Review Article

JCBFM

Journal of Cerebral Blood Flow & Metabolism
2018, Vol. 38(7) 1149–1179

DOI: 10.1177/0271678X18771440
journals.sagepub.com/home/jcbfm
SAGE

Systematic review of the pharmacological agents that have been tested against spreading depolarizations

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Abstract

Spreading depolarization (SD) occurs alongside brain injuries and it can lead to neuronal damage. Therefore, pharmacological modulation of SD can constitute a therapeutic approach to reduce its detrimental effects and to improve the clinical outcome of patients. The major objective of this article was to produce a systematic review of all the drugs that have been tested against SD. Of the substances that have been examined, most have been shown to modulate certain SD characteristics. Only a few have succeeded in significantly inhibiting SD. We present a variety of strategies that have been proposed to overcome the notorious harmfulness and pharmacoresistance of SD. Information on clinically used anesthetic, sedative, hypnotic agents, anti-migraine drugs, anticonvulsants and various other substances have been compiled and reviewed with respect to the efficacy against SD, in order to answer the question of whether a drug at safe doses could be of therapeutic use against SD in humans.

Keywords

AMPA receptor, GABA receptor, neurovascular coupling, NMDA receptor, pharmacology, spreading depolarization

Received 4 December 2017; Revised 11 March 2018; Accepted 23 March 2018

Introduction

Spreading depolarization (SD) is a massive depolarization wave of neuronal and glial cells that propagates at a rate of 2–9 mm/min through cerebral gray matter.[1] It is characterized by the abruptly developing, near-complete, and sustained breakdown of transmembrane ion gradients, neurotransmitter release, increased energy metabolism, water shifts, and depression of electrical activity. Today, there is enough evidence showing the presence of SD in migraine with aura (MA). SDs also occur in cerebrovascular diseases such as stroke, subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), and intracerebral hemorrhage (ICH). In these conditions, SD occurrence has been associated with neuronal damage, necrosis, degeneration, and poor clinical outcome.[2–4] The pathological effects of SD can be in part explained due to its impact on cerebral hemodynamics that produce a cycle of events that have a cumulative effect progressively increasing the degree and spatial extend of ischemia. It is well known that SDs in a healthy, adequately supplied tissue has only slightly damaging, innocuous effects.[5–12] In contrast, when neurovascular coupling is impaired or the tissue is inadequately perfused, SD promotes spreading ischemia, excitotoxicity, oxidative stress, worsen hypoxia and neuronal death, therefore, having a negative impact on clinical outcome.[13]

In the clinical setting, the therapeutic modulation of SD has gained expectations. Pharmacological targeting of SD in the clinic is still in its infancy. Several experimental studies indicate that SD can be modulated by drugs. According to these observations, pharmacological modulation of SD in the clinical setting as a neuroprotective therapy could be feasible. In this article, we focus on the pharmacological agents that have been used against SDs. It is a systematic presentation, classification, and evaluation of drugs that have been tested against SD (Figure 1). After an exhaustive search, we found 114 substances whose therapeutic

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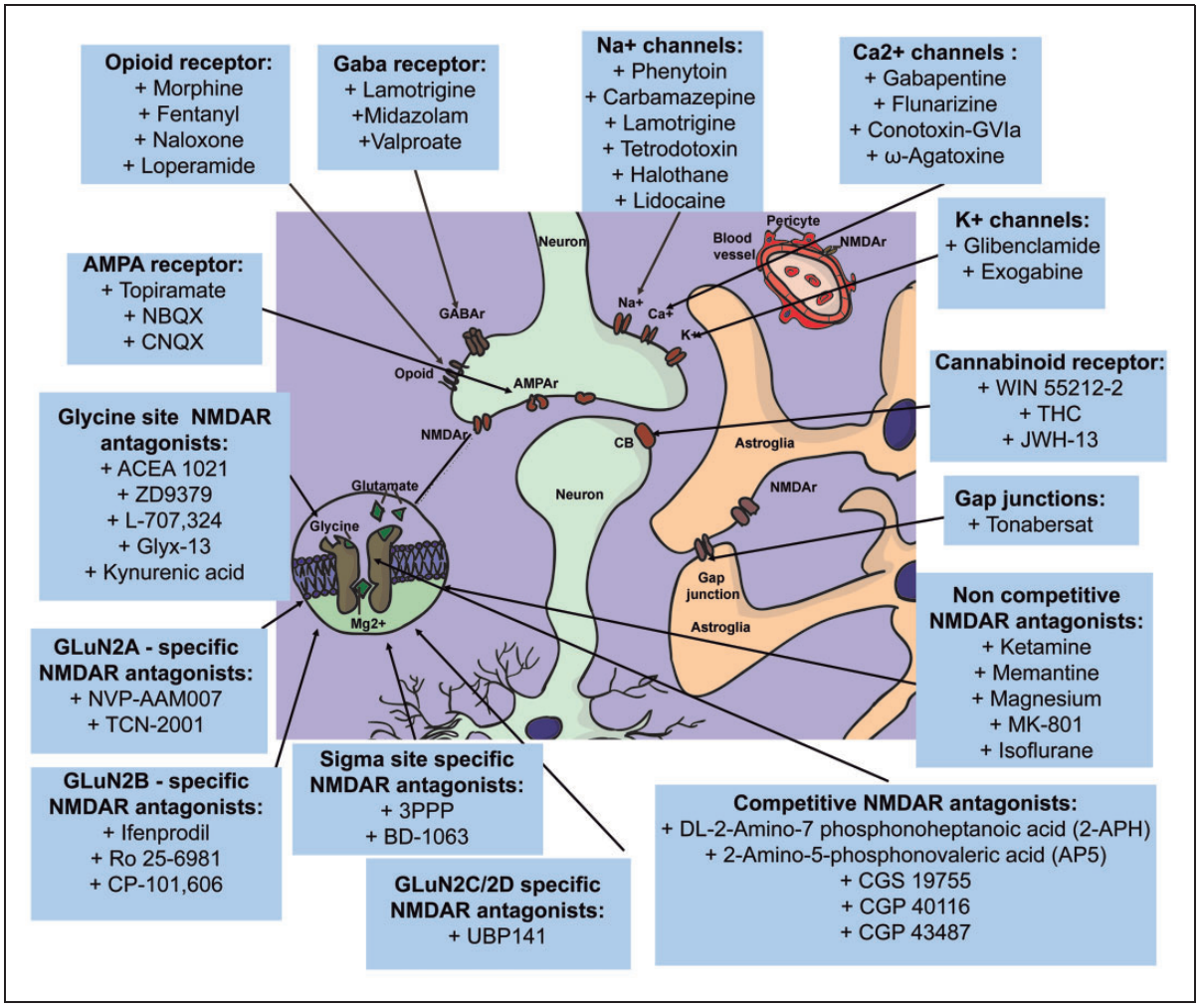

Figure 1. Various target points play a role in the antagonization of SDs. Among others, NMDA-, GABA-, opioid-, AMPA, and cannabinoid receptors. Moreover, a variety of channels is involved. These channels can be found on neurons, astrocytes, and pericytes. Most substances antagonize SD via a complex machinery that involves multiple of these target points. Substances in the figure are assigned to a target point which they are mostly associated with.

effect on SD has been investigated, either individually or in direct comparison with each other. We give as part of the introductory segment a brief overview of the relevant aspects of the physiopathology of this phenomenon, followed by the clinical implication in neurological diseases before approaching our main topic. For a more comprehensive and vast description of the cellular and molecular mechanisms and the clinical role of SDs, we refer to the following reviews.[2–4,13–16]

Relevant aspects of the physiopathology of spreading depolarizations

Physiologically, SD corresponds to a self-propagating wave-front of depolarization with neuronal and glial cell implication. It can be accompanied by depression of the electrocorticography (ECoG) activity of a fast negative potential changes, and it usually spreads at a characteristic speed of 2–9 mm/min,[1] and resolves after 5–15 min.[14,15]

Underlying the depolarization, there is a breakdown of ion gradients, such as K^+ and H^+ increases and Na^+, Ca^{2+}, and Cl^- decreases. This ionic interchange favors neuronal swelling and dendrite distortion. There are also pH changes – extracellular pH becomes first alkaline and then acidic. The acidosis is associated with the production of CO_2 and lactic acid by a pronounced oxygen and glucose consumption related to the increased metabolism, which is necessary to restore the ion homeostasis through the activation of Na^+/K^+-ATPase and Ca^{2+} pumps.[14–16] SD also induces the release of neurotransmitters into the extracellular space such as glutamate, which activates NMDA,

AMPA, or kainate receptors that can lead to excitotoxicity and cellular damage.[14–16]

SDs can be elicited by a variety of stimulus such as high-frequency electrical pulses, direct current, mechanical stimulation, basicity, hypo-osmolarity, hyperthermia, hypoxia, hyperkalemia, and hypoglycemia, and a variety of chemical agents, such as K^+ and glutamate,[13,15] hypotonic exposure,[17] and edothelin-1.[18] The mechanisms of SD induction and propagation in different pathological situations is unclear. The two most important hypotheses are based on extracellular K^+ and glutamate diffusion mechanisms versus intracellular propagating agents (including K^+ and Ca^{2+}) through gap junctions.[15,19]

The mechanisms underlying the cerebral hemodynamic responses to SD are not fully understood. SD is associated with increases in energy metabolism that require large increases in regional cerebral blood flow (rCBF). This reaction corresponds to a normal vascular coupling which describes the increase in rCBF supply in response to physiological neuronal activation and the reduction of rCBF with neuronal deactivation. SD has been associated with increments of more than 100% of rCBF, known as spreading hyperemia. However, a brief reduction of rCBF and/or a sustained suppression of rCBF known as spreading oligemia has been detected following the hyperemic response.[20,21]

In pathological conditions, SD exerts drastic hemodynamic changes. Under hypoxic circumstances, SD can induce an inverse neurovascular coupling, consisting of a prolonged and intense hypoperfusion, also known as spreading ischemia.[13–15] The shift from spreading hyperemia to spreading ischemia can be triggered by the decrease in NO availability together with the increase of K^+ concentrations. Therefore, during pathological conditions, spreading ischemia can render neural tissue vulnerable to secondary damage up to the development of widespread necrosis.[22]

Clinical implication of spreading depolarizations

Occurrence of SD in the human brain and its role in the pathophysiological basis of several neurological conditions have been addressed in the clinical sciences. There is sufficient evidence showing that SD has an important role in different neurovascular conditions such as stroke, SAH, TBI, and ICH.[2–4] A relation between SDs and MA has also been well documented.[23] Different mechanisms for SD development after these conditions have been postulated.

Several studies indicate the association between SD occurrence and functional neuronal damage, neurological degeneration, and poor clinical outcome. The deleterious effects in patients after brain injury have been related with the drastic hemodynamic changes to SD.[2,13,24–26] We briefly review the impact of SD on different cerebrovascular diseases and MA.

Subarachnoid hemorrhage

SAH as a consequence of aneurismal rupture is a common condition frequently leading to poor outcome and death. Delayed cerebral ischemia (DCI) constitutes the most important cause of morbidity and mortality after SAH. A link between SD and SAH has been established in a plethora of studies.[27–29] In this regard, the incidence of SD in SAH has been reported in more than 70% and has been related to the development of DCI.[27,28] It is believed that increases in basal K^+ attributable to erythrocytolysis, blood clot hemolytic products and decrease of N^+ pump activity (due to vasospasm of cerebral arteries) are triggering factors for SD initiation.[13,30]

The major morphological and pathological impact that SDs have in patients with SAH is a decrease in the flow of oxygen and nutrients to metabolically active neurons and a dysbalance of vasoconstrictor and vasodilator agents.[31] Therefore, when appearing as clusters may lead to delayed neurological deficits and development of new infarcts.[27,28] Spreading ischemia has been well detected in patients with aneurysmal SAH and DCI.[27,28]

In this scenario, factors such as reduction of rCBF, microcirculatory dysfunction, microthrombosis, and hemolytic blood products may provide an important source of SDs leading to spreading ischemia and cortical infarction.[13,32] This speaks in favor of SDs as an etiological factor that may contribute to the development of DCI. Therefore, the pharmacological modulation of SDs in SAH may lead to reduction of secondary brain damage and DCI development, resulting in an improvement of patients' outcome.

Traumatic brain injury

Evidence of the development of SDs after TBI has been well supported in different studies. In TBI patients, SD has been registered between 50 and 60% and seems to increase its incidence with lower levels of mean arterial pressure and cerebral perfusion pressure.[26,33] Hypotension, hypoperfusion, and hyperthermia occur commonly in the clinical setting of TBI; they constitute potential triggers of SD.[34] Recently, Hinzman et al.[35] showed the presence of inverse neurovascular coupling to SD in a group of 24 patients who were subjected to craniotomy after severe TBI. Supporting the association between SD, spreading ischemia and the exacerbation of brain injury after TBI,[35] therefore, the major pathological impact that SD has in TBI patients is

probably the mismatch of energy supply-demand and a lower perfusion.[34] As a result, SDs in TBI contribute to lesion expansion and promote effects of secondary insults that often accompany TBI. In consequence, the control of SDs after TBI might be used to guide the therapeutic decision making in each patient.

Stroke

After an ischemic insult, the presence of SD has been reported in up to 100% of the patients; they arise from the edge of the ischemic core and propagate through the penumbra area.[36] The number and duration of SDs after ischemic brain lesions has shown to have a correlation with secondary neuronal damage and further infarct expansion.[22] And Also, it has been postulated that SDs are the underlying mechanism of cytotoxic edema in grey matter.[13] A plethora of evidence validates the notion of SD as a pathological mechanism leading to secondary damage after stroke.[37,38] Ischemia-mediated breakdown of ionic homeostasis is thought to initiate the SD ignition.[13] It also has been shown how the supply-demand oxygen-transients mismatch after somatosensory activation of peri-infarct cortex is capable to trigger SDs due to an increase demand or reduced oxygen supply, showing an adverse effect on ischemic tissue outcome.[39]

The high incidence of SD after stroke and the deleterious consequences points out the relevance of SD therapeutic modulation after an ischemic event in order to reduce the infarct growth. This is in particular challenging, due to the experimental data, indicating that the induced disruption can outweigh the effect of the therapeutic drug (e.g., an NMDA receptor antagonist), and SDs might still occur.[40] Nevertheless, the drug might still be very efficacious in the peri-ischemic penumbra. Here, an antagonization of SD could hypothetically unction as a preconditioning and even promote regeneration and plasticity.[22,41]

Intracerebral hemorrhage

ICH is a severe disease with high ICU mortality and morbidity[42] and perihematomal edema progression strongly contributes to neurological deterioration and worse outcome.[43] SD has been detected in patients with ICH,[24] and it is hypothesized to contribute to the lesion development, although it is not fully clear to which degree.[2] Firstly, Fabricius et al. observed SD in two out five patients with ICH,[24] and recently, a prospective observational trial by Helbok et al. recorded SD in a cohort of poor grade ICH patients in whom hematoma evacuation was performed.[44] Helbok et al. reported the highest SD incidence rate in humans with ICH so far (67%). An increasing hemorrhage volume in ICH is thought to increase the risk of SDs through the extracellular accumulation of K^+.[44] Since SD facilitates dendritic beading, neuronal swelling, and cytotoxic edema, SD might aggravate or even induce edema formation in the perihematomal brain tissue of ICH patients.[44] A therapeutic approach of SD might decrease SD edema expansion.

Migraine with aura

It has been suggested that SDs are responsible for MA in the human visual cortex by showing a retinotopic visual percept induced by SD during aura[45] supported by MRI-BOLD studies[46] and various animal models.[47–49] There is evidence that SD activates the trigeminovascular system, hence provoking headache.[50] In patients with MA, episodic dysbalance of excitation and inhibition and a hyperactivity of cortical circuits have been proposed as a trigger of SDs.[51] Even though MA is usually injurious and not associated with neuronal damage, spreading ischemia is hypothesized to be the underlying mechanism of migrainous stroke.[13] The pharmacological modulation of SDs in MA can serve as a translational therapeutic model to other pathological settings.

Pharmacological targeting of SD

Today, an overwhelming body of evidence supports the concept that prevention of SD or containment of its expansion means less brain damage and is thus of the highest clinical relevance. Treating SD could improve functional outcome. An ideal treatment strategy for SD would have the potential for a pleiotropic effect by positively modulating several of the implicated pathophysiological mechanisms at once. However, energy-depleted tissue complicates the therapeutic targeting that there are still only a few targets that can be successfully addressed by drugs.

Various strategies have been proposed against SD, among them (1) blocking SD initiation, (2) modulating of SD propagation, (3) reduction of SD amplitude, (4) deceleration of SD progression, (5) reduction of SD hemodynamic response, and (6) reversal of the inverse response. All of this can be achieved by addressing various target points, such as NMDA, GABA, AMPA, or opioid receptors and many more. The most effective substances that are applied in humans are ketamine and valproate (Table 1). An antagonism of inverse coupling has been achieved by vasodilators. A partial antagonist effect of adenosine, by shortening of the hypoperfusion, has been observed in SD in rodents.[52]

While the present review focuses on pharmacological substances that inhibit SD, there are some additional strategies that have been investigated but will not be

Table 1. Summary of results.

Most effective agents against SD	Number	Amplitude	Propagation	Threshold	Duration	Frequency	
NMDAR antagonist (clinically used)	Ketamine	↓	↓	↓	↑	↓	↓
	Memantine	↓	↓	↓			
NMDAR antagonist (animals only)	MK-801	↓	↓	↓	↑	↓	↓
Anesthetic agents	Isoflurane	↓	=	↓	=	=	↓
	Sevoflurane	=	=	=	=	=	↓
Anti-migraine drugs	Valproate	↓	↓	=	↑	=	↓
	Topiramate	↓	=	↓	↑	↓	↓

"↓" Means a reductive effect was observed after drug administration, "=" means no effect was noticed, and blank space means the parameter was not tested, "↑" means that the examined parameter was increased after drug administration. Typical parameters under investigation are number, amplitude, propagation, threshold, duration, and frequency. Experimental settings and models are heterogeneous, comprising different animals (chicken, rat, cat, mouse, and swine) and various forms of SD induction (KCl and electrical stimulation). Among the most effective drugs are ketamine, MK-801, and topiramate.

addressed in depth. Hyperglycemia has been associated with a lower incidence of SD.[53,54] Moreover, in experiments with KCl-induced SD, hypoglycemia was shown to prolong the SD but had no effect on amplitude, incidence, or propagation.[55] Hyperoxia has been shown to inhibit SD.[56,57] Recently, transcutaneous vagus stimulation has been shown to be efficacious in reducing the susceptibility to KCl and electrically induced SD.[58]

Methods

Although the treatment of SD is of high clinical importance, it is underreported in medical literature; the present review focused on the following answerable questions: (A) "Which drugs have been tested against SD in vivo and in vitro?" (B) "How efficient are they in reducing incidence and characteristic features of SD?" and (C) "Is a translation into clinical practice feasible or imaginable?" The search for evidence was performed in three databases: PubMed, Science Direct, and Web of Science. The search terms included variations on the condition ("spreading depression, spreading depolarization, cortical depression, anoxic depolarizations, peri-infarct depolarizations") combined with treatment-related terms ("prevention, treatment, effect, reduction, inhibition, therapy") and specific target points ("NMDA-, AMPA-, GABA-, opioid, serotonin-receptor, anesthetic, sedative, hypnotic, analgesic agents"). The search was limited to the English language and publications from January 1986 to the present (September 2017). For more details on the strategies used for each database, please contact the authors. The main inclusion and exclusion criteria (language and date) were applied during the screening of the titles and abstracts, whereas the other criteria (experiment type and animal) were addressed in full text review. A total of 138 articles were selected for full text review. Of these, 132 articles were selected for final inclusion. Various strategies have been proposed to target and modulate SD. The properties of SD that have been targeted are the number, amplitude, propagation, threshold, duration, frequency, and hemodynamic response. Only articles that investigated a drug's effect on number, amplitude, propagation, threshold, duration, frequency, and pial diameter were selected for analysis.

Substances

NMDA receptor antagonists/agonists

NMDA receptor is the target of the most potent inhibitors of SD. We therefore discuss its pathophysiologic role as well as some representative agents.

The NMDA receptor is a heterotetrameric ionotropic glutamate receptor, and expression studies indicate that the functional receptor is composed of at least one NR1 subunit and one or more NR2 subunits.[59,60] The highest affinity endogenous ligands of its agonist binding site are L-glutamate and aspartate.[61,62] The NMDA receptor controls a non-selective cation channel (with permeability for Na^+, K^+, and Ca^{2+} ions) that is gated by Mg^{2+} in a voltage-dependent manner. In its activated state, this channel can be blocked by various competitive, non-competitive, and glycine site-specific antagonists as well as others. Thus, NMDA receptor antagonists such as ketamine can interfere with SD initiation and expansion by increasing the threshold for K^+ and neurotransmitters, and its duration by reducing the influx of Na^+ and Ca^{2+}.[63] The NMDA receptor has been hypothesized to play a definitive role in neurodegenerative conditions, neuronal death, and various brain disorders.[64–68]

Failure of NMDA receptor antagonists in clinical trials

The concept of glutamate-induced excitotoxicity served as rationale for the integration of NMDA receptor

antagonists into human trials. Although experimental studies have widely shown that the pharmacological blockade of ionotropic glutamate receptors reduces ischemic damage, clinical trials with classical AMPA and NMDA glutamate receptor antagonists have provided negative results.[69–71] The main factors that are hypothesized to cause this failure are:[72–74]

- Quality of the molecules (pharmacokinetic deficiencies, inability to reach effective concentrations in the penumbra, shot neuroprotective time window, inappropriate receptor subunit selectivity, high drug toxicity in humans.[75]
- Inequivalent doses compared to rodents[75]
- Development of tolerance,[12] for example, upregulation of NMDAr
- Side effects, among others, blocking of normal synaptic NMDA activity that promotes neuronal survival[76] and blocking of neurogenesis at different stages of recovery.[75,77,78]
- Administration of NMDAr antagonists at a critical period after brain trauma exacerbates brain damage[78]
- Bad design of clinical trials

It is important to recognize that the relationship of the dose to produce inhibition of SD in humans is still unknown for those substances, and the effect on SD was not monitored in those studies. At that time, there was no certain evidence that SDs occurred in humans.

Therapeutic use of NMDA receptor antagonists might be a balancing act. It is known that NMDA receptor play a role in the recovery and neuroplasticity after brain injury.[79–84] For example, >40 mg/kg/h s-ketamine inhibited ischemia-induced-neurogenesis,[85] but the doses tested in that laboratory study in rodents are approximately 10 times the magnitude of the doses used in humans. Long time therapy and high doses of NMDA receptor blocking may at some point interfere with the recovery of brain functions. For example, NMDA receptor agonist in a late phase after stroke facilitated recovery in rats.[79]

One possible approach to modulating the NMDA receptor-mediated synaptic transmission in pathological conditions is to do so without altering the physiological excitatory transmission. For instance, Ifenprodil and its analogs block NMDA receptors in a voltage-independent manner without causing a significant reduction in the agonist potency. Ifenprodil's pharmacological profile includes the ability to increase the potency of ambient protons to block the NMDA receptors.[86] Since ischemic tissue is characterized by a reduction of pH (at approximately 6.5),[87] it has been hypothesized that because Ifenprodil acts on the proton sensors, it may represent a means of optimizing the design of a new class of neuroprotectants that would target the NMDA receptor only in the pathological condition but not in physiological conditions. This is just one example of potential "loopholes" in the problem of the NMDA receptor.

A total of 42 articles that described tests of NMDA receptor agents were identified. These articles examined 24 NMDA receptor antagonists with respect to their efficacy in modulating or possibly even blocking the initiation, propagation, velocity, threshold, amplitude, and duration of spreading depolarizations (Table 2). The following NMDA receptor antagonists among others have received scrutiny: ketamine, Mk-801, phencyclidin, memantine, Glyx-13, NVP-AAM077, TCN 201, and Ro 25-698. Although most of these substances have been proven to modulate some of the characteristics of SD, only few can inhibit the induction of SD, for instance ketamine and MK-801.

Table 2 provides the insight that NMDA receptor is a key contributor to the propagation and initiation of spreading depolarizations and hence a potent target in the treatment of SDs. At the same time, NMDAr antagonism has so far not been successfully translated into clinical neuroprotection. More precisely, the table reveals that the number of SD is the most successful target (as evidenced in 36 articles),[12,40,41,62,63,66–68,88–117] whereas an inhibitory effect on amplitude has only been described in nine articles.[62,89,90,93,105,107,109,110,114] The threshold has only been under scrutiny in experiments, in which SD is electrically induced and was successfully increased in all of them.[63,91,97,118]

Ketamine. Resting on the premise that ketamine noncompetitively blocks the NMDA receptor and thus restricts the perimembranous cation flow thereby influencing SD, many randomized blinded experiments in vivo and in vitro have been conducted that have successfully demonstrated ketamine's potency. Effective dosages to affect SD incidence range from 2 mg/kg/h to 200 mg/kg/h.[12,66]

Marrannes et al. demonstrated that ketamine causes a significant dose-dependent reduction of electrically induced SD in alfentanil-anesthetized adult rats. At a dose of 40 mg/kg, ketamine increased the SD threshold, decreased the propagation velocity, and decreased the duration of the accompanying extracellular DC, K^+, and Ca^{2+} changes. At 80 mg/kg, the elicitation of SD was completely inhibited.[63] Amemori and Bures found that ketamine at a dose of 100 mg/kg blocked the occurrence of SD in rats, but the blockade induced by subsequent ketamine injections weakened and finally disappeared.[12] Rashidy-Pour et al.[62] observed a similar outcome. Ketamine at 50 mg/kg indeed blocked the elicitation of SD. The blockade by the first ketamine

Table 2. NMDA receptor antagonists.

Drug	Reference	Species	Type	SD induction	Dosage	Results					
						Number	Amplitude	Propagation	Threshold	Duration	Frequency
Main NMDA receptor antagonists (commonly used, well known substances)											
Ketamine	Hernández-Cáceres et al.[40]	Rat	In vivo	CH3CO2K	6.25/12.5/25/50/100 mg/kg/day ip.	↓	=	↓			
Ketamine	Gorelova et al.[164]	Rat	In vivo	CH3CO2K	50 mg/kg ip.			↓			
Ketamine	Marrannes et al.[63]	Rat	In vivo	Electrical	10/40/80 mg/kg/day ip.	↓	=	↓	↑	↓	
Ketamine	Amemori and Bures[12]	Rat	In vivo	CH3CO2K	200 mg/kg ip. + 3 × 100 mg/kg/h	↓	↑				
Ketamine	Verhaegen et al.[118]	Rat	In vivo	Electrical	50 mg/kg iv.			↓	↑		
Ketamine	Martin et al.[88]	Rat	In vivo	Electrical	50 mg/kg ip.	↓		↓			
Ketamine	Rashidy-Pour et al.[62]	Rat	In vivo	KCl	5 × 50 mg/kg ip.	↓	↓	↓			
Ketamine	Krüger et al.[89]	Rat	In vitro	KCl	100 μM	↓	↓			↓	
Ketamine	Sakowitz et al.[66]	Humans	Case report	Brain injury	2–3 mg/kg/h iv.	↓					
Ketamine	Hertle et al.[41]	Humans	Retrospective analysis	Brain injury	200 mg	↓					
Ketamine	Sanchez-Porrás et al.[90]	Swine	In vivo	KCl	2/4 mg/kg/h iv.	↓	↓	↓		↓	
Ketamine	Schiefecker et al.[68]	Humans	Case report	ICH	100 mg/h iv.	↓					
Ketamine	Hertle et al.[67]	Humans	Retrospective analysis	Brain injury	100–300 mg/h iv.	↓					
MK-801	Lauritzen and Hansen[91]	Rat	In vivo	Electrical	3/12 mg/kg	↓	=		↑		
MK-801	Nellgard and Wieloch[92]	Rat	In vivo	Mechanical	Injection of 0.1 mg/kg ip.	↓					
MK-801	Gill et al.[93]	Rat	In vivo	MCAO	Injection of 3 mg/kg ip.	↓	↓			↓	
MK-801	Willette et al.[94]	Rat	In vivo	KCl	Injection of 0.3/1/3 mg/kg iv.	↓		↓			
MK-801	Rashidy-Pour et al.[62]	Rat	In vivo	KCl	Injection of 2.5 mg/kg ip.	↓		↓			
MK-801	Obrenovitch and Zilkha[95]	Rat	In vivo	K^+	Injection of 1 mg/kg iv.	↓		↓			
MK-801	Miettinen et al.[96]	Rat	In vivo	KCl	Injection of 3 mg/kg ip.	↓		↓			
MK-801	Marrannes et al.[97]	Rat	In vivo	Electrical	3.1 mg/kg	↓	=	↓	↑		
MK-801	Koroleva et al.[98]	Rat	In vivo	MCAO	Injection of 0.5 mg/kg ip.	↓					
MK-801	van der Hel et al.[99]	Rat	In vivo	KCl	Injection of 3 mg/kg iv.	↓	=	=			↓
MK-801	Kunimatsu et al.[100]	Rat	In vivo	BCAO	Injection of 2 mg/kg ip.	↓					
MK-801	Anderson and Andrew[101]	Rat	In vitro	KCl	100 μM	↓					
MK-801	Peeters et al.[102]	Rat	In vivo	KCl	2 mg/kg ip.	↓		↓			
MK-801	Richter et al.[103]	Rat	In vivo	KCl	3 mg/kg	↓					
MK-801	Dhir et al.[104]	Mice	In vivo	KCl	0.5/2 mg/kg ip.	↓	=				
MK-801	Wang et al.[105]	Chicken	In vitro	KCl	Local application of 10 μmol/L	↓	↓	↓			

(continued)

Table 2. Continued

Drug	Reference	Species	Type	SD induction	Dosage	Results					
						Number	Amplitude	Propagation	Threshold	Duration	Frequency
MK-801	Richter et al.[106]	Rat	In vitro	KCl	3 mg/kg ip.	↓					
MK-801	Oláh et al.[107]	Rat	In vivo	KCl	200 mg/kg ip.	↓	↓				
MK-801	Shatillo et al.[108]	Rat	In vivo	KCl	10 mg/kg ip.	↓					
MK-801	Bu et al.[109]	Rat	In vivo	K^+	3/10/30 μmol/L via microdialysis	↓		↓			
MK-801	Srienc et al.[110]	Rat	In vitro	Photothrombosis	3 mg/kg	↓	↓	↓			
Memantine	Peeters et al.[102]	Rat	In vivo	KCl	1/3/10 mg/kg ip.	↓					
Memantine	Santos et al., 2017 (unpublished data)	Swine	In vivo	KCl	1.5 mg/kg iv.	=	↓			↓	
Memantine	Srienc et al.[110]	Rat	In vivo	Photothrombosis	10 mg/kg	=					
Magnesium	van der Hel et al.[99]	Rat	In vivo	KCl	90 mg/kg iv.	↓	=	=			↓
Magnesium	Rodrigues et al.[111]	Chicken retina	In vitro	Mechanical	1–4 mM superfusion	↓					
Magnesium	Van Harreveld[112]	Chicken retina	In vitro	KCl	10 mM	↓					
Magnesium	Shibata and Bures[113]	Rat	In vivo	KCl	10% $MgCl^2$	↓					
Magnesium	Santos et al.[114]	Swine	In vivo	KCl	20 mmol/L local apllic., 40 ml iv.	↓	↓			↓	
Further NMDA receptor antagonists (less known substances)											
Phencyclidine	Marrannes et al.[97]	Rat	In vivo	Electrical	10 mg/kg/day ip.	=		↓	↑		
2-APH	Marrannes et al.[97]	Rat	In vivo	Electrical	10/40 mg/kg/day ip.	↓		↓	↑		
2-APH	Rashidy-Pour et al.[62]	Rat	In vivo	KCl	2.5 mg/kg ip.	↓					
2-APH	Lauritzen and Hansen[91]	Rat	In vivo	Electrical	4.5 mg/10 mg/kg	↓					
AP5	McLachlan[165]	Rat	In vivo	KCl	500 μM	↓					
AP5	Rashidy-Pour et al.[62]	Rat	In vivo	KCl	10^{-3} mol/L	.					
AP5	Anderson and Andrew[101]	Rat	In vitro	KCl	50/100 μM	↓					
AP5	Martens-Mantai et al.[115]	Rat	In vitro	KCl	50 μmol/L			↓			
CGS 19755	Nellgard and Wieloch[92]	Rat	In vivo	Mechanical	0.75 mg/kg ip.	↓					
CGP 40116	Nellgard and Wieloch[92]	Rat	In vivo	Mechanical	0.25 mg/kg ip.	↓					
CGP 43487	Nellgard and Wieloch[92]	Rat	In vivo	Mechanical	1.5 mg/kg ip.	↓					
ACEA 1021	Martin et al.[88]	Rat	In vivo	Electrical	12/40/80/mg/kg/day ip.	=		↓			
ZD9379	Tatlisumak et al.[116]	Rat	In vivo	MCAO	5 mg/kg bolus + 5 mg/kg/h iv.	↓					
L-707, 324	Obrenovitch and Zilkha[95]	Rat	In vivo	Potassium	5/10 mg/kg iv.	↓		↓			
Glyx-13	Zhang et al.[148]	Rat	In vitro	K^+	Bath application of 1/10/50 μM		=	↓			

(continued)

Table 2. Continued

Drug	Reference	Species	Type	SD induction	Dosage	Results					
						Number	Amplitude	Propagation	Threshold	Duration	Frequency
KYNA	Oláh et al.[107]	Rat	In vivo	KCl	300 mg/kg ip.	↓	=				
KYNA	Chauvel et al.[166]	Chicken retina	In vivo	KCl	300 mg/kg ip.			=			↓
KYNA	Chauvel et al.[150]	Rat	In vivo	KCl	300 mg/kg ip.						↓
KYNA	Anderson and Andrew[101]	Chicken retina	In vitro	KCl	2 mM	↓					
NVP-AAM007	Wang et al.[105]	Chicken retina	In vitro	KCl	Local application of 0.03/0.1/0.3 μmol/L	↓	↓	↓			
NVP-AAM007	Bu et al.[109]	Rat	In vivo	K^+	0.3/1/3 μmol/L via microdialysis	↓	↓				
NVP-AAM007	Bu et al.[109]	Rat	In vitro	K^+	0.3/1/3 μmol/L		↓	↓			
TCN-2001	Shatillo et al.[108]	Rat	In vivo	KCl	10 mg/kg ip.	=					
TCN-2001	Bu et al.[109]	Chicken retina	In vitro	K^+	1/3/9 μmol/L		↓	↓			
Ifenprodil	Shatillo et al.[108]	Chicken retina	In vivo	KCl	10 mg/kg ip.	↓					
Ro 25-6981	Wang et al.[105]	Chicken retina	In vitro	KCl	Local application of 1/3/10 μmol/L		↓	=			
Ro 25-6981	Peeters et al.[102]	Adult rat	In vivo	KCl	1/3/10 mg/kg ip.	↓					
CP-101,606	Wang et al.[105]	Chicken retina	In vitro	KCl	Local application of 1/3/10 μmol/L	=	=	=			
CP-101,606	Peeters et al.[102]	Adult rat	In vivo	KCl	1/3/10 mg/kg ip.	↓					
CP-101,606	Menniti et al.[117]	Rat	In vivo	Electrical	1/3.2/10 mg/kg iv.	↓	↓	↓			
UBP141	Wang et al.[105]	Chicken retina	In vitro	KCl	Local application of 1/3/10 μmol/L	=	=	=			
3PPP	Anderson and Andrew[101]	Rat	In vitro	KCl	100 μM	=					
BD-1063	Anderson and Andrew[101]	Rat	In vitro	KCl	100 μM	=					
Loperamid	Anderson and Andrew[101]	Rat	In vitro	KCl	100 μM	=					
Spiperone	Anderson and Andrew[101]	Rat	In vitro	KCl	100 μM	↓					
4-IBP	Anderson and Andrew[101]	Rat	In vitro	KCl	30 μM	↓					

injection lasted for 30–45 min. The blocking effect of subsequent injections gradually declined and was not recognizable after a fifth ketamine injection.[62] Krüger et al.[89] studied the effect of 100 μM ketamine on the characteristics of a KCl-induced SD in parietal cortical slices of adult rats. He ascertained that ketamine significantly reduced the amplitude of the first SD peak and blocked the second SD peak when compared with the controls.[89] Hernández-Cáceres et al.[40] examined the ketamine-induced blockade of SD in pentobarbital-anesthetized rats and presented evidence that ketamine prevented the propagation of SD at 12 mg/kg and at higher doses. The blockade was maximal 20 min after the injection.[40] Our group, Sanchéz-Porras et al. used a gyrencephalic swine model to examine ketamine's effects against SDs. In this swine model, an intensive-medicine setting is recreated in which the animal is monitored for up to 30 h. The major results were that s-ketamine at the human equivalent maximum dose of 2 mg/kg/h decreased the KCl-induced SD spreading and had an effect on the amplitude of SD deflections, as well as on the duration and speed. Moreover, during infusion of this dose of ketamine, there was a sustained decrease in the hemodynamic response following SD. However, only at 4 mg/kg/h of ketamine could the SD induction and expansion be completely inhibited.[90] In another experimental setting, we found ketamine's influence on the vasculature during SD. We observed a decrease of contractility during oligemia but not under hyperemia.[119]

The experiments and clinical trials involving humans are particularly relevant. Kaube et al.[120] assumed that SD is pathophysiologically relevant for the genesis of the auras of migraines and thus investigated the question whether the aura experienced by some patients with familial hemiplegic migraine can be stopped by intranasal ketamine. In 5/11 patients, ketamine reproducibly reduced the severity and duration of the auras.[120] Hertle et al.[41] documented an association between the relative β-frequency and SD. The relative β-frequency was suppressed up to 2 h prior to SD when compared to periods that were not followed by SD. An inverse correlation of the administration of ketamine with the occurrence of spreading depolarizations has been noted.[41] Case reports document the effect of ketamine in two patients with traumatic brain injury and aneurysmal SAH (aSAH),[66] as well as a patient with perihematomal edema.[68] Another case report described a patient with aSAH who displayed a cluster of SDs under ketamine. The patient subsequently developed severe delayed ischemic strokes and died.[27] Most recently, our research group, Santos et al. described a suppressive effect of S-ketamine on SD in patients with aSAH (Santos et al., unpublished data). Sixty-six aSAH patients were prospectively monitored, including ECoG. We retrospectively compared relevant collected variables of patients who received ketamine at any time (n=33) vs. no-ketamine. A multivariable analysis including Poisson, negative binomial, and linear mixed models were performed to show the effect of ketamine on SD incidence and characteristics. On patient level, the mean dose of 2.81 mg/kg/h ketamine started at a mean of 4.6 days after ictus for a mean of 8.1 days was not enough to show significant differences between groups in the total monitoring time of 17 days. But upon analyzing hourly data and considering when ketamine was given or not, we found a clear effect of SD incidence reduction and changes in its electrical characteristics. Doses above the recommended therapeutic range (>2 mg/kg/h) were more effective than therapeutic doses in SAH patients. A reduction of efficacy over the monitoring days in patients was not documented. In order to reach neuroprotection, our results favor a patient individualized ketamine schema with soon start of ketamine and adaptation of the dose to the patient's conditions, timing after ictus and to the detection of SDs.

Memantine. Memantine is an uncompetitive NMDA receptor antagonist that has been clinically approved for the treatment of Alzheimer's symptoms.[121–123] This drug is already used as a migraine-preventive drug in clinical studies, and the results have been promising.[124,125] Currently, positive effects of memantine on cognition in demented patients have been obtained.[126] Specifically, it has the potential to improve neuronal plasticity and learning in old animals[127] and an ability to enhance learning in rats with learning deficits caused by entorhinal cortex lesions.[128] Moreover, it has been observed that memantine reduced the frequency of auras as well as headache in migraneurs, which also suggests an association with SDs.[124] Memantine's pharmacological profile suggests that it has the capacity to block excessive activation of NMDA receptors without affecting normal signaling by the receptor and thus better preserves a critical balance.[129] Memantine's potential to modulate SD has until now only been subject of few experiments (Table 2). Experiments in an in vitro chicken retina model showed a concentration-dependent inhibition of NMDA-evoked SD. A dosage of 12.67 ± 0.99 μM was required to achieve an inhibition of 50% of SD.[121] Moreover, memantine showed a significant dose-dependent reduction of the number and amplitude of SD in rats at a dose of 10 mg/kg.[102] However, its scientific status is equivocal. Srienc et al. tested memantine in rats in which the retinal vessels had been occluded by photothrombosis and observed no significant effect, but there was a trend towards a reduction of incidence.[110] Recently, our group (Santos et al.) tested memantine at

a dose of 1.5 mg/kg against KCl-induced SD in a gyrencephalic porcine model. An analysis using ECoG and IOS revealed that memantine applied within the therapeutic range had no suppressive effect on SD. Nevertheless, the amplitude and duration were reduced after the eighth stimulation, at which time the memantine blood concentrations were 200 to 300% of the therapeutic range. A possible reason for these observations might be that the increased potassium concentration of the 11 mM preconditioning reduced the efficacy of NMDA receptor antagonists to suppress SD. In vivo experiments in rats suggest that an increased extracellular K^+ concentration reduce the efficacy of NMDA receptor antagonists to suppress SDs.[130]

MK-801. MK-801 is a well-characterized, potent, and selective NMDA receptor antagonist that has been tested for the suppression of cortical and retinal SD in various in vivo and in vitro experiments on rats, cats, and chickens (Table 2). A complete blockade of the elicitation of SDs is in the range of 2–3 mg/kg,[62,63,91,100,131] but experiments such as those conducted by Nellgard and Wieloch showed that even smaller dosages such 0.10 mg/kg inhibited mechanically elicited SD.[92] A potency of MK-801 has also been observed by numerous other investigators.[93,95,98,108]

Although it is a sufficiently potent inhibitor of SD that it is often used as a positive control in experiments, MK-801 has various reported side effects: MK-801 induces marked regional alterations in the local cerebral glucose utilization in rats,[132] and a dose of 0.2 mg/kg has been reported to be sufficient to alter object recognition memory.[133] Recently, repetitive MK-801 administration has also been documented to induce structural changes that resemble schizophrenia and a dementia-like degeneration in the rat brain.[134] At a dose of 0.1 mg/kg, MK-801 also exhibits anxiolytic and antinociceptive effects in primates,[135] which raises the question whether it must be considered for further studies.

Magnesium. Magnesium's multifaceted pharmacological profile includes neuroprotection. Experiments in rodents have shown that the infarct size after MCAO can be reduced by an application of magnesium.[136,137] Despite these promising results, clinical randomized controlled trials in which magnesium was used as an intervention in acute stroke demonstrated neither neuroprotection nor reduced death or disability.[138] Recently, Yamamoto et al. investigated a potentially preventive effect of continuous cisternal irrigation with $MgSO_4$ on the cerebral vasospasms associated with SAH in a randomized controlled trial but found no protective effect on delayed cerebral ischemia nor on the clinical outcome.[139]

Neurophysiologically, magnesium has versatile effects including the inhibition of intracellular Ca^{2+} influx and blocking the NMDA-activated channels.[140] Magnesium's neuroprotective properties and physiological profile provide a rationale for various trials to examine its potential to inhibit SD (Table 2).

Shibata and Bures showed magnesium's potential to inhibit KCl-induced reverberating SD in rats.[113] van der Hel et al.[99] similarly observed a significant reduction of the frequency, a delay of the latency and a significant blockade of the generation of KCl-induced SD in rats at 90 mg/kg. Magnesium's inhibitory potential was also observed in in vitro chicken models.[111,112] More recently, our group, Santos et al. investigated magnesium's effect against SD in the gyrencephalic swine model. A local administration and an intravenous bolus of $MgSO_4$ were tested. Local application of a dose of 10 mmol/L$MgSO_4$ significantly reduced the amplitude of the oligemic response of SD. In contrast, an intravenous application did not alter SD, which indicates that the blood–brain permeability, high renal elimination, and low bioavailability need to be considered when examining magnesium's therapeutic potential against SD.[114] The same principle can be applied for most therapeutic agents.

Further noncompetitive NMDA receptor antagonists: Phencyclidine, 2-APH, AP5, CGS 19755, CGP 40116, CGP 43487, ACEA 1021, ZD9379, L-707, 324, Glyx-13, KYNA, NVP-AAM007, TCN-2001, ifenprodil, Ro 25-6981, CP-101,606, UBP141, 3PPP, BD-1063, loperamid, spiperone, and 4-IBP.

Various non-competitive NMDA receptor antagonists have been tested against SD. Some will be presented in detail in this section. For more details, see Table 2.

Lauritzen and Hansen[91] and Marrannes et al.[63] observed that DL-2-amino-7-phosphonoheptanoic acid suppressed the incidence of electrically induced SD in rats at a dose of 10 mg/kg, whereas a much higher dose of 160 mg/kg of 2-APH is required to reach complete suppression.

The competitive NMDA-receptor antagonists *CGS 19755* (cis-4-phosphonomethyl-2-piperidine carboxylate), *CGP 40116* (D-(E)-2-amino-4-methyl-5-phosphono-3-pentenoic acid), and its carboxylester *CGP 43487* have been shown to inhibit the elicitation of mechanically induced SD in the rat cortex at doses of 0.75 mg kg^{-1}, 0.25 mg kg^{-1}, and 1.50 mg kg^{-1}, respectively.[92]

Since the NMDA receptor channel complex contains a glycine recognition site that must be occupied for activation, it can be hypothesized that antagonism of the glycine site might counteract SD. *ACEA 1021* (5-nitro-6,7-dichloro-1,4-dihydro-2,3-quinoxalinedione) minimized cerebral infarct volumes.[141,142] Martin et al.[88] examined ACEA-1021 for its influence on the

threshold and propagation rate of electrically induced SD. Although the threshold was unaffected, a dose-dependent deceleration of SD was noted. The elicitation of SD was not inhibited by ACEA 1021 at any dose.88

ZD9379 is a soluble, potent, bioavailable full antagonist at the glycine site.[116] It reduced the number of SDs and the infarct size in rats with a permanent MCAO at a dose of 5 mg/kg according to Tatlisumak et al.[143]

L-707, 324 is a high affinity antagonist at the glycine site of the NMDA receptor that has shown in vivo potency against seizures.[144] Its effectiveness against SD has been investigated by Obrenovitch and Zilkha.[95] A dose of 10 mg/kg was required to block the induction of SD, whereas 5 mg/kg was sufficient to completely inhibit propagation, but the effect on SD was rather moderate compared to that of a classical inhibitor as MK-801.

Glyx-13 is an NMDA-receptor modulator with glycine-site partial agonist properties that recently has been shown to produce rapid antidepressant responses.[145] Its physiological profile permits Glyx-13 to act as an agonist of the NMDA receptor in the absence of saturating D-serine while acting as an antagonist at high concentrations of D-serine. During SD, which elicits the release of high levels of glutamate and D-serine, GLYX-13 is likely to act as an antagonist that would prevent the over-activation of NDMA receptors.[146,147] Its interaction with SD has only recently came under the spotlight. Glyx-13 has been observed to increase the refractory period of hippocampal rat SD, to limit the propagation of SD, and to reduce the amplitude of the negative field potential shift and restored the dendritic spines.[148] Since Glyx-13 is not an NMDA receptor antagonist, but rather an allosteric modulator, therapeutic application could be facilitated because the side-effects of NMDA receptor channel blockers would be avoided.

Kynurenines, and particularly the endogenous kynurenic acid, exhibit a strong modulatory potential on the neuronal structures in the brainstem, which may play a crucial role in the pathogenesis of migraine.[149] Kynurenic acid suppresses SD[107,150] and the precursor L-kynurenin also suppresses SD waves and reduced c-fos immunoreactivity and neuronal nitric oxide synthase, which are associated with SD as well as with migraines.[150–153] A therapeutic use is improbable because Kynurenic acid facilitates pathological pathways[154] and is involved in the development of manic or psychotic symptoms.[155]

GluN2A, GluN2B, and GluN2C/2D: Specific NMDA antagonists against SD. The GluN2A-selective NMDA receptor antagonist NVP-AAM077 reduced the amplitude and propagation rate of KCl-induced SDs in chicken retina,[105,109] 30-fold more potent than MK-801. To a slightly lesser extent, the GluN2A-specific antagonist TCN2001 also reduced the amplitude and deaccelerated SD in the chicken retina.[109] Contrasting results for TCN-201 in chick retina were found by Shatillo et al., who used BOLD fMRI to examine the drug's effect against SD but found no inhibitory effect.[108]

Ro 25-698, a GluN2B-selective receptor antagonist, reduced the amplitude to 51.1% of the initial values at a concentration of 10 μmol/L[105] in chicken retina, and similar inhibitory potential was documented in KCl-induced SD in rats.[102]

CP-101,606, a GluN2B-selective receptor antagonist, prevents the death of rat hippocampal neurons[156] and reduces the size of infarcts caused by subdural hematoma in rats.[157] Nevertheless, CP-101,606 was ineffective against SD in Wang et al.'s chicken retina model.[105] Different results were obtained by Peeteres et al. who described a dose-dependent reduction in the SD numbers and amplitude.[102] Similarly, Menniti et al.[117] observed that CP-101,606 inhibited SD generation at a dose of 2.25 mg/kg bolus + 2.25 mg/kg/h intravenous infusion. Additionally, the amplitude and propagation velocity were also decreased in a dose-dependent manner.[117]

Sigma site antagonists/agonists against SD. Sigma receptors can be found throughout the body and CNS,[158,159] and the evidence suggests that sigma ligands are associated with neuroprotection.[160–162] The exact role of sigma receptors in the pathogenesis of SD is yet to be elucidated.

We reviewed five sigma site-specific NMDA receptor antagonists BD-1063, 3PPP, 4-IBP, carbetapentane, and dextromethorphan.

Anderson and Andrew tested carbetapentane and dextromethorphan against KCl-induced SD in rat brain slices. Both drugs at a dose of 100 μM blocked the generation of SD and prevented the tissue swelling that usually follows SD.[101] Moreover, Anderson and Andrew examined 4-IBP, a ςR agonist that has only insignificant cross reactivity at the NMDA receptor sites compared to other sigma agonists.[163] 4-IBP showed a blocking effect against KCl-induced SD in rodents at a dose of 100 μM, but did not prevent the secondary swelling.[101] Another ςR agonist that has an inhibitory effect against SD is *SK&F 10047*, which showed a dose-dependent inhibition of the incidence of KCl-induced SD in rats.[94] In contrast, the ς1 R antagonists BD-1063 and (+)-3-PPP had no inhibitory effects on the KCl-induced SD in rat brain slices.[101]

Anesthetic, sedative, hypnotic, and analgesic agents

SD susceptibility is modulated by general anesthetics.[118,167–171] An anesthetic agent that combines effectiveness against SD and clinical applicability is sevoflurane. To our knowledge, sevoflurane has been tested against KCl-induced SD only by Kitahara et al.[168] in rats. A dose-dependent reduction in the frequency and a dose-dependent increase in the DC current have been observed, whereas the number, amplitude, and duration of SD seemed to be unaffected.[168]

Isoflurane has been examined in six studies with ambiguous results. Similar to most volatile anesthetics, isoflurane acts via various mechanisms and affects different channels and receptors at various levels of the brain. Muscle relaxation is likely induced by isoflurane's potentiation of glycine receptor activity. Moreover, it antagonizes NMDA receptor and affects the calcium ATPase, ATP synthase, and GABA receptors. Importantly, isoflurane has various adverse effects, such as hypotonia and cardiodepression. Additionally, isoflurane has been associated with neurodegeneration, promotion of apoptosis, and an increase of the amyloid beta protein levels that are associated with Alzheimer's disease.[172] Currently, volatile alternatives as sevoflurane are preferred over isoflurane for clinical use. A protective effect of isoflurane against the initiation of SD has been described in various experiments.[168,169,173,174] Specifically, there is evidence for isoflurane's potential to suppress the SD frequency[168,173] and to reduce the propagation speed,[173] whereas the amplitude of SD seems to be unaffected by this agent.[168]

The exact mechanisms by which anesthetics inhibit are yet to be clarified, but may involve their ability to partially antagonize the NMDA receptor. For instance, isoflurane has been associated with a reduction of neuronal depolarization as a reaction to a glutamate and NMDA application[175] and can even reduce the mean open time of the NMDA channel.[176]

Further anesthetic agents that have been tested against SDs but were proven to be either ineffective or only to have a modulatory effect at doses that could never be applied in humans include *dexmedetomidine*,[173,177] *benzocaine*,[181] *debucain*,[178] *lidocaine*,[179–181] *midazolam*,[41] *equithesin*,[182] and *thionembutal*.[167]

Table 3 provides the insight that most anesthetic agents exert little or no influence against SD; hence, future investigation should focus on more promising substances. Table 3 shows that none of the potential characteristics of SD (number, amplitude, duration, frequency, and propagation) is a successful target for anesthetic substances. Although three articles show some inhibition against the number of SD,[104,169,174] the majority describes no inhibition,[41,167–169,171,179,182,183] or even an increased amplitude after drug administration.[41] Even more ambiguous results are observed for the effect on frequency. While three articles describe an inhibition,[167,168,173] two describe an increase.[168,184] Duration[168,173,184] has not been affected by any tested anesthetic drug.

Anti-migraine drugs

There is evidence that SD plays a causative role in all migraine types, including migraine without aura.[185] First, the phenomenological resemblance (e.g., velocity, hyperexcitability and electrocorticogram suppression) between SDs and the scintillating phenomenon that can be observed during migraine supports that SD is the electrophysiological mechanism for the migraine aura.[186] Second, chronic administration of anti-migraine drugs has been shown to have an inhibitory effect on SD.[50] Third imaging studies of migraine with aura.[45,46,187,188] The resulting hypothesis that SD suppression may be a function of anti-migraine drugs has been fueled by new discoveries. In particular, the anti-migraine effect of vagus stimulation (that has been successfully applied against migraine[189–191]) has recently been tested in the context of SD by Chen et al.[58] He observed an inhibitory effect of noninvasive as well as direct stimulation against KCl-induced SD in rats.[58]

In contrast, SD-blocking substances have come under scrutiny for a potential anti-migraine effect. Ketamine, a proven blocker of SD, has been shown to stop the neurological aura symptoms in some patients but had no effect on the headache.[120]

Many migraine drugs from different pharmacological classes have been tested against SD so far,[50,97,102,110,179,185,192–207] and topiramate and flunarizine were most effective since they exerted an inhibitory effect in all of the revised studies.

Valproate

Valproate was originally used as an anticonvulsant and has a multifaceted action spectrum: it inhibits voltage-dependent sodium channels and T-type calcium currents, augments the action of glutamic acid decarboxylase, and modulates the extracellular signal-regulated kinase pathway.[208] Evidence supports its efficacy in migraine prevention and acute migraine therapy.[209] Approximately one to three months of valproate or topiramate treatment additionally suppress cortical hyperexcitability in migraineurs.[210–212] Currently, valproate is a promising substance for the therapy of SD. A recent study by Ayata et al.[50] investigated the efficiency of topiramate, valproate,

Table 3. Review of the effect of analgesic, sedative, and hypnotic agents against SDs.

	Anesthetic agents					Results					
Drug	Reference	Species	Type	SD induction	Dosage	Number	Amplitude	Propagation	Threshold	Duration	Frequency
Isoflurane	Kudo et al.[173]	Rat	In vivo	KCl	0.7 MAC			↓			↓
Isoflurane	Kudo et al.[184]	Rat	In vivo	KCl	1%			=		=	=
Isoflurane	Kitahara et al.[168]	Rat	In vivo	KCl	0.5/1/2.0 MAC	=	=			=	↓
Isoflurane	Piper and Lambert[169]	Cat	In vivo	Mechanical	15–30%	↓					
Isoflurane	Takagaki et al.[174]	Rat	In vivo	Kcl, MCAO	1 MAC	↓					
Isoflurane	Verhaegen et al.[118]	Rat	In vivo	Electrical	1 MAC			=	=		
Sevoflurane	Kitahara et al.[168]	Rat	In vivo	KCl	0.5/1/2.0 MAC	=	=			=	↓
Urethane	Kudo et al.[185]	Rat	In vivo	KCl	1.7 ± 0.2 g/kg/h			=		=	↑
Urethane	de Souza et al.[184]	Rat	In vivo	KCl	1.0 g/kg	=					
Urethane	Guedes and Barreto[167]	Rat	In vivo	KCl	1.0 g/kg	=		↓			
Halothane	Kitahara et al.[168]	Rat	In vivo	KCl	1 MAC	=	=			=	↑
Halothane	Piper and Lambert[169]	Cat	In vivo	Mechanical	60 mg/kg ip.	↓					
Halothane	Verhaegen et al.[118]	Rat	In vivo	Electrical	1 MAC			=	=		
Halothane	Saito et al.[171]	Cat	In vivo	KCl	60 mg/kg iv.	↓					
α-chloralose	Kudo et al.[185]	Rat	In vivo	KCl	87 ± 31 mg/kg/h			=		=	=
α-chloralose	Piper and Lambert[169]	Cat	In vivo	Mechanical	60 mg/kg ip.	=					
α-chloralose	Saito et al.[171]	Cat	In vivo	KCl	60 mg/kg iv.	=					
α-chloralose	Guedes and Barreto[167]	Rat	In vivo	KCl	40 mg/kg	=		↓			
Pentobarbital	Kudo et al.[173]	Rat	In vivo	KCl	0.7 MAC			=			=
Pentobarbital	Kitahara et al.[168]	Rat	In vivo	KCl	1 MAC	=	=			=	↑
Morphine	Hertle et al.[41]	Human	Retrospective analysis	Brain injury	8 mg median drug dose	=					
Fentanyl	Hertle et al.[41]	Human	Retrospective analysis	Brain injury	0.15 mg median drug dose	=					
Sufentanil	Hertle et al.[41]	Human	Retrospective analysis	Brain injury	0.06 mg median drug dose	=					
Propofol	Kudo et al.[173]	Cat	In vivo	KCl	0.7 MAC			=			=
Propofol	Dhir et al.[104]	Mice	In vivo	KCl	120/200 mg/kg ip.	↓	↓	↓			
Propofol	Hertle et al.[41]	Humans	Retrospective analysis	Brain injury	150 mg median drug dose	=					
Propofol	Kudo et al.[173]	Cat	In vivo	KCl	0.7 MAC			=			=
Midazolam	Hertle et al.[41]	Humans	retrospective analysis	Brain injury	22.3 mg median drug dose	↑					
Debucain	Risher et al.[178]	Human /mice	In vitro/vivo	Photothrombosis	1 μM	=			↑		
Lidocain	Ayad et al.[180]	Rabbit	In vivo	Ischemia	0.2 mg/kg/min		↓	↓	↑		

(continued)

Table 3. Continued

Anesthetic agents						Results				
Drug	Reference	Species	Type	SD induction	Dosage	Number	Amplitude	Propagation	Threshold	Duration	Frequency
Lidocain	Kaube and Goadsby[179]	Cat	In vivo	Mechanical	5 mg/kg iv.	=	=	=			
Equithesin	Sonn and Mayevsky[182]	Rat	In vivo	KCl	0.3 ml/100 g ip. injection	=		=			↓
Thionembutal	Guedes and Barreto[167]	Rat	In vivo	KCl	40 mg/kg	=		↓			
Dexmedetonidine	Kudo et al.[173]	Rat	In vivo	KCl	0.7 MAC			↓			↓

"↓" Means a reductive effect was observed after drug administration, "=" means no effect was noticed, and "↑" means that the tested parameter was increased by drug. Typical parameters under investigation are number, amplitude, propagation, threshold, duration, and frequency. Propofol, isoflurane, and lidocaine show strong inhibitory effect while fentanyl and morphine for example exert no effect. Experimental settings and models are heterogeneous, comprising different animals (chicken, rat, rabbit, and swine) and various forms of SD induction (KCl and electrical stimulation).

propranolol, amitriptyline, and methysergide against SD. Chronic daily application of these agents correlated with a dose-dependent deceleration of SD by 40% to 80% and a reduction of susceptibility whereas a single dose was ineffective.[50] Further studies support the idea that chronical application is effective,[185,202] while some groups report no effect at all.[179]

Tonabersat

Tonabersat is a novel putative migraine prophylactic agent with a unique stereospecific binding site in the brain. In animal models, tonabersat has shown an inhibitory potential against SD and cerebrovascular responses to trigeminal nerve stimulation.[213] With respect to its efficacy in humans, tonabersat failed to significantly reduce the number of headache days in migraineurs when compared to placebo, but it is usually well tolerated.[214] With respect to its effect against SD, we found positive preliminary results, showing a potential to reduce the number of SD,[192–194] to decelerate SD[192,194] and to modulate hemodynamic response.[193]

Topiramate

Topiramate is generally used as an anticonvulsant for epilepsy. Pharmacologically, topiramate positively modulates the $GABA_A$ receptors. $GABA_A$ receptors are pentameric ligand-gated ion channels that are involved in neuropathic pain and migraine among other effects and consequentially constitute a therapeutic target.[215–218] In regard to efficacy against SD, there are promising results.

Ayata et al.[50] showed that 60 and 80 mg/kg/day of topiramate reduced the number of SDs by 30% and 50%, respectively, whereas 40 mg/kg/day was ineffective. Furthermore, an almost complete abolishment of SD was observed after 17 weeks of topiramate treatment, whereas 1 week of treatment even at a high dose (80 mg/kg/day) had little effect, which suggests that a sustained treatment is necessary for a significant suppression.[50] Moreover, a suppressive effect on SD frequency and propagation[196] and a modulatory effect on hemodynamic response[195] have been reported.

Other modulators of the $GABA_A$ receptor, such as TPA023, NS11394, and SL651498, have been documented to exert some inhibition against SD in an in vitro chicken model,[219] suggesting that $GABA_A$ receptors, especially the $\alpha 2$ subtype, might be a responsive therapeutic target.

Flunarizine

Flunarizine is a large hydrophobic fluorinated piperazine derivative that is used in the prophylaxis of

Table 4. Review of the effect of anti-migraine drugs against SDs.

	Anti-migraine drugs					Results					
Drug	Reference	Species	Type	SD induction	Dosage	Number	Amplitude	Propagation	Threshold	Duration	Frequency
Tonabersat	Read et al.[192]	Cat	In vivo	KCl	3–10 mg/kg/day ip.	↓		↑		↓	
Tonabersat	Smith et al.[193]	Cat	In vivo	KCl	3–10 mg/kg/day ip.	↓					
Tonabersat	Bradley et al.[194]	Cat	In vivo	KCl	10 mg/kg/day ip.	↓		↑		↓	
Tonabersat	Read et al.[192]	Rat	In vivo	KCl	10 mg/kg/day ip.	↓					
Topiramate	Akerman and Goadsby[195]	Cat, rat	In vivo	Mechanical	30 mg/kg/day iv.	↓		=			
Topiramate	Unekawa et al.[196]	Rat	In vivo	KCl	50, 100, 200, or 600 mg/kg ip.			↓	↑		
Topiramate	Ayata et al.[50]	Rat	In vivo	Electrical, KCl	40–80 mg/kg/day	↓	=	↓	↑	=	
Topiramate	Tozzi et al.[197]	Rat	In vitro	K^+	100 μM	↓					
Flunarizine	Marrannes et al.[97]	Rat	In vivo	Electrical	20–40 mg/kg/day ip.; per os 3 × 20 mg/kg/day		=	=	=	↓	
Flunarizine	Marrannes et al.[97]	Rat	In vivo	Electrical, KCl	10–20 mg/kg/day ip.; per os 20 mg/kg/day						
Flunarizine	Hansen and Lauritzen[37]	Rat	In vivo	Mechanical	Per os 20 mg/kg/day		=	=			
Flunarizine	Wauquier et al.[198]	Rat	In vivo	Mechanical	40 mg/kg/day ip.	↓					
Flunarizine	Li et al.[199]	Rat	In vivo	KCl	3 mg/kg ip.	↓	↓		↑	↓	
Flunarizine	Ashton et al.[200]	Guinea pig	In vitro	Electrical	40 mg/kg × 2 per os		↓				
Valproate	Kaube and Goadsby[179]	Cat	In vivo	Mechanical	3.5–7 mg/kg/day iv.	=	=	=			
Valproate	Peeters et al.[102]	Rat	In vivo	KCl	200 mg/kg ip.	=	=				
Valproate	Tepe et al.[201]	Rat	In vivo	KCl	75 mg/kg ip.	=					=
Valproate	Bogdanov et al.[185]	Rat	In vivo	KCl	200 mg/kg/day ip.	↓		↓			
Valproate	Hoffmann et al.[202]	Rat	In vivo	Electrical, KCl	200 mg/kg/day ip./iv.				↑		
Valproate	Ayata et al.[50]	Rat	In vivo	Electrical, KCl	25/50/100/200 mg/kg/day ip.	↓	=	↓	↑	=	
Sumatriptan	Bradley et al.[194]	Cat	In vivo	KCl	0.3 mg/kg iv.	=		↑		=	
Sumatriptan	Read et al.[192]	Rat	In vivo	KCl	0.3 mg/kg iv.	=					
Sumatriptan	Moskowitz et al.[203]	Rat	In vivo	KCl	0.3 mg/kg iv.	=					
Sumatriptan	Srienc et al.[110]	Rat retina	In vitro	Photothrombosis	3 mg/kg iv.	↓			=		↓
Sumatriptan	Knapp et al.[204]	Rat	In vivo	KCl	0.6 mg/kg ip.	↓					
Sumatriptan	Wiedemann et al.[205]	Chicken	In vitro	KCl	1.5 mM	↓	↓	↓			
Dihydroergotamine	Kaube and Goadsby[179]	Cat	In vivo	Mechanical	15 mg/kg iv.	=		=			
Ergotamine	Wiedemann et al.[205]	Chicken	In vivo	KCl	10–20 μM	=		=			
Lamotrigine	Bogdanov et al.[185]	Rat	In vivo	KCl	15 mg/kg/day ip.	↓		=			
Riboflavin	Bogdanov et al.[185]	Rat	In vivo	KCl	20 mg/kg/day ip.	↓		=			
Propranolol	Ayata et al.[50]	Rat	In vivo	Electrical, KCl	20 mg/kg/day ip.	=	=	=	=	=	

(continued)

Table 4. Continued

	Anti-migraine drugs					Results					
Drug	Reference	Species	Type	SD induction	Dosage	Number	Amplitude	Propagation	Threshold	Duration	Frequency
Propranolol	Ayata et al.[50]	Rat	In vivo	Electrical, KCl	20 mg/kg/day ip.	↓	=	↓	=	=	
Propranolol	Richter et al.[206]	Rat	In vivo	Mechanical	Topical application of 250 −1 μmol/L to 1 mmol/L	=	=	↓		=	
Propranolol	Peeters et al.[102]	Adult rat	In vivo	KCl	Ip injection of 20 mg/kg ip.	=					
Propranolol	Wiedemann et al.[205]	Chicken	In vitro	KCl	500 μmol	↓	↓	↓			
Methylsergide	Ayata et al.[50]	Rat	In vivo	Electrical, KCl	Ip injection of 0.1 and 1 mg/kg/day ip.	↓	=	=	=	=	
Methylsergide	Wiedemann et al.[205]	Chicken	In vitro	KCl	100 μmol	↓	↓	↓			
Amitryptolin	Ayata et al.[50]	Rat	In vivo	Electrical, KCl	Ip injection of 10/20 mg/kg/day ip.	↓	=	=	=	=	
Clonidin	Wiedemann et al.[205]	Chicken	In vitro	KCl	100–500 μM	=	=	=			
Lisuride	Wiedemann et al.[205]	Chicken	In vitro	KCl	100–200 nM	=	=	=			
Iprazochrome	Wiedemann et al.[205]	Chicken	In vitro	KCl	100–200 μM	=	=	=			
Isoprenalin	Kaube et al.[207]	Cat	In vivo	Transection	Topical application of 0.1/1%	=		=			
Amylnitrite	Kaube et al.[207]	Cat	In vivo	Transection	Topical application of 0.05%	=		=			

"↓" Means a reductive effect was observed after drug administration, "=" means no effect was noticed, and "↑" means that the tested parameter was increased by drug. Typical parameters under investigation are number, amplitude, propagation, threshold, duration, and frequency. Most substances exert an inhibitory effect on the number of SDs. Only few inhibit more than one variable, for instance, flunarizine, sumatriptan, and propranolol. Experimental settings and models are heterogeneous, comprising different animals (chicken, rat, and cat) and various forms of SD induction (KCl and electrical stimulation).

Table 5. Review of the further substances that have been tested against SDs.

						Results							
Drug	Reference	Species	Type	SD induction	Dosage	Number	Amplitude	Propagation	Threshold	Duration	Frequency	IOS area	Pial diameter
Further substances that have been tested against SD													
Lithium	de Aguiar et al.[236]	Rat	In vivo	KCl	50 mg/kg ip.			↓					
Quinpirole	Haarmann et al.[234]	Rat	In vitro	KCl	10–200 μmol/l		↑	=		↑			
Sulpiride	Haarmann et al.[234]	Rat	In vitro	KCl	0.1–10 μmol/l		↓	=		↓			
BIBN4096BS	Tozzi et al.[197]	Rat	In vitro	K^+	0.01–1 μM							↓	
CGRP 8-37	Tozzi et al.[197]	Rat	In vitro	K^+	3/10 μM							↓	
CGRP 8-37	Colonna et al.[237]	Rabbit	In vivo	KCl	Topical 12.8 μM								↓
CGRP 8-37	Wahl et al.[238]	Cat	In vivo	KCl	5×10^{-9}–10^{-6} M								↓
CGRP 8-37	Reuter et al.[239]	Rat	In vivo	KCl	(5×10^{-7} M)								↓
MK-8825	Tozzi et al.[197]	Rat	In vitro	K^+	0.1–10 μM							↓	
SNC80	Pradhan et al.[240]	Mice	In vivo	KCl	Ip. injection of 10 mg/kg	↓							
Naloxone	Guedes et al.[230]	Rat	In vivo	KCl	10 mg/kg/day			↓					
Naloxone	Rocha-de-Melo et al.[231]	Rat	In vivo	KCl	10 mg/kg/day sc.			↓					
SL651498	Wang et al.[219]	Chicken retina	In vitro	KCl	10 μmol/L local application	↓	↓	↓					
Tpa023	Wang et al.[219]	Chicken retina	In vitro	KCl	50 μmol/L local application	↓	↓	↓					
NS11394	Wang et al.[219]	Chicken retina	In vitro	KCl	3 μmol L^{-1} local application	=	=	=					
Bicuculline	Martens-Mantai et al.[115]	Rat	In vitro	KCl	10 μmol/L local application			↓					
NBQX	Krüger et al.[89]	Rat	In vitro	KCl	10 μM	=	=						
NBQX	Kertész et al.[232]	Chicken retina	In vitro	Kainat	Up to 10 μM	↓			↑				
NBQX	Lauritzen and Hansen[91]	Rat	In vivo	Electrical	10/20 mg/kg	=	=		=				
NBQX	Kunimatsu et al.[100]	Rat	In vivo	BCAO	30 mg/kg ip.	=							
NBQX	Nellgard and Wieloch[92]	Rat	In vivo	Mechanical	10 mg/30 mg ip.	=							
NBQX	Gressens et al.[233]	Chicken retina	In vitro	AMPA, MCAO	3 × 30 mg/kg ip.				↑				
CNQX	Anderson and Andrew[101]	Rat	In vitro	KCl	10 μM	=		=	=				
CNQX	Martens-Mantai et al.[115]	Rat	In vitro	KCl	10 μmol/L local application			↑					

(continued)

Table 5. Continued

Drug	Reference	Species	Type	SD induction	Dosage	Results							
						Number	Amplitude	Propagation	Threshold	Duration	Frequency	IOS area	Pial diameter
GYKI 52466	Kertész et al.[232]	Chicken retina	In vitro	Kainat	20 μM	↓			↑				
GYKI 52466	Gressens et al.[233]	Chicken retina	In vitro	AMPA	1/3/10 mg/kg ip.				↑				
GYKI 53655	Kertész et al.[232]	Chicken retina	In vitro	Kainate	20 μM	↓			↑				
EGIS 8332	Gressens et al.[233]	Chicken retina	In vitro	AMPA, MCAO	1/3/10 mg/kg ip.				↑				
EGIS 1068	Gressens et al.[233]	Chicken retina	In vitro	AMPA, MCAO	1/3/10 mg/kg ip.				↑				
WIN 55212-2	Martens-Mantai et al.[115]	Rat	In vitro	KCl	5 μmol/L local application			↑					
THC	Kazemi et al.[235]	Rat	In vitro	KCl	1–20 μM		↓	↓		↓			
WIN 55212-2	Kazemi et al.[235]	Rat	In vitro	KCl	1–10 μM		↓	↓		↓			
JWH-13	Kazemi et al.[235]	Rat	In vitro	KCl	1–20 μM		=	=		=			
8-OH-DPAT	Krüger et al.[89]	Adult rat	In vivo	KCl	10/100 μM ip.					↓			
Metoprolol	Kaube and Goadsby[179]	Cat	In vivo	Mechanical	25 mg/kg/day iv.	=	=	=					
Metoprolol	Alemdar et al.[241]	Rat	In vivo	KCl	5 mg/kg infusion	=				=			
Isoprenaline	Kaube et al.[207]	Cat	In vivo	Mechanical	0.1–1% local application	=		=					
TTX	Ashton et al.[200]	Guinea pig	In vitro	Electrodal	1.25×10^{-6} M				↑				
TTX	Sheardown[242]	Chicken retina	In vitro	NMDA, kainate	0.1 μM	=							
TTX	Tobiasz and Nicholson[243]	Rat	In vivo	KCl	10^{-5} M			=					
TTX	Aitken et al.[244]	Rat	In vitro	Hypoxia	1 μM	↓			↑				
TTX	Müller and Somjen[245]	Rat	In vitro	Hypoxia	1 μM				↑				
TTX	Akerman et al.[246]	Rat	In vivo	Mechanical	10 μg/kg								↓
TTX	Tozzi et al.[197]	Rat	In vitro	K^+	1 μM							↓	
ω-Conotoxin-GVIa	Akerman et al.[246]	Cat	In vivo	Mechanical	20 μg/kg ip.			=					=
ω-Conotoxin-GVIa	Richter et al.[227]	Rat	In vivo	KCl, mechanical	10^{-6} M		↓	=					
calciseptine	Akerman et al.[246]	Cat	In vivo	Mechanical				=					=
Cadmium chloride	Akerman et al.[246]	Cat	In vivo	Mechanical				=					=
ω-agatoxin	Richter et al.[227]	Rat	In vivo	KCl, mechanical	10^{-6} M	=		=					
Nimodipine	Richter et al.[227]	Rat	In vivo	KCl, mechanical	10^{-5} M	=		=					

(continued)

Table 5. Continued

Drug	Reference	Species	Type	SD induction	Dosage	Results							
						Number	Amplitude	Propagation	Threshold	Duration	Frequency	IOS area	Pial diameter
Glibenclamide	Akerman et al.[246]	Cat	In vivo	Mechanical	30 mg/kg ip.			=					=
NG-Nitro-l-Arginine	Wahl et al.[238]	Cat	KCl	In vivo	10^{-4} M								=
Zaprinast	Wang et al.[247]	Rat	Electrical	In vivo	300 μM		↓						
Sildenafil	Wang et al.[247]	Rat	Electrical	In vivo	300 μM		=						
Amylnitrite	Kaube et al.[207]	Cat	Transection	In vivo	0.05% topical	=		=					
Isoprenaline	Kaube et al.[207]	Cat	Transection	In vivo	0.1–1% topical	=		=					
shrimp carotinoid	Bezerra Rde et al.[248]	Rat	Ethanol	In vivo	30 μg/kg/day			↓					
SC-560	Varga et al.[249]	Rat	CAO, KCl	In vivo	25 μM								=
SC-560	Gariepy et al.[250]	Rat	Mechanical	In vivo	500 μM								=
NS-398	Varga et al.[249]	Rat	CAO, KCl	In vivo	100 μM								=
NS-398	Gariepy et al.[250]	Rat	Mechanical	In vivo	1 mM								=
L161,982	Varga et al.[249]	Rat	CAO, KCl	In vivo	1 μM								↓
Naproxen	Gariepy et al.[250]	Rat	Mechanical	In vivo	100 μM								=
Ozagrel	Gariepy et al.[250]	Rat	Mechanical	In vivo	1 mM								=
PEA	Richter et al.[251]	Rat	KCl	In vivo	20 mg/kg body weight	=	=	=		=			
Garlic extract	Marschollek et al.[252]	Rat	KCl	In vivo; in vitro	1 ml/L; 500 μL/L		↓	=		=			
Caffeine	de Aguiar et al.[253]	Rat	In vivo	KCl	30 mg/kg ip.				=				
Caffeine	de Aguiar et al.[253]	Rat	In vivo	KCl	30 mg/kg ip.				=				
Gangliosides	Fernandes de Lima et al.[254]	Chicken retina	In vitro	Mechanical	20 μM			↓				↓	
Yohimbine	Richter et al.[206]	Rat	In vivo	Mechanical	1.75 mmol/L			↓					=
Clonidin	Richter et al.[206]	Rat	In vivo	Mechanical	0.56 mmol/L	=	=	↓					=
Norepinephrine	Richter et al.[206]	Rat	In vivo	Mechanical	1 mmol/L	=	=	↓					=
TNF	Richter et al.[255]	Rat, mouse	In vivo	KCl	0.05/5 ng	↓	↓	↓					
Furosemide	Read et al.[256]	Cat	In vivo	KCl	0.2/2/20 g/kg iv.					↓			
IGF-1	Grinberg et al.[257]	Rat	In vitro	Electrical	40/100 ng/mL				↑				
INFγ	Pusic and Kraig[258]	Rat	In vitro	KCL	50,000 U nasally				↑				
Dimethylsulfoxide	Sun et al.[259]	Rat	In vivo	KCl	0.1/0.4/2/4% iv.								↓
Propylthiouracil	Guedes and Pereira-da-Silva[260]	Rat	In vivo	KCl	8 mg/kg ip.			↓					
Pilocarpine	Guedes and de Vasconcelos[261]	Rat	In vivo	KCl	45/95/190 mg/kg ip.		↓	↓					
Pilocarpine	De Vasconcelos et al.[262]	Mouse	In vivo	KCl	190 mg/kg ip.		↓	↓					

(continued)

Table 5. Continued

Drug	Reference	Species	Type	SD induction	Dosage	Results						
						Number	Amplitude	Propagation	Threshold	Duration	Frequency	IOS area	Pial diameter
Fluoxetine	Costa Monteiro et al.[263]	Rat	In vivo	KCl	10 mg/kg/day per os			↓				
Fluoxetine	dos Santos et al.[264]	Rat	In vivo	KCl	5/10/20/40 mg/kg/day			↓				
Citalopram	Guedes et al.[265]	Mouse	In vivo	KCl	20 mg/kg ip.			↓				
TPEA	Dietz et al.[266]	Mouse	In vitro	Ouabain	50 µM	↓			↑			
BAPTA	Dietz et al.[266]	Mouse	In vitro	Ouabain	1 mM	↓			↑			

"↓" Means a reductive effect was observed after drug administration, "=" means no effect was noticed, and "↑" means that the tested parameter was increased by drug. Typical parameters under investigation are number, amplitude, propagation, threshold, duration, frequency, IOS area, and pial diameter. Most substances show little or no effect. Experimental settings and models are heterogeneous, comprising different animals (chicken, rat, mouse, and cat) and various forms of SD induction (KCl and electrical stimulation).

migraine.[220–224] Flunarizine possesses neuronal calcium channel blocking activity.[225] In contrast to other Ca^{2+}-entry blockers, flunarizine does not modify the myogenic activity of vascular smooth muscle.[198] This particularity is important because it implies that flunarizine can render cells unresponsive to vasoconstrictive stimuli, without interfering with the normal control of tissue perfusion.[198] Evidence also exists for its efficacy against SD. Certain investigators only observed Flunarizine's effects on hemodynamic response of SDs, but not on the characteristics of SDs,[200,226] while other investigators observed Flunarizine's effect on hemodynamic response as well as SD characteristics.[97,199]

Flunarizine's suppressive effect on the number of SDs might originate from a blockade of L-, N-, and P/Q-type voltage-gated Ca^{2+} channels[227] and flunarizine's shortening effect on duration may be attributed to its inhibitory effect on the cortical hypoperfusion induced by SD.[226]

Sumatriptan

Sumatriptan is effective in migraine by acting on the serotonin system. Its effects are mediated through vasoconstriction and blockade of neurologic inflammation. Few experiments on sumatriptan's inhibition of SD have been performed. A dose-dependent reduction of the numbers and amplitude and a deceleration of KCl-induced SDs in isolated chicken retinas at a dosage from 0.05 to 2.00 mM[205,228] was observed in the late 1990s, while more recently published studies support these observations.[110,204] However, the scientific status of this agent is ambivalent, and some studies observed no reductive effect on SD.[194,203,229]

Additional anti-migraine drugs that were effective against SDs are lamotrigine,[185] riboflavin,[185] methylsergide,[50,205] amitryptoline,[50] and propranolol,[50,205,206] but only a few experiments exist. Various anti-migraine agents have shown no effects against SD. Among these are dihydroergotamine,[179] ergotamine,[205] clonidine,[205] lisuride,[205] iprazochrome,[205] isoprenaline,[207] and amylnitrite.[207]

Table 4 provides the insight that, to date, a variety of in vivo and in vitro models suggest that prophylactic drugs are effective against SD if applied chronically over a long period of time.[179,193,205] These substances need to be tested in adequate dosages and in further settings. Table 4 shows that the most successful target of anti-migraine drugs is SD number,[50,110,192–195,197–199,204,205] while amplitude and propagation show ambiguous results. Especially, propagation is reported to be increased by certain anti-migraine drugs.[192,194]

Further agents tested against SD

In addition to the substances discussed above, we reviewed 54 other articles and identified 60 more substances that had been tested against SDs. Among them are AMPA receptor antagonists, ion channel blockers, cannabinoid receptor agonists, and various other agents such as *garlic extract* and *shrimp carotenoid*. The diversity of anti-SD substances underlines the complexity of SD and indicates that more research is necessary.

Table 5 shows that some of the substances that are less known for an inhibitory effect against SD (naloxone,[230,231] GYKI 52466,[232,233] sulpiride,[234] and THC[235]) show potential to reduce SD number, propagation, and duration and must not be forgotten.

Conclusions

The most effective group of drugs that are effective to block SD incidence and characteristics are NMDAr antagonists. Still, a refinement of the glutamate receptor antagonist therapy is necessary, including more subtype selectivity or a plural inhibition of glutamate excitotoxicity.

Neuroprotection using SD as a target must be scrutinized in more realistic scenarios, rather than animal models that do not translate to the human gyrencephalic brain, because neither of the strategies tested using them could be translated into the clinic. We have to consider not interfering with neuronal survival and neurogenesis, important factors in the rehabilitation of the patients.

Different from other neuroprotective targets, targeting SD can be finely adjusted and individualized, because we have the possibility to measure SDs in real time using ECoG.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Edgar Santos was supported by the Postdoc Fellowship Program of the Faculty of Medicine Heidelberg.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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