans (Schultheiss et al., 2001).

The plasma concentration after ingestion of sildenafil 100 mg is 1 µg/ml and is maximal after ~1 h (Jackson et al., 1999). The intracellular increase in cGMP and the enhancement of relaxation by NO occurs well below this plasma concentration of sildenafil (Jeremy et al., 1997; Ballard et al., 1998). With the study design and the number of patients included, we have previously been able to detect a 6% change in the diameter of the middle cerebral arteries (Kruuse et al., 2000). To our surprise, sildenafil was not able to dilate the middle cerebral arteries significantly in the presently used dose when including a similar number of subjects. Thus, the increase in the smooth muscle cells of cGMP may not be enough for a dilatory response. This could be due to a low basic level of cGMP production in the cerebral arteries or to rapid elimination by cGMP-degrading phosphodiesterases other than PDE5. Alternatively, the PDE5 in the cerebral arteries may be an isoform that is not sufficiently inhibited by sildenafil, or sildenafil may not be well distributed in the smooth muscle cells of the cerebral arteries.

The possible threshold for pain induction by arterial dilatation is not known, which makes it impossible to exclude the possibility that even a minor dilatation (not measurable by the methods used here) is of importance. However, the normal day-to-day variation in blood velocity has been found to be 16% and variation from heartbeat to heartbeat to be 10% for the middle cerebral artery (Thomsen and Iversen, 1993), and this is not associated with headache. Previous studies
have shown that an initial change in blood velocity above this threshold is associated with concomitant headache and later development of migraine (Thomsen et al., 1994; Lassen et al., 1995, 2002). Because sildenafil did not change the diameter of the middle cerebral arteries significantly with methods similar to those used in previous studies of migraine induction, we propose that the site of action of sildenafil in the induction of migraine is either the perivascular sensory nerve terminals or the CNS, including the brainstem. This seems consistent with previous studies showing that sildenafil acts not only on vascular smooth muscle cells but also on sensory nerve fibres in the stimulation of penile erection (Ballard et al., 1998; Medina et al., 2000), and that it modulates central NO–cGMP pathways in the rat brain (Sato et al., 1998). The increase in cGMP activates cyclic nucleotide-dependent protein kinases and cyclic nucleotide-gated ion channels in vascular and perhaps neuronal tissue (Garthwaite and Boulton, 1995). This might cause hyperexcitability of perivascular nerve terminals and sensory nerve fibres, or it might facilitate impulse transmission in the CNS. However, further studies are needed for a full understanding of the mechanisms and possible interactions with the effects of other signalling molecules, such as CGRP.

The possibility that the migraine-generating effect of sildenafil is caused by an effect on the cerebral veins cannot be ruled out. However, sildenafil has been found to have only a minor effect on veins (Jackson et al., 1999; Wallis et al., 1999). Furthermore, application of Queckensted’s manoeuvre to increase the pressure on the venous sinuses did not increase the pain in migraine patients during a migraine attack, which argues against a role of dilating venous sinuses in migraine pain (Dauggaard et al., 1998).

If sildenafil induces migraine by increasing the responsiveness of central pain neurons, it should be possible to demonstrate increased responses to sensory stimuli. However, we found no significant increase in the tenderness of the pericranial muscles in the initial phase of headache generation, which argues against primary CNS sensitization. We therefore favour the hypothesis that sensitization and hyperexcitability of perivascular sensory nerve terminals or first-order sensory neurons are involved in migraine generation. However, new studies applying techniques for the quantitative measurement of the effects of migraine-generating compounds on the sensory nerve system should be performed in order to elucidate this aspect of migraine generation.

The present results are not only important for our understanding of migraine mechanisms but also have implications for the clinical use of sildenafil in male impotence. Since 80% of migraine sufferers are likely to get an attack of migraine after the use of sildenafil at a therapeutic dose, patients should be warned in the package insert that, if they have migraine, there is a high likelihood of having an attack after the use of sildenafil.

In conclusion, the present study suggests a novel biochemical mechanism for induction of migraine which seems independent of an initial dilatation of the middle cerebral arteries. In the clinical use of sildenafil, better information about the risk of migraine should be given.

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References


Wallis RM, Corbin JD, Francis SH, Ellis P. Tissue distribution of phosphodiesterase families and the effects of sildenafil on tissue cyclic nucleotides, platelet function, and the contractile responses of trabeculae carnea and aortic rings in vitro. Am J Cardiol 1999; 83: 3C–12C.


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