Published in final edited form as:

Expert Rev Neurother. 2012 March ; 12(3): 297–306. doi:10.1586/ern.12.13.

Pharmacological targeting of spreading depression in migraine

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Abstract

Migraine, particularly with aura, is a genetically heterogeneous disorder of ion channels, pumps or transporters associated with increased cortical excitability. Spreading depression, as one reflection of hyperexcitability, is the electrophysiological event underlying aura symptoms and a trigger for headache. Endogenous (e.g., genes and hormones) and exogenous factors (e.g., drugs) modulating migraine susceptibility have also been shown to modulate spreading depression susceptibility concordantly, suggesting that spreading depression can be a relevant therapeutic target in migraine. In support of this, several migraine prophylactic drugs used in clinical practice have been shown to suppress spreading depression susceptibility as a probable mechanism of action, despite belonging to widely different pharmacological classes. Hence, susceptibility to spreading depression can be a useful preclinical model with good positive and negative predictive value for drug screening.

Keywords

animal models; hormones; ion channels; migraine; prophylaxis; spreading depression

Migraine is among the most common neurological disorders with a prevalence of 10–15% worldwide [1]. The typical migrainous head pain in the trigeminal area is of pulsating quality, usually ipsilateral to the dysfunctional hemisphere and increasing with physical exertion. The pain phase is temporally limited, in the vast majority of cases within 4–72 h. A third of patients with migraine also suffer from transient focal neurological symptoms, termed aura. Aura typically begins minutes to hours prior to the headache, but may occur during the headache phase or even in the absence of headache. The most interesting aspects of aura are the ‘spreading’ character, suggesting an underlying mechanism that propagates slowly along adjacent brain tissue, and its spontaneous resolution within approximately 20 min in most cases.

Over the past few decades, a large body of data has accumulated suggesting that spreading depression (SD) is the electrophysiological substrate of migraine aura and a potential trigger for headache [2]. For example, functional MRI during an attack has shown a brain oxygen level-dependent transient closely resembling SD, which was retinotopically congruent with the patient’s visual aura perception [3]. Genetic factors enhancing susceptibility to migraine aura also enhance susceptibility to SD when tested in transgenic mice expressing mutations

associated with familial hemiplegic migraine (FHM) or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [4-6]. Moreover, SD is capable of activating central and peripheral trigeminovascular nociceptive pathways with a latency matching that occurs between aura and headache in migraineurs [7-9]. Last, but not least, migraine prophylactic drugs have been shown to suppress SD [10], suggesting that SD is a relevant pharmacological target in migraine.

SD is an intense depolarization of neuronal and glial membranes that propagates in brain tissue at a rate of approximately 3 mm/min, irrespective of functional divisions or arterial territories [11]. Evoked when local extracellular K^+ concentrations exceed a critical threshold, SD is associated with disruption of membrane ionic gradients, with massive K^+ and glutamate efflux believed to first depolarize and then hyper polarize adjacent neurons to facilitate spread. SD can be evoked pharmacologically by application of glutamate, K^+ and Na^+/K^+ -pump inhibitors, by electrical stimulation and by tissue injury, such as trauma, hemorrhage or ischemia, in both lissencephalic and gyrencephalic cortices. Direct evidence for the occurrence of SD in human brain *in situ* has been obtained using subdural electrophysiological recordings [12-14] and intracortical multiparametric electrodes [15].

The susceptibility to SD is genetically determined and further modulated by numerous endogenous and environmental factors, such as hormones, weather, stress, food and drugs. Several experimental models have been developed to assess the susceptibility of brain tissue to SD, *in vivo* and *in vitro*, each with its own advantages and drawbacks [16]. Because SD is an all-or-nothing event, there are basically two main outcome measures:

- The SD threshold; that is, the lowest stimulus intensity that is sufficient to induce SD;
- The number of SDs that develop upon continuous supra threshold stimulation.

Such models allow the testing of pharmacological efficacy to suppress SD susceptibility. A correlation with drugs' clinical effectiveness in improving migraine supports as proof of principle the SD theory of migraine.

Migraine drugs suppress SD

Review of literature yields 19 reports of 21 migraine drugs (16 prophylactic and five abortive/analgesic) tested on SD, *in vivo*, by seven independent laboratories or groups of investigators over the past 25 years (Tables 1 & 2; Figure 1) [17-34].

The most commonly investigated species has been the rat (82% of studies), followed by the cat (22% of studies). SD was triggered by topical potassium chloride (KCl) (58% of studies) or electrical (46% of studies), or mechanical stimulation (22% of studies), and was detected using extracellular slow direct current potential recordings (54% of studies), laser Doppler flowmetry combined with single unit firing (12% of studies) or by MRI (one study). Efficacy has been tested from 15 min to 2 h after a single dose of drug in 54%, after 1 to 7 days of repeated dosing in 18% or after 4 weeks to 4 months of chronic treatment in 24% of the investigations. A dose response with at least two dose levels has been tested in only 24% of the studies. Importantly, independent confirmation of efficacy from different laboratories is present for only one drug (valproate). All these underscore the heterogeneity among the studies, and the need for standardization of drug testing on SD susceptibility as a surrogate model for migraine susceptibility.

Table 3 provides a summary of studies of migraine drugs on SD susceptibility published to date, based on their efficacy profile. Many prophylactic drugs that have been shown to be conclusively efficacious in clinical trials also suppress SD susceptibility experimentally

(e.g., the anticonvulsant valproate, β -blocker propranolol, serotonin antagonist methysergide and antidepressant amitriptyline) [10]. A meta-analysis of prospective, controlled trials found that anticonvulsants reduce migraine frequency by approximately 1.3 attacks per 28 days compared with placebo and more than double the number of patients with a reduction of migraine frequency by >50% relative to placebo [35]. Interestingly, migraine prophylactic drugs are similarly effective on migraine with and without aura, supporting the theory of cortical SD not only being a key factor in migraine aura pathogenesis, but also in migraine without aura. For some drugs, efficacy on SD required chronic daily treatment for weeks to months [10,17,19], reminiscent of the gradual build up of efficacy in migraineurs to reduce attack frequency and severity [36,37]. The requirement for prolonged treatment to suppress SD and improve migraine may reflect pharmacokinetic factors (e.g., gradual build up of therapeutic tissue levels) or mechanisms involving gene expression and ultrastructural changes. These data provided the first compelling evidence supporting the notion that SD is a final common target in migraine prevention.

Topiramate is another clinically efficacious drug that has been tested on SD in the experimental setting. It required chronic treatment to suppress SD susceptibility in one study [10], but prevented mechanical SD occurrence 30 min after a single dose in another [21]. The two studies, however, differed significantly in key design aspects, including route of drug administration (intraperitoneal vs intravenous), SD trigger (electrical and KCl vs mechanical stimulation), and SD susceptibility end points (SD threshold and frequency using direct current recordings vs SD occurrence using laser Doppler and single-unit firing), which may explain the discrepant results.

Recently, gabapentin, another commonly used drug in migraine prophylaxis, was also shown to suppress SD susceptibility [20]. This was not surprising since gabapentin targets the $\alpha_2\delta$ subunit of voltage-gated calcium channels [38], in particular the $\text{Ca}_v2.1$ channel, which is an important modulator of SD susceptibility [5,39]. However, in contrast to previously tested prophylactic drugs, SD suppression by gabapentin was observed within 1 h after a single intravenous dose. While chronic oral treatment with a lower dose did not appear to suppress SD, higher doses were not tested using the chronic treatment paradigm. These data suggest that chronic treatment is not a requisite for SD suppression by all migraine prophylactic drugs. Notably, gabapentin appeared to be less efficacious in SD suppression than some other prophylactic drugs tested to date, which may explain its relatively low clinical efficacy in migraine.

Tonabersat, a benzoylaminobenzopyran anticonvulsant that binds with high affinity at a stereoselective site on both glia and neurons, suppressed SDs triggered by topical KCl in rats and cats 90 min after a single intraperitoneal dose, monitored using electrophysiological recordings or MRI in four reports by one group of investigators [22-25]. Although its mechanism of action is still unclear, tonabersat was clinically tested in acute migraine attacks in a randomized, placebo-controlled, dose-ranging study, based on its acute SD inhibitory effect. The results were mixed. While the international subset of patients reported migraine relief (defined as the proportion of patients whose headache intensity changed from grade 2 or 3 to grade 0 [none] or 1 [mild] headache), North American participants did not [40]. The discrepancy might have been due to a higher proportion of migraine with aura in the tonabersat group compared with the placebo group among North American patients, although one might expect higher efficacy in migraine with aura based on the SD inhibitory profile. An alternative explanation is prior exposure to sumatriptan. Approximately two-thirds of the North American participants had previously used sumatriptan, compared with only a quarter of the international participants, and headache relief was higher in sumatriptan-naïve patients. For example, the expectation of a triptan-like effect in patients with sumatriptan history may have masked the response to a novel agent that did not

produce such an effect. In another acute migraine trial, however, tonabersat did not show efficacy and sumatriptan-naïve patients reported similar response rates compared with those who took sumatriptan [41]. Slow oral absorption could have limited tonabersat's efficacy in acute migraine where dosing was initiated hours after symptom onset. This caveat could be circumvented by chronic prophylaxis, which was tested in a randomized, double-blind, placebo-controlled study [42]. While the mean number of migraine headache days per month was unchanged, the responder rate (50% reduction in migraine attacks) was higher and rescue medication use was significantly lower in the tonabersat group; sub-group analysis for migraine with or without aura was not presented. As a potential confounder, the placebo responder rate was higher than anticipated based on previous trials. The results of a second randomized, double-blind, placebo-controlled crossover trial were more promising in that tonabersat appeared to reduce the number of aura attacks and the number of aura attacks followed by headache [43]. However, there was no significant effect on the number of migraine headache days. Despite failing to achieve improvement in the primary end points, both trials showed strong trends [42,43]. These data suggest congruence between efficacy in experimental SD models and clinical efficacy, although independent confirmation of tonabersat's efficacy on SD and data from larger clinical studies will undoubtedly be more definitive.

Lamotrigine is a potent sodium channel blocker and a glutamate receptor antagonist that suppressed SD experimentally after chronic treatment in one study; efficacy of a single dose has not been tested in this model [18]. Clinical results have been conflicting: two open-label studies reported efficacy on attack frequency [44,45], while the randomized, double-blind, placebo-controlled studies have been negative [46,47]. All studies were based on analysis of a headache diary. In an open-label pilot study, lamotrigine prophylaxis reduced the number of attacks of migraine with aura, but the intensity of pain and duration of headache of residual attacks remained unchanged [44]. In another study, lamotrigine did not reduce migraine attack frequency, which might have been due to a large difference in base-line frequency between active treatment and placebo groups [46]. In a controlled prospective open-label study, lamotrigine decreased aura frequency, duration and symptoms in migraineurs with aura [45]. Moreover, 75% of patients who experienced a reduction in aura frequency also observed a significant decrease in headache. By contrast, a randomized, double-blind, placebo-controlled crossover trial showed no change in attack frequency in migraineurs with or without aura with lamotrigine [47], although a short follow-up (1 month) was a serious limitation. Therefore, although it is possible that, as with tonabersat, lamotrigine is more efficacious in migraine with perceived aura, clinical trials to date have not been conclusive.

Flunarizine is a calcium channel blocker efficacious in migraine prophylaxis [35], and one of the earliest drugs tested on SD. The experimental data were conflicting among studies, presumably because of considerable heterogeneity in experimental designs and potential technical caveats [26-30]. Flunarizine has not been tested in standard SD susceptibility models used today.

Magnesium deficiency may play a role in migraine pathogenesis by increasing neuronal excitability via glutamate receptors. In fact, ionized magnesium levels were reported to be low in more than 50% of migraineurs during attacks, and magnesium replacement reportedly alleviates migraineurs with aura symptoms and photophobia and phonophobia across all migraineurs [48-50]. Consistent with this, systemic administration of magnesium reduces SD frequency induced by topical KCl in rats [51].

The predictive value of experimental models of SD susceptibility for drug efficacy in migraine prophylaxis was further enhanced by screening negative controls; that is, drugs

clinically proven to be ineffective in migraine. For example, oxcarbazepine, conclusively shown to be ineffective in migraine prophylaxis [52], also failed to suppress SD susceptibility either acutely after a single dose or after chronic treatment for 5 weeks [19]. Similarly, *D*-propranolol, which is anecdotally ineffective in migraine, also did not suppress SD, suggesting enantiomer specificity. Riboflavin, a critical cofactor in oxidative metabolism and the generation of energy in the mitochondria [53], did not inhibit SD in rats after prolonged treatment [18]. Data on clinical efficacy of riboflavin on migraine are controversial. Some studies report ineffectiveness [54], while one placebo-controlled trial [55] and one randomized open-label trial [56] documented a migraine-preventive effect when administered at high doses.

Abortive and analgesic drugs efficacious in migraine are unlikely to target SD as their mechanism of action. SD is a brief electrophysiological event lasting minutes and by the time the aura is perceived it is probably too late to pharmacologically interfere owing to pharmacokinetic considerations. Indeed, all abortive drugs tested so far have been ineffective on SD in experimental models (Table 2). Conversely, the SD inhibitor tonabersat has been largely ineffective as an abortive agent in two clinical trials, although once again trial design issues may have confounded the interpretation [40,41]. Nevertheless, it is possible that drugs with mechanisms of action directly interfering with critical events during SD will have a predictable inhibitory effect that develops acutely after a single dose. For example, the NMDA receptor blocker ketamine has been demonstrated to reproducibly reduce the severity and duration of neurological deficits that are manifest during migraine aura in a subset of migraineurs with aura [57]. No doubt the majority of such direct and potent acute SD inhibitors will have unacceptable side effects (e.g., ketamine and the general anesthetic nitrous oxide), and only a handful of drugs will have rapid onset of action and be clinically well tolerated. Such drugs can perhaps be used as 'preemptive abortive drugs' when an attack is predictable; that is, when predisposing circumstances and trigger factors are known.

Gonadal hormones as SD modulators

Migraine occurs more frequently in adult women (18%) than in men (6%), while prevalence is similar in boys and girls (4%) [58,59]. A female preponderance has also been described in FHM and sporadic hemiplegic migraine (female-to-male ratios of 5:2 and 17:4, respectively) [60]. Data suggest that gonadal hormones modulate the genetically determined SD susceptibility and account for the gender differences in the incidence of migraine [61-63]. For example, female FHM type 1 mutant mice are more susceptible to SD when compared with male mice [5], associated with facilitated re-entrant corticosubcortical spread [39]. The sex difference is abolished by oophorectomy and senescence, implicating gonadal hormones rather than sex chromosome-related developmental differences in synaptic organization and structure to explain the SD phenotype. Accordingly, in migraineurs with aura, plasma estrogen concentrations were higher during normal menstrual cycle [64], and the incidence of attacks shows an association with high circulating estrogen levels as seen during ovulation, pregnancy and with certain oral contraceptives [64-67]. Mechanistically, estrogen increases cortical excitability, as has been detected by transcranial magnetic stimulation [68]. Conversely, menopause or oophorectomy improve migraine attack severity and frequency in patients with FHM as well as more common migraine subtypes [69-73]. From a mechanistic standpoint, estrogen has multiple effects on neuronal structure and gene expression that can augment excitability [61-63]. However, menstrual migraine typically occurs during estrogen withdrawal rather than high estrogen levels [74]. An explanation for this apparent paradox could be that during the luteal phase, not only do estrogen levels drop, but other neurotransmitters, such as progesterone, also decline to an even stronger extent. In contrast to estrogen, progesterone exerts an inhibitory effect by increasing the opening time

of GABA_A receptors, as shown in mouse spinal cord neurons [75]. Moreover, menstrual migraine attacks typically occur without aura [76], which could imply that the hormonal changes trigger an attack via a different mechanism than influencing cerebral excitability.

As an additional mechanism to explain the sex difference in migraine susceptibility, testosterone and its synthetic derivatives have been demonstrated to improve migraine in both men and women [77-82]. Observational studies from the early 1950s reported that testosterone decreases both migraine attack frequency and severity starting 4–6 weeks after treatment onset in 90% of female and male patients; this effect was sustained for at least 2 months after treatment cessation [78,80]. More recently, men treated with gonadotrophins for infertility experienced a marked improvement in their migraine with aura attacks [83]. Lastly, in a small cohort of male-to-female transsexuals, anti-androgen therapy increased migraine with aura to female levels [84]. Recent experimental data suggest that an androgenic suppression of SD susceptibility underlies these clinical observations. In FHM type 1 mutant mice, orchiectomy augmented SD susceptibility, which could be prevented by chronic testosterone replacement [77]. Testosterone suppressed SD via androgen receptor-dependent mechanisms, because its effect on SD was prevented by the androgen receptor blocker flutamide. Because chronic testosterone replacement was required to reverse the effects of orchiectomy on SD, changes in gene expression and cellular morphology were likely responsible. In contrast to female hormones, much less is known about the mechanisms of androgenic modulation of excitability [85].

Experimental models of SD susceptibility & caveats

Much of our current understanding of SD mechanisms and migraine comes from animal studies. However, heterogeneity among the studies has hampered data interpretation and reproducibility. Based on our experience, several critical aspects of experimental study design must be highlighted, ranging from the choice of species and anesthesia, to systemic physiological monitoring, methods to trigger and detect SD and drug treatment protocols, to eliminate potential confounders, improve reliability, facilitate comparisons across studies and increase clinical relevance of preclinical findings. In general, *in vitro* studies can be high-throughput but expose the tissue to trauma and hypoxia during preparation, and do not reproduce common clinically relevant pharmacokinetic considerations (e.g., absorption, blood–brain barrier permeability) and physiological factors (e.g., blood flow). They have not been predictive of clinical drug efficacy. We believe *in vivo* experimental models of SD susceptibility are superior for drug screening in migraine prophylaxis. However, systemic physiological parameters (i.e., body temperature, arterial blood pressure, pH, partial pressure of carbon dioxide and partial pressure of oxygen) are critical determinants of SD susceptibility and must be monitored in all *in vivo* studies for drug screening to eliminate the confounding effects of drugs on systemic physiology. Although in theory gyrencephalic species are expected to better represent the human brain, rodents will likely remain the species of choice in drug screening for practical and ethical reasons, notwithstanding the caveats associated with differences in intrinsic SD susceptibility and drug metabolism. Furthermore, mouse studies allow the testing of drugs in genetically modified animals expressing migraine mutations identified in patients. Methods to trigger and detect SD, and SD attributes used as efficacy end points, have also been variable. In our experience, the electrical threshold to induce SDs, and the frequency of SDs evoked by continuous topical KCl application, are the most reliable indicators when recorded electrophysiologically. Certain anesthetics (e.g., ketamine) inherently suppress SD susceptibility, and thus are less suitable for drug screening compared with others (e.g., α -chloralose, urethane and barbiturates) [86-88]. Ideally, the mechanism of action of the chosen anesthetic should not overlap with that of the drug being screened (e.g., barbiturate anesthesia when testing a GABAergic drug). Lastly, universal principles of drug development, such as pharmaco

kinetics, properties of the lead, administration route, and dose–response and treatment duration–response relationships, also apply in migraine drug screening. Of course, investigator blinding and proper selection of placebo as well as positive and negative controls are important quality-control measures. Independent confirmation of efficacy from more than one laboratory or investigative team is a time-tested approach in drug screening.

Expert commentary

Until recently, drug discovery in migraine has been serendipitous. A large body of data has accumulated implicating SD as a critical pathophysiological step and a potential therapeutic target in migraine, upstream to the nociceptive pathways [2]. Research so far has revealed strong congruence between clinical efficacy in migraine prophylaxis, particularly with aura, and preclinical suppression of SD susceptibility, endorsing the latter as a predictive drug screening tool. However, major issues remain in proper design and conduct of preclinical drug screening in SD susceptibility models, some of which are alluded to above. Equally important in drug development is proper clinical trial design and this too needs improvement based on lessons learned from past trials [89]. Not to be forgotten is the fact that migraine is a heterogeneous headache disorder, and as such, it probably has multiple independent triggers with some pathophysiological overlap. Therefore, it is unlikely that a single experimental model such as SD faithfully represents the entire spectrum of migraine disorder. This, however, does not diminish the utility of SD susceptibility as a screening tool, even if it is relevant for only a subset of migraineurs, particularly because most prophylactic drugs that suppress SD appear to be equally efficacious on migraine with and without aura.

Five-year view

Future studies, particularly independent confirmation of existing data, will undoubtedly build confidence in experimental models of SD susceptibility, highlight certain models among others and help refine them for universal use. At the same time, new clinical trial data will provide further substrate for more rigorous assessment of the negative and positive predictive value of such models. Better understanding of the cellular mechanisms initiating and sustaining SD (e.g., channels and energetics) will also help guide rational and targeted drug design. As a novel avenue of investigation, quantitative assessment of SD susceptibility not only allows the investigation of drugs but also of lifestyle changes (e.g., stress, diet and obesity, exercise and sleep hygiene) that clearly modulate migraine susceptibility in the clinical setting. There is strong evidence for enhanced, often genetic, cortical excitability in migraineurs as one mechanism of their susceptibility to migraine [90, 91]. However, preclinical drug testing has exclusively been carried out in normal (i.e., wild-type) animals. Therefore, it will be important to extend drug testing to genetically engineered mouse models expressing human migraine mutations [5,6], since some drugs may show selective efficacy on genetically enhanced SD susceptibility. Lastly, spreading depolarization waves akin to SD occur in brain injury states such as trauma, stroke and subarachnoid hemorrhage, and worsen tissue and neurological outcome [92–94]. Therefore, research into SD inhibitors is also expected to have collateral impact on other brain disorders.

Acknowledgments

Financial & competing interests disclosure

This work was in part supported by the NIH (NS061505), Harvard Catalyst – The Harvard Clinical and Translational Science Center (NIH Award #UL1 RR 025758 and financial contributions from Harvard University and its affiliated academic healthcare centers) and American Heart Association (SDG 2610275). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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Key issues

- Spreading depression (SD) is the electrophysiological event underlying migraine aura and a trigger for headache.
- Drugs clinically efficacious in migraine prophylaxis suppress SD as a common mechanism of action.
- Experimental models of SD susceptibility show promise as preclinical drug screening assays in migraine prophylaxis.
- Gonadal hormones that modulate migraine susceptibility also modulate SD susceptibility in the same direction.
- Standardization of SD susceptibility testing will facilitate drug screening.

Figure 1.
The timeline of publications about migraine drug effects on spreading depression.

Table 1
Studies testing the efficacy of migraine prophylactic drugs on spreading depression

Drug	Species	Monitor	Dose (mg/kg/day), route	Duration of pretreatment	Trigger	Susceptibility	Speed	Dur	Amp	Ref.
Valproate	Cat	LDF + SUA	3.5–7, iv.	60 min	Mech	↔	↔	ND	ND	[17]
	Rat	DC	200, ip.	1 week	Elec, KCl	↔	↔	↔	↔	[10]
			25–200, ip.	≥4 weeks	Elec, KCl	↓	↓	↔	↔	[10]
			200, ip.	4 weeks	KCl	↓	↓	ND	↔	[18]
			200, iv.	60 min	Elec, KCl	↔	↔	↔	↔	[19]
Lamotrigine	Rat	DC	200, ip.	5 weeks	Elec, KCl	↓	↓	↑	↔	[19]
			15, ip.	4 weeks	KCl	↓	↔	ND	↓	[18]
			100–200, iv.	60 min	Elec, KCl	↓	↔	↔	↔	[20]
			50, p.o., b.i.d.	5 weeks	Elec, KCl	↔	↔	↔	↔	[20]
			30, iv.	30 min	Mech	↓	↔	↔	↔	[21]
Topiramate	Rat	DC	80, ip.	1 week	Elec, KCl	↔	↔	↔	↔	[10]
			60–80, ip.	≥4 weeks	Elec, KCl	↓	↓	↔	↔	[10]
Tonabersat	Cat	DC	3–10, ip.	90 min	KCl	↓	ND	↔	↔	[22]
	Cat	DC	3–10, ip.	90 min	KCl	↓	ND	↔	↔	[23]
	Cat	MRI	10, ip.	90 min	KCl	↓	↑	↓	ND	[24]
	Rat	DC	10, ip.	90 min	KCl	↓	ND	ND	ND	[25]
Flunarizine	Rat	DC	20–40, ip.	105 min	Elec	↔	ND	↔	↔	[26]
			20, p.o., b.i.d.	36 h	Elec	↔	ND	↓	↔	[26]
			20, p.o.	5 days	Mech	↔	↔	ND	↔	[27]
			30, p.o. + 10, ip.	1 days	Mech, Elec	↓	ND	ND	ND	[28]
			40, ip.	60 min	Mech	↓	ND	ND	ND	[29]
DL-propranolol	Rat	DC	10–20, ip.	105 min	Elec	↔	ND	↓	ND	[30]
			20, p.o. b.i.d.	36 h	KCl	↓	ND	↓	ND	[30]
			20, ip.	105 min	Elec	↔	ND	↔	↔	[26]

Drug	Species	Monitor	Dose (mg/kg/day), route	Duration of pretreatment	Trigger	Susceptibility	Speed	Dur	Amp	Ref.
D-propranolol	Rat	DC	20, p.o. b.i.d.	5 days	Mech	↔	↔	ND	↔	[27]
			20, ip.	60 min	Elec, KCl	↔	↔	↔	↔	[10]
			20, ip.	≥4 weeks	Elec, KCl	↓	↓	↔	↔	[10]
D-propranolol	Rat	DC	20, ip.	≥4 weeks	KCl	↔	↔	↔	↔	[10]
Oxcarbazepine	Rat	DC	200, p.o.	90 min	Elec, KCl	↔	↔	↔	↔	[19]
			100, p.o.	5 weeks	Elec, KCl	↔	↔	↔	↔	[19]
Metoprolol	Cat	LDF + SUA	25, iv.	60 min	Mech	↔	↔	ND	N	[17]
Clonidine	Rat	DC	1.25–10, ip.	105 min	Elec	↔	ND	↔	↔	[26]
Methysergide	Rat	DC	10, ip.	105 min	Elec	↔	ND	↔	↔	[26]
			10, p.o.	5 days	Mech	↔	↔	ND	↔	[27]
			0.1–1, ip.	≥6 weeks	KCl	↓	↔	↔	↔	[10]
Pizotifen	Rat	DC	10, ip.	105 min	Elec	↔	ND	↔	↔	[26]
Amitriptyline	Rat	DC	20, ip.	60 min	Elec, KCl	↔	↔	↔	↔	[10]
			10–20, ip.	≥4 weeks	Elec, KCl	↓	↓	↔	↔	[10]
Fluoxetine	Rat	DC	10–40, sc.	≥25 days	KCl	ND	↓	↔	↔	[31]
Citalopram	Rat	DC	20, ip.	1 week	KCl	ND	↓	↔	↔	[32]
Riboflavin	Rat	DC	10, ip.	4 weeks	KCl	↔	↔	ND	↔	[18]

↔: No change; ↑: Increase; ↓: Decrease; Amp: Spreading depression amplitude; b.i.d.: Twice a day; DC: Direct current recordings; Dur: Spreading depression duration; Elec: Cathodal stimulation; ip.: Intraperitoneal; iv.: Intravenous; KCl: Potassium chloride stimulation; LDF: Laser Doppler flowmetry; Mech: Mechanical stimulation; ND: Not determined; p.o.: Oral; sc.: Subcutaneous; SUA: Single unit activity.

Adapted from [16].

Table 2
Studies testing the efficacy of migraine abortive and analgesic drugs on spreading depression

Drug	Species	Monitor	Dose (mg/kg), route	Pretreatment (min)	Trigger	Susceptibility	Speed	Dur	Amp	Ref.
Sumatriptan	Cat	MRI	0.3, iv.	15	KCl	↔	↔	↔	ND	[24]
	Cat, rat	DC	0.3, iv.	15	KCl	↔	ND	ND	↔	[33]
	Rat	DC	0.3, iv.	30	KCl	↔	ND	↓	↔	[34]
	Rat	DC	0.3, iv.	15	KCl	↔	ND	ND	ND	[25]
Dihydroergotamine	Cat	LDF + SUA	15, iv.	60	Mech	ND	↔	ND	ND	[17]
Ergotamine	Rat	DC	0.31–20, ip.	105	Elec	↔	ND	↑	↔	[26]
Acetylsalicylic acid	Cat	LDF + SUA	30, iv.	60	Mech	ND	↔	ND	ND	[17]
Lignocaine	Cat	LDF + SUA	5, iv.	60	Mech	ND	↔	ND	ND	[17]

↔: No change; ↑: Increase; ↓: Decrease; Amp: Spreading depression amplitude; DC: Direct current recordings; Dur: Spreading depression duration; Elec: Cathodal stimulation; ip: Intraperitoneal; iv.: Intravenous; KCl: Potassium chloride stimulation; LDF: Laser Doppler flowmetry; Mech: Mechanical stimulation; ND: Not determined; SUA: Single unit activity.
Adapted from [16].

Table 3
Summary of migraine drug efficacy on spreading depression susceptibility

Drug	Effect on SD [†]		Clinical efficacy in migraine	
	≤7 days treatment	≥4 weeks treatment	With aura	Without aura
Valproate	↔ (2)	↓ (2)	+	+
DL-propranolol	↔ (3)	↓ (1)	+	+
Methysergide	↔ (2)	↓ (1)	+	+
Amitriptyline	↔ (1)	↓ (1)	+	+
Topiramate	↔ (1) / ↓ (1)	↓ (1)	+	+
Gabapentin	↓ (1)	ND	+	+
Tonabersat	↓ (1)	ND	+/- [‡]	
Lamotrigine	ND	↓ (1)	+/- [‡]	
Flunarizine	↔ (1) / ↓ (1)	ND	+	+
Oxcarbazepine	↔ (1)	↔ (1)	-	
D-propranolol	↔ (1)	↔ (1)	-	
Riboflavin	↓	↔ (1)	+/- [‡]	
Metoprolol	↔ (1)	ND	-	
Clonidine	↔ (1)	ND	+/- [‡]	
Pizotifen	↔ (1)	ND	-	
Sumatriptan	↔ (2)	ND	-	
Ergotamine	↔ (1)	ND	-	

↔: No change; ↓: Decrease; ND: Not determined; SD: Spreading depression.

[†] Numbers indicate the number of independent laboratories from which the data were obtained.

[‡] Inconclusive.