



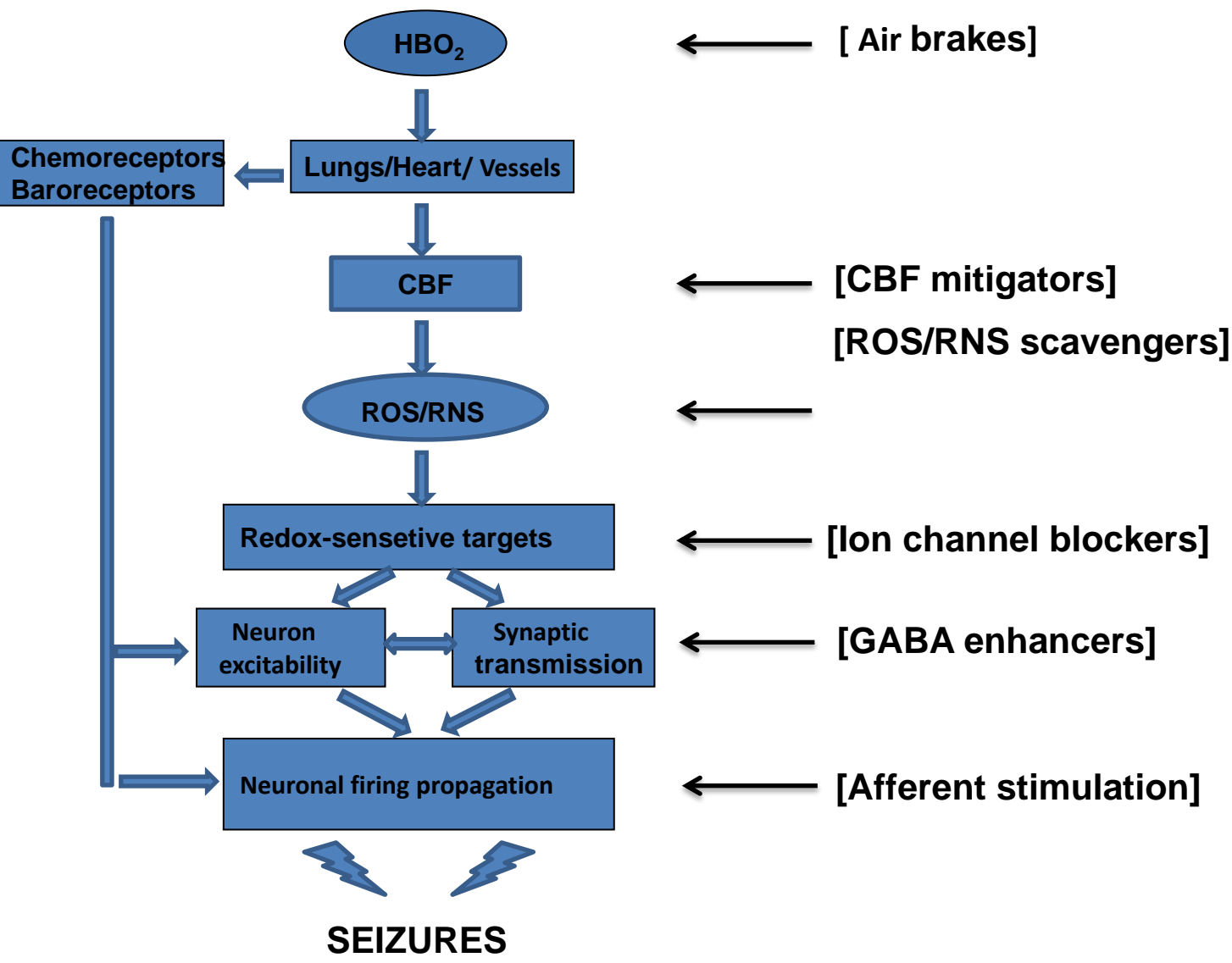
Critical Events in CNS O₂ Toxicity and Novel Approaches for Delaying Oxygen Seizures

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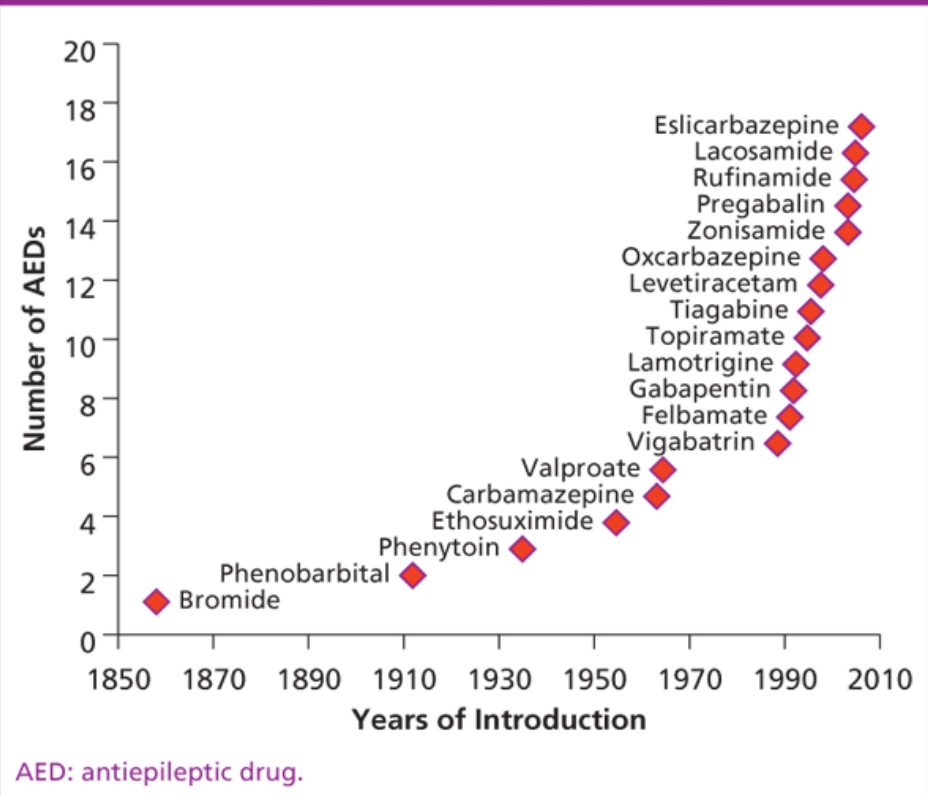
Background: CNS O₂ toxicity develops in a progression of events: hyperemia supplants an initial protective cerebral vasoconstriction; antioxidant defenses are overwhelmed; and excessive ROS/RNS production, combined with impaired afferent restraint of CNS excitability, triggers abnormal neuronal firing. We are testing a novel approach to alter this progression using a rational selection of antiepileptic drugs (AEDs) and FDA-approved vasoactive agents.



Aims:

- To screen FDA-approved antiepileptic drugs (AEDs) and vasoactive agents for efficacy in preventing oxygen seizures in mice
- To use the selected AEDs and vasoactive agents to assess their effects on physiological responses

Figure 1: Surge in Development of Antiepileptic Drugs Offers New Options in Epilepsy Management



Brodie M. 9th European Congress on Epileptology (ECE 2010). "A new vision for epilepsy management? From key learnings to new developments in the next decade" Symposium.

<http://www.peerviewpress.com/o1/b32>

Methods

Animals: Anesthetized and conscious SD rats

HBO₂: 2.5 - 6 ATA

Measurements: Arterial and ventricular pressures, cardiac output, heart rate, cerebral blood flow, total protein in bronchoalveolar lavage (BAL) fluid

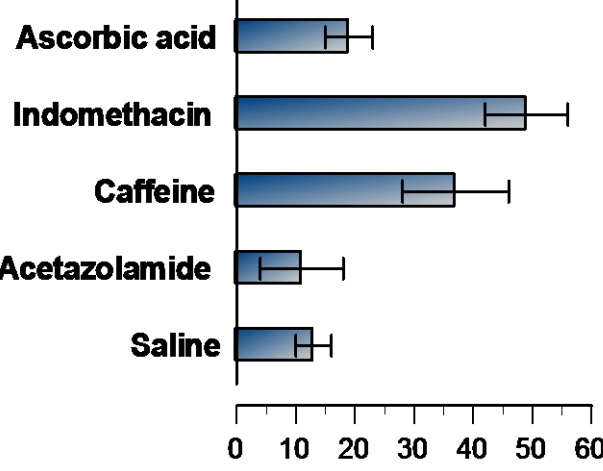
Monitoring: EEG, ECG, renal sympathetic nerve activity (RSNA) and body temperature

Calculations: Systemic and cerebral vascular resistance, baroreflex sensitivity

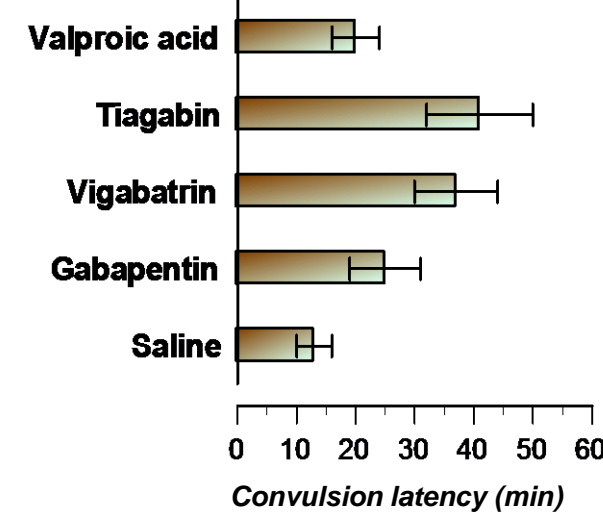
Interventions: Aortic and carotid baroreceptor deafferentation, electrical stimulation of aortic depressor nerve

Screened FDA- approved antiepileptic drugs and vasoactive agents for oxygen seizures prevention in mice

CBF mitigators:



GABA enhancers:



Selected AEDs and Vasoactive Agents for Assessment of Physiological responses

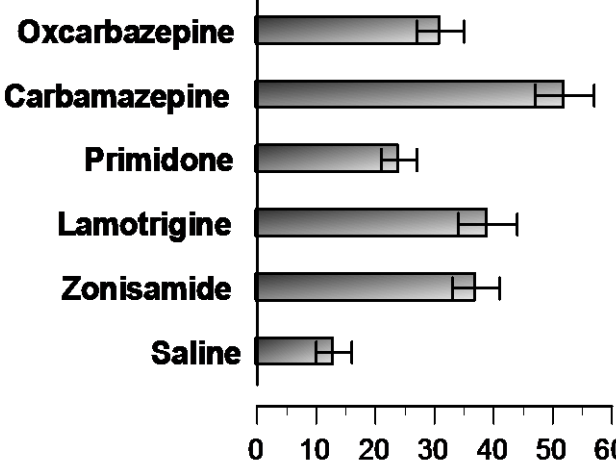
Sodium Channels Blocker:

Carbamazepine [Tegretol®]
Lamotrigine [Lamictal®]

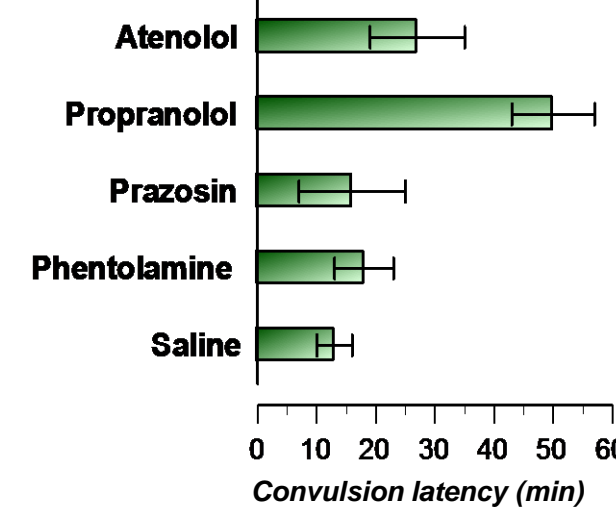
GABA Enhancers:

Vigabatrin [Sabril®]
Tiagabine [Gabitril®]

Na⁺ channel blockers:



Sympathetic inhibitors:



CBF Mitigators:

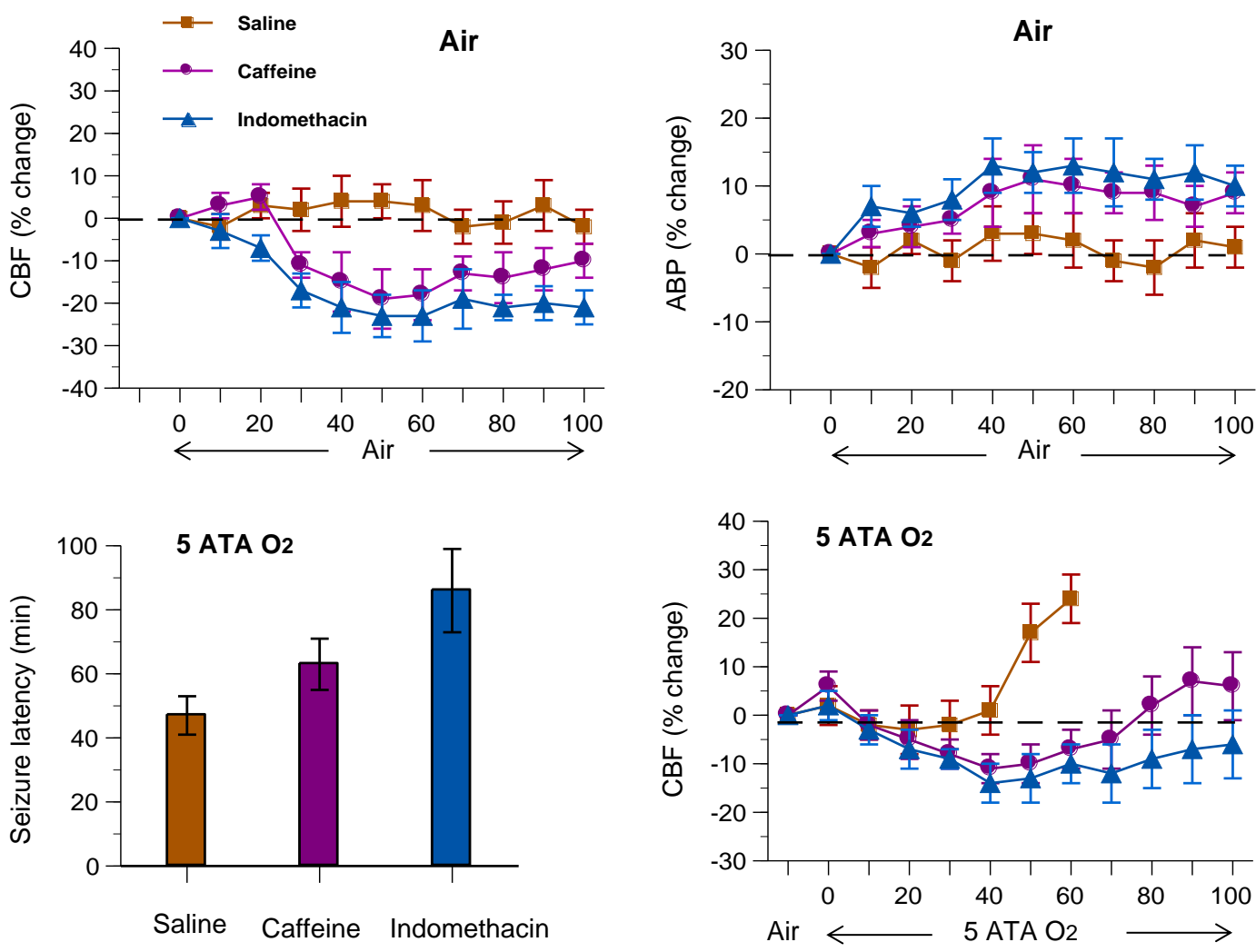
Indomethacin
Caffeine

ROS scavenger:

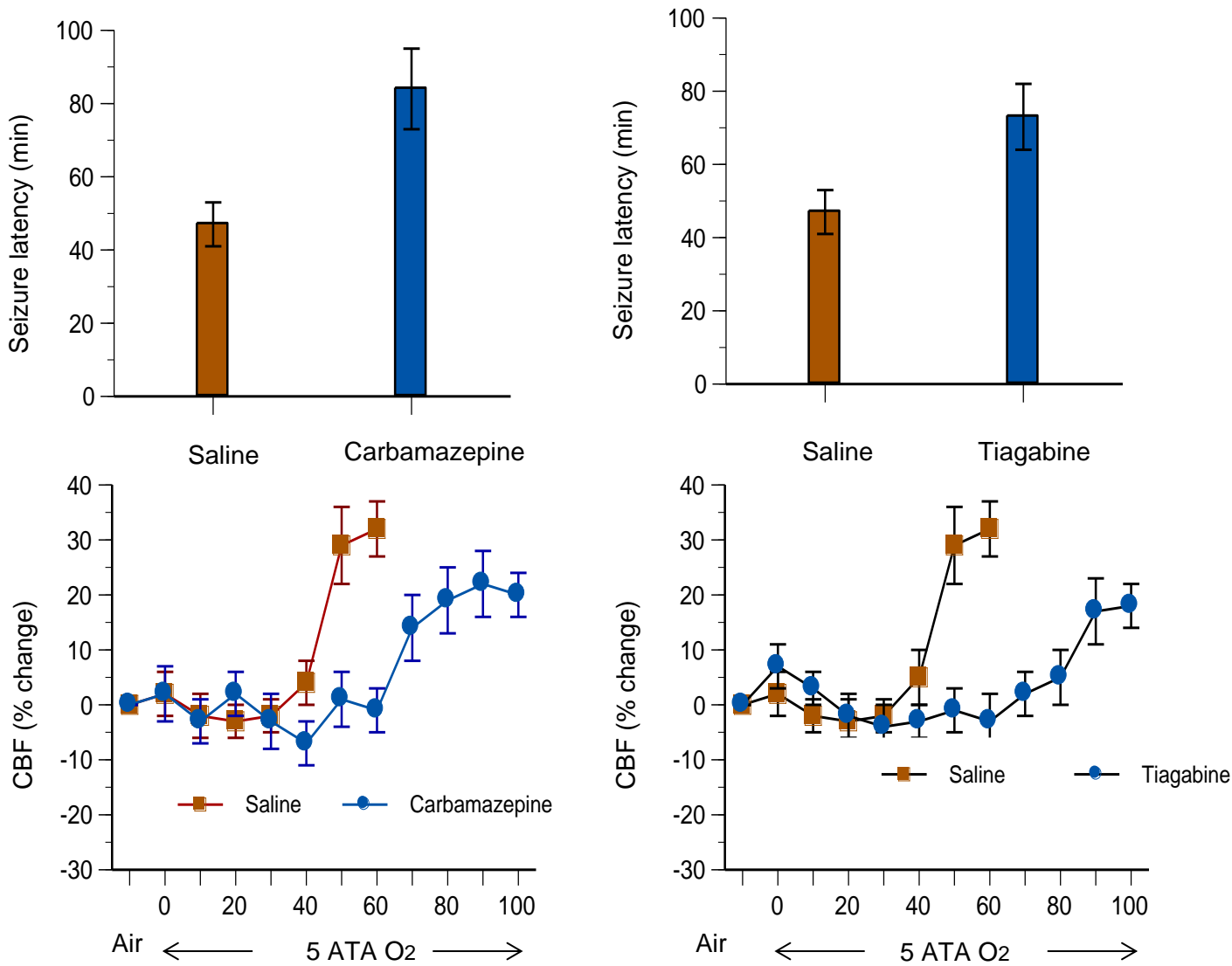
Ascorbic acid

Sympathetic Inhibitor:

Propranolol



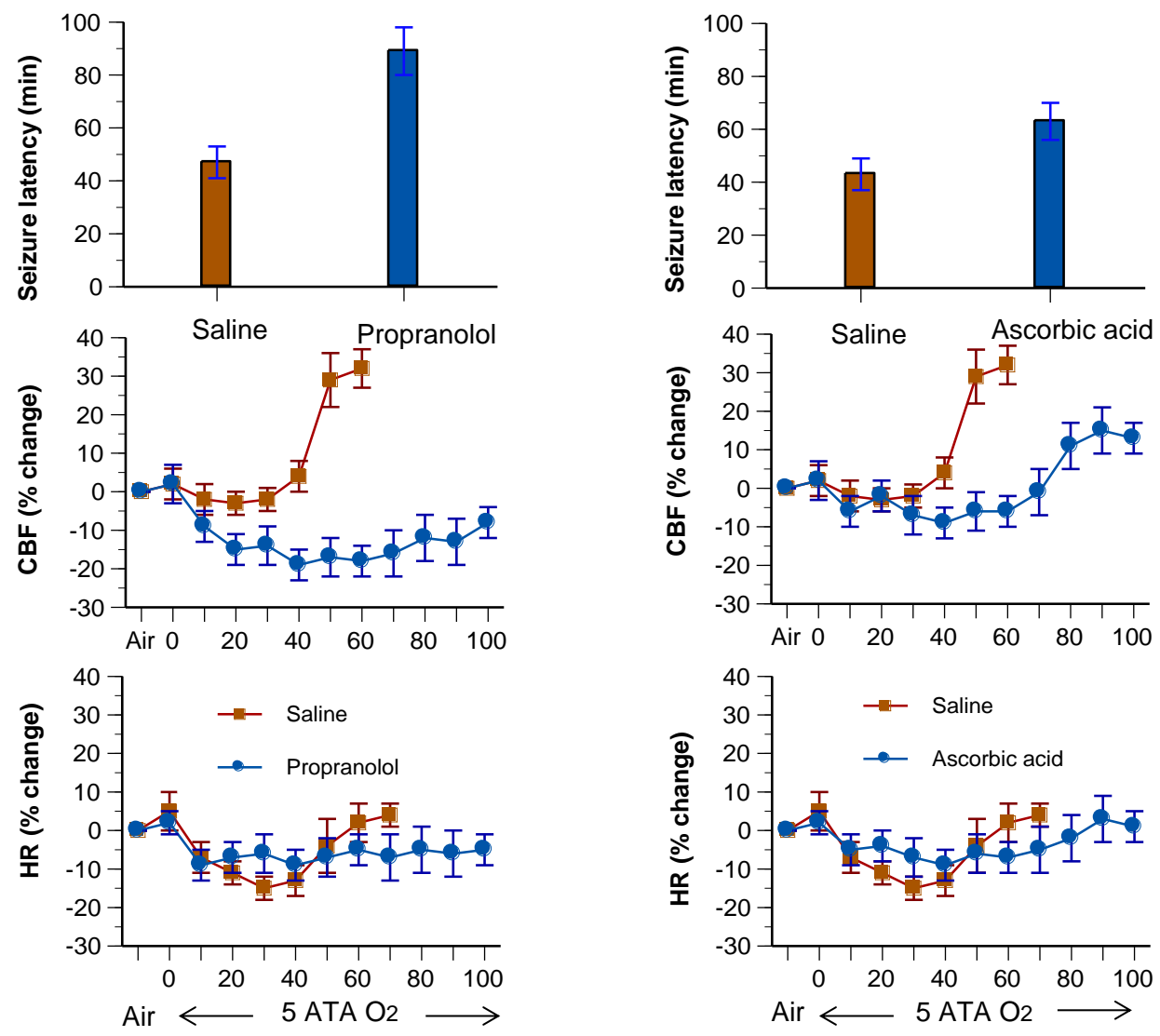
Physiological Responses and Seizure Latency in Rats treated with Caffeine or Indomethacin



Physiological Responses and Seizure Latency in Rats treated with Carbamazepine or Tiagabine

Conclusions

- Some FDA-approved drugs can significantly delay seizures in HBO₂
- Based on known mechanisms of action, these drugs can be useful for investigating mechanisms of CNS O₂ toxicity
- AEDs used clinically to treat epilepsy may be offered for an effective pharmacologic intervention that significantly extends the safe duration for human exposed to HBO₂

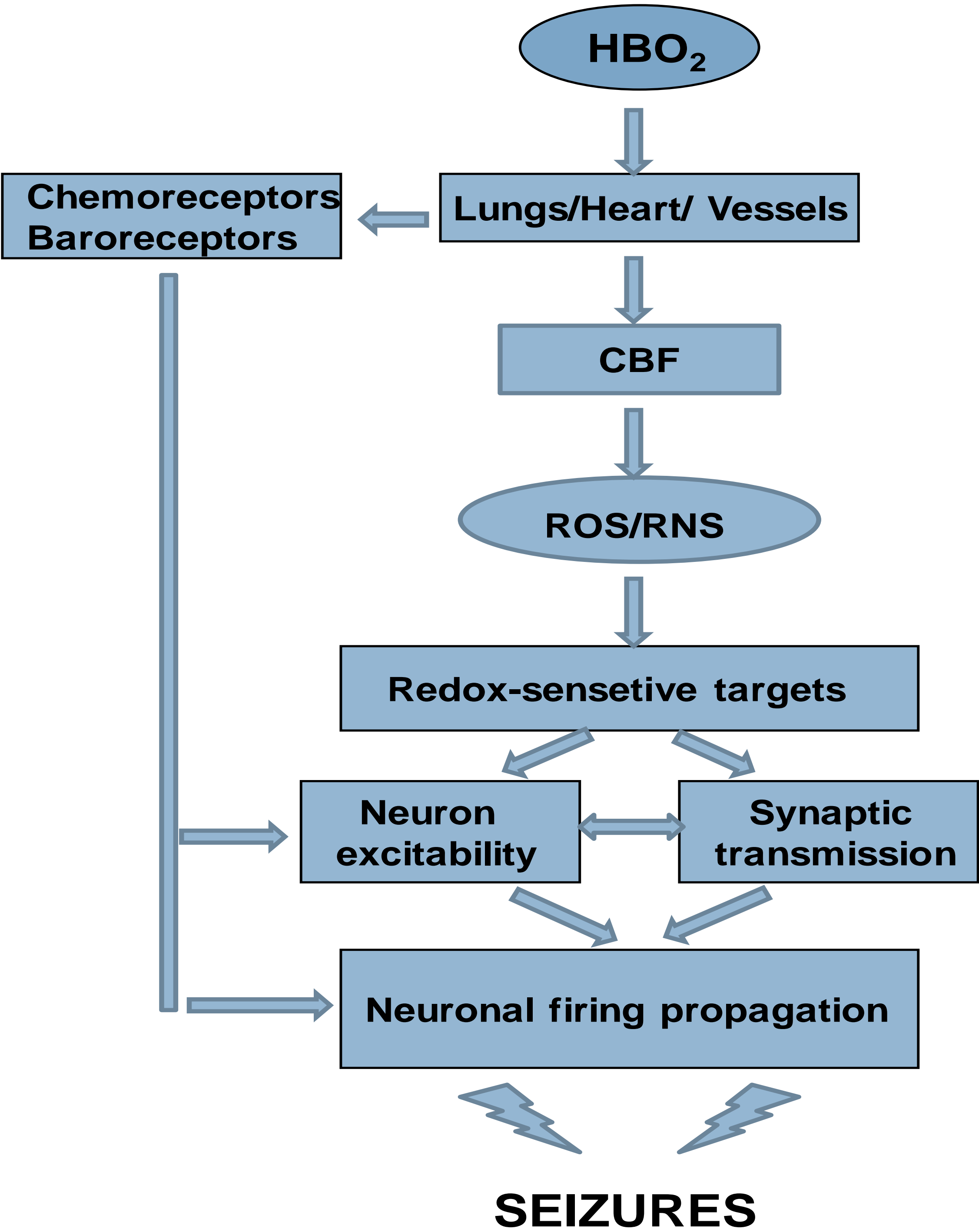


Physiological Responses and Seizure Latency in Rats treated with Propranolol or Ascorbic acid

Supported by the Office of Naval Research



Events of Oxygen Seizures Progression



Targets for Oxygen Seizures Prevention

- ← [Air brakes]
- ← [CBF mitigators]
- ← [ROS/RNS scavengers]
- ← [Ion channel blockers]
- ← [GABA enhancers]
- ← [Afferent stimulation]

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