

the characterization of potential neuropharmacological targets

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Goal: illustrate the applicability of computational modeling to neuropharmacological investigation.

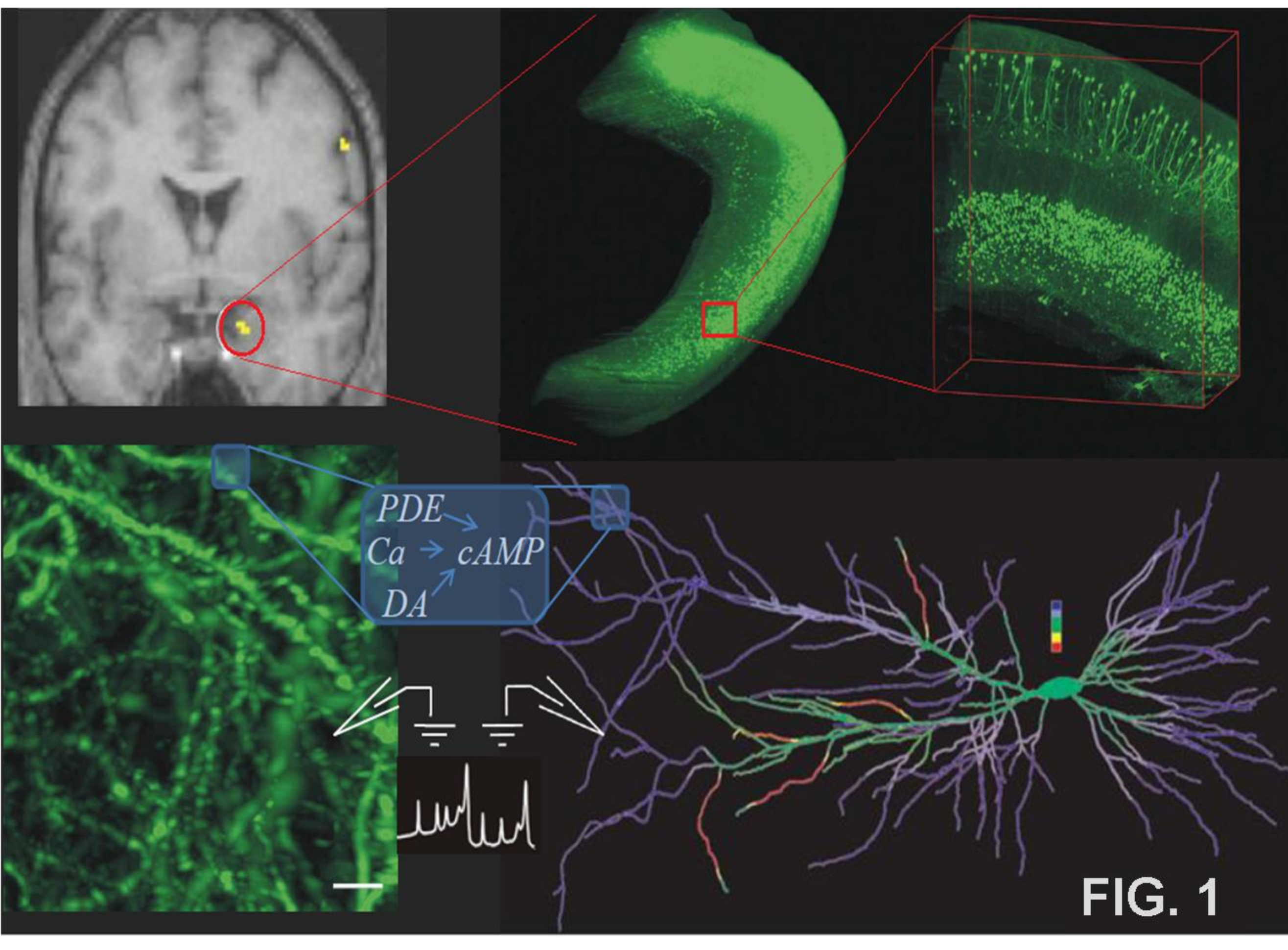


FIG. 1 From neuroimaging and neurophysiology experiments to cellular and sub-cellular biophysiological and biochemical models.

The identification and characterization of potential pharmacological targets is a fundamental problem at the intersection of medicinal chemistry and the neurosciences. Psycho- and neuro-active drugs typically work in nerve cells by affecting one or more aspects of electrophysiological activity. An integrated understanding of neuropharmacological agents requires bridging the gap between their molecular mechanisms and the biophysical determinants of neuronal function. Computational neuroscience and bioinformatics can play a major role in this functional connection. Robust quantitative models exist describing all major active membrane properties under endogenous and exogenous chemical control. These include voltage-dependent ionic channels (sodium, potassium, calcium, etc.), synaptic receptor channels (e.g. glutamatergic, GABAergic, cholinergic), and G protein coupled signaling pathways (protein kinases, phosphatases, and other enzymatic cascades). Simulations can elucidate, explain, and predict the effect of chemical agonists, antagonists, and modulators in the nervous system.

FIG. 1 adapted from Winston et al. 2002 and Dodi et al. 2007 permission granted by "Nature Publishing Group"

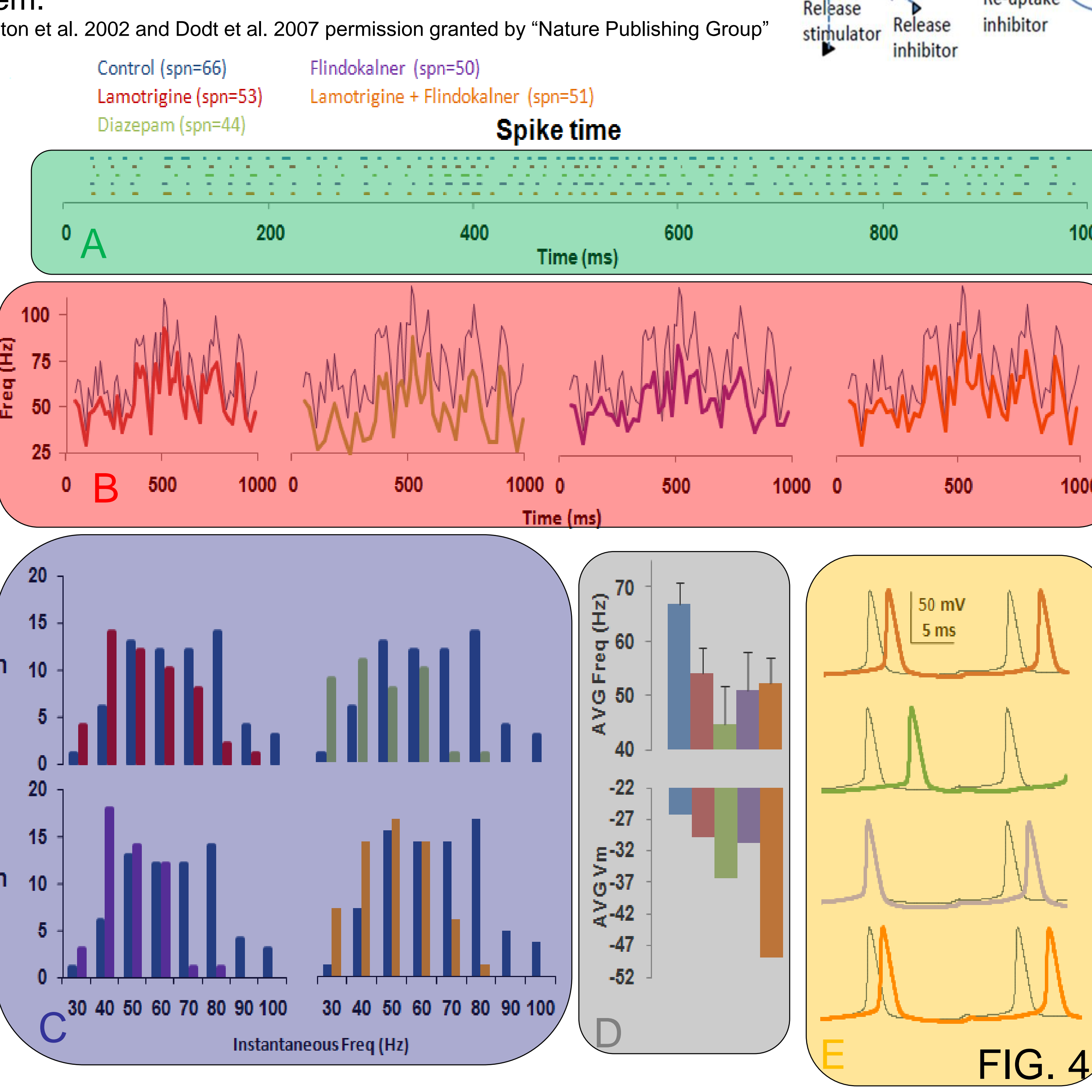
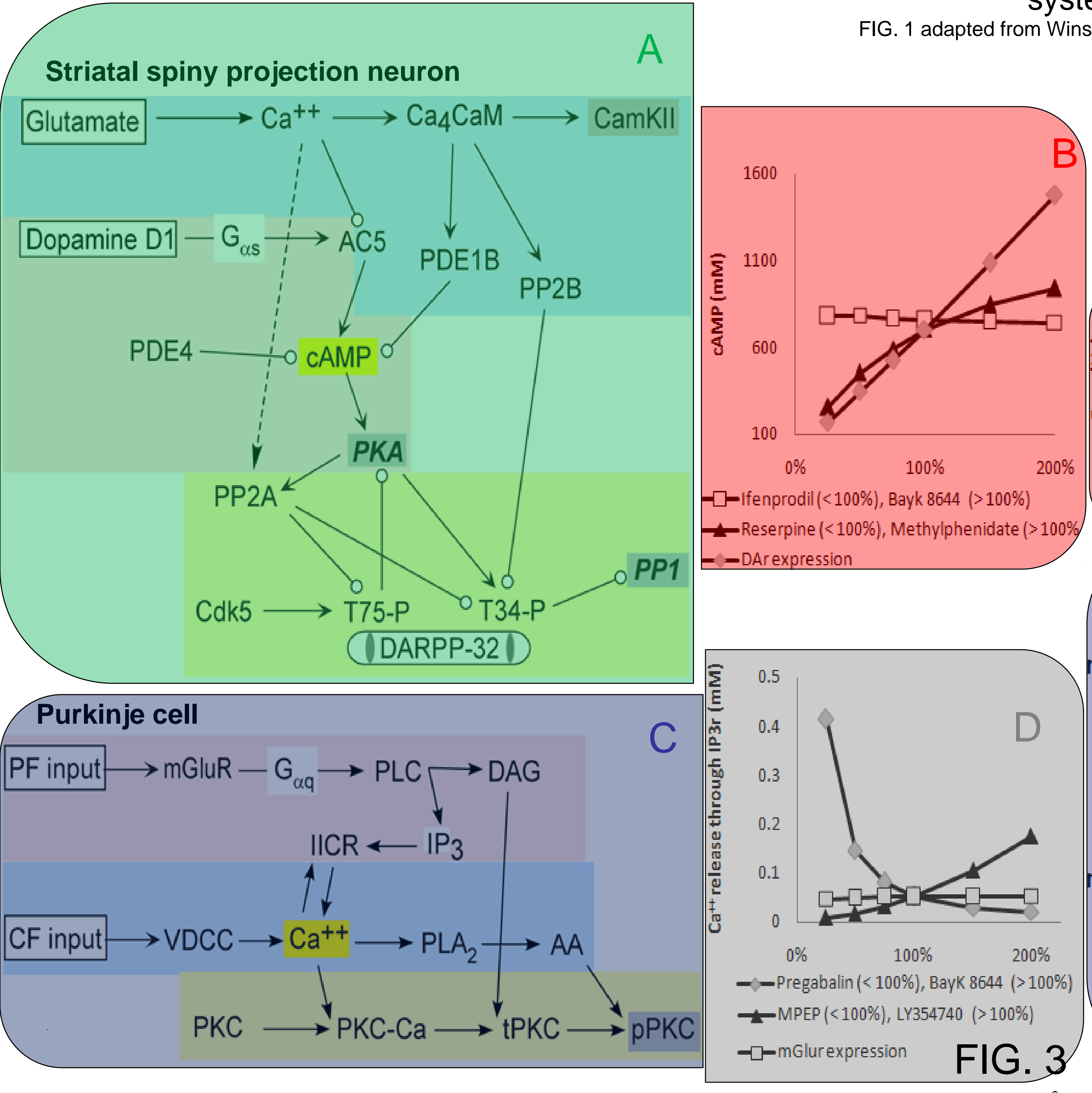


FIG. 3 Two intracellular signaling models of molecular dynamics involved in plasticity.

A) Striatal spiny projection neurons signaling pathways involved in the production of cAMP by DA and Glu inputs.

B) Dose-dependent effects on cAMP of drugs modulating DA reuptake (Reserpine and methylphenidate), DAR density (DAR expression) and Ca^{++} influx (ifenprodil and Bayk 8644).

C) 3 biochemical pathways included in the Purkinje cell model: Parallel fiber (PF) activation leads to IP_3 and DAG production. CF stimulation leads to Ca^{++} elevation and contributes to Ca^{++} release. Calcium, DAG, and AA activate pPKC.

D) Dose dependent effect of drugs modulating Glu release (MPEP and LY354740), GluR density (mGluR expression), and intracellular Ca^{++} concentration (pregabalin and Bayk 8644) on the IP_3 R dependent release of intracellular Ca^{++} from the ER.

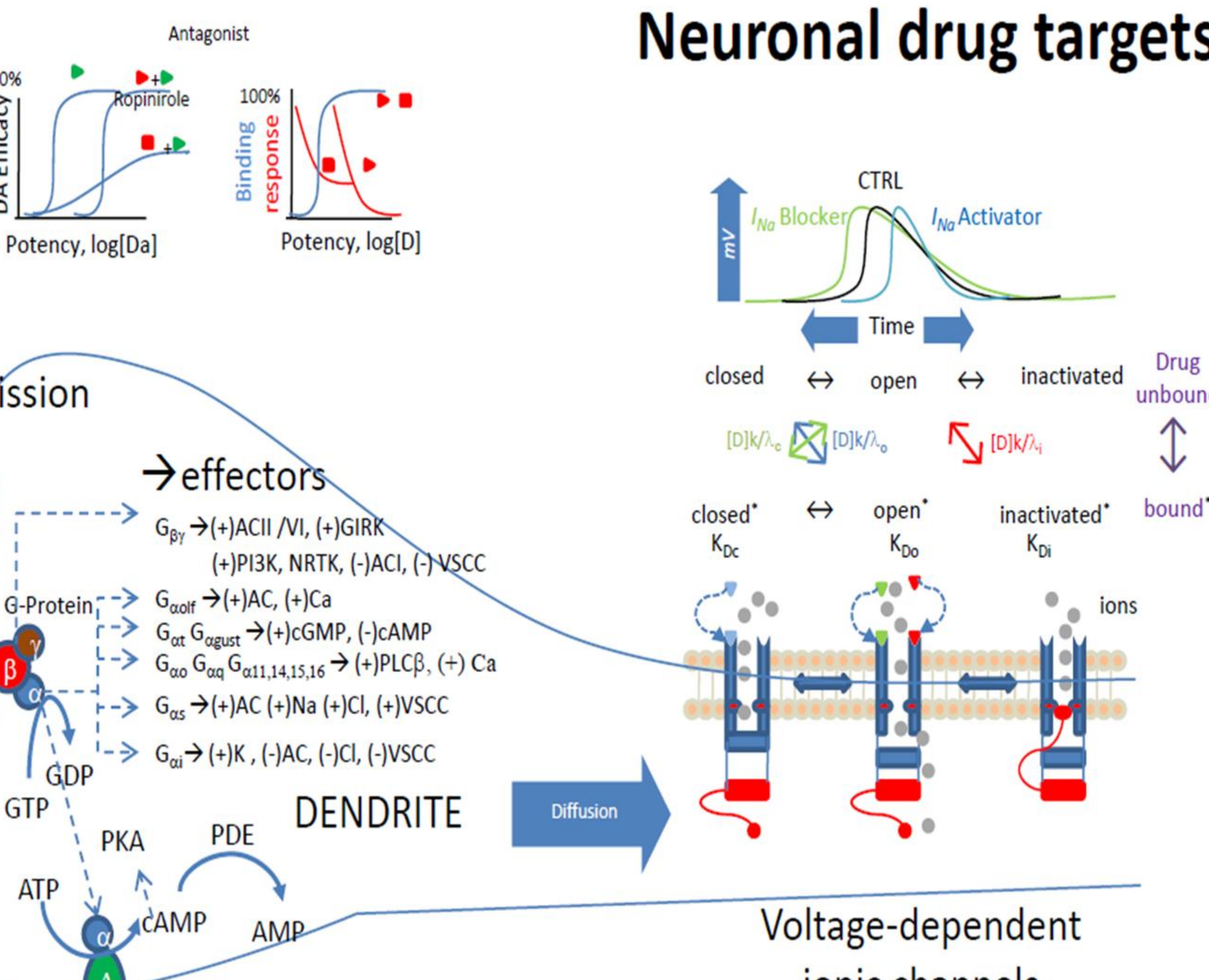


FIG. 2, TABLE 1 and 2 Neuronal drug targets.

Presynaptically a drug can stimulate or inhibit a neurotransmitter release, reuptake or breakdown. Once released, the natural ligand binds to specific receptors. Postsynaptically the receptor-drug interactions (full/partial, agonist/antagonist) are characterized in terms of potency, efficacy, and binding or response and they can be competitive or not depending on whether the natural ligand and drug share the same binding site. Metabotropic receptors are associated with a GTP-binding protein complex.

Voltage-dependent ionic channels-Drug interaction. Depending on the membrane potential and on their kinetic properties, ionic channels can be described by up to four functional states (activated, deactivated, inactivated and deinactivated). A specific drug (D) can bind to each of these states with specific association (k) and dissociation (λ) constants and affinities (K).

FIG. 4 Computational neuropharmacology & electrophysiology.

Antiepileptics targeting different neuronal mechanisms can differently...

A) Affect spike patterns and sequences.

B) Abate the instantaneous frequencies.

C) Favor certain frequency ranges, cutting off others.

D) Modulate membrane voltage keeping the output frequencies constant.

E) Affect the timing of the first and second spike.

FIG. 5 Molecular structures and functions of drugs interacting with the simulated mechanisms. (A) Lamotrigine, anticonvulsant and mood stabilizer used to treat epilepsy and bipolar disorder. It inhibits voltage-dependent Na^{+} channels, reduces glutamate release, inhibits AMPA, and shifts the inactivation voltage dependence of the I_h current. (B) Diazepam, benzodiazepine prescribed to treat of anxiety, insomnia, seizures, alcohol withdrawal, and muscle spasms. It is a powerful GABA_A agonist. (C) Flindokalner, K⁺ activator is a candidate for treating post-stroke neuroprotection. (D) Reserpine is used as antipsychotic blocks the norepinephrine, serotonin, and dopamine reuptake. (E) Methylphenidate, used to treat ADHD, chronic fatigue syndrome, and daytime drowsiness due to narcolepsy, binds the DA transporter inhibiting its reuptake. (F) Bupropion is an atypical antidepressant acting as DA reuptake inhibitor and as a nicotinic antagonist and a norepinephrine reuptake inhibitor. (G) Ifenprodil, a candidate drug in schizophrenia, is a selective, non-competitive NMDA antagonist which reduces cell excitability by blocking Ca^{++} influx. (H) LY354740, is a drug candidate for the treatment of anxiety and drug addiction. It is a highly selective agonist of mGluR2/3. (I) Pregabalin used to treat neuropathic pain, generalized anxiety disorder and as an adjunct therapy for partial seizures. It inhibits P/Q type Ca^{++} channels by binding to their $\alpha_2\delta$ subunit. (J) Bayk 8644, is an experimental drug candidate acting as mood regulator and as an L-type Ca^{++} channel activator. (K) MPEP is a drug candidate to treat epilepsy, pain, neurodegenerative diseases, and anxiety. It is a highly selective and potent mGluR and AMPA antagonist.

Conclusions: The use of the computational neuropharmacological approach will soon generate an avalanche of studies aimed at the resolution of many brain conditions.

This work was supported in part by R01 grant NS396000 to GAA, funded by NINDS, NIMH, and NSF; by R01 grant AG025633 to GAA, funded by NIA under the CRCNS program; by SGER grant 747864 to GAA, funded by NSF; and by NSF CRCNS through NIAAA R01 016022-01 to KTB.

TABLE 1: Drugs interacting with Neurotransmitter Receptors*

Family (G-protein)	Drug (brand name)	Drug action(s)	Brain region	Condition	Ref [†]
5-HT _{1A,1B,1D} (G _{i1})	Esiperon (Relpax)	Agonist	Trigeminal sensory nerve endings, intracranial blood vessels	Migraine	52, 53
	Vilazodone	Partial Agonist (SSRI)	Cortex, hippocampus	Depression	54, 55
	Fluoxetine (Prozac)	Reuptake inhibitor	Dentate gyrus	Depression, obsessive-compulsive disorder	56, 57
	Quelapine (Seroquel)	Antagonist	Frontal cortex, striatum, limbic system, anterior pituitary gland	Bipolar disorder, schizophrenia	58, 59, 60
	TGBA01AD	Reuptake inhibitor (5-HT _{1A} agonist)	N/A	Depression	61
	5-HT _{1A} (G ₁₂)	SGS-518	Antagonist	N/A	Schizophrenia
5-HT _{2A,2C} (G ₁₂)	Benzaze	Antagonist (also for 5-HT _{1A})	Frontal cortex, striatum, hippocampus	Neurodegenerative diseases	63, 64, 65, 66
	5-HT _{2C} (G ₁₂)	Olanzapine (Zyprexa)	Antagonist (also for 5-HT _{1A} , 5-HT _{2A})	Frontal cortex, hippocampus	Schizophrenia
5-HT _{2A} (G ₁₂)	Mirtazapine (Remeron)	Antagonist	Central amygdala, anterior insula, septum	Depression	69, 70, 71, 72, 73, 74
mGluR _{1,2,3,4,7} (G ₁₂)	LY354740	Agonist	Striatum, hippocampus, cortex, cerebellum	Anxiety	75, 76, 77
	MPEP	Antagonist (also for AMPA)	Striatum, thalamus, cortex, amygdala	Epilepsy, pain, neurodegenerative diseases	78, 79, 80, 81
	Lamotrigine (Lamictal)	Release inhibitor (Ca ²⁺ and I _h blocker)	Striatum, thalamus, cortex, hippocampus, amygdala	Epilepsy, bipolar disorder	11, 67, 78, 79
	TAN-950A	Agonist	Hippocampus/CA1	Neurodegenerative disease	80, 81
NMDA ²⁺	Apigenin	Antagonist	Hippocampus, cortex	Neurodegeneration, Parkinson, brain injury, cardiovascular ischemia	82, 83, 84, 85
	ifenprodil	Non-competitive antagonist (Ca ²⁺ blocker)	Hippocampus/CA3, prefrontal cortex, amygdala, striatum	Schizophrenia	85, 86
AMPA ¹⁺	Talampri	Non-competitive antagonist	Amygdala	Epilepsy, Parkinson	87, 88, 89, 90
	S-16986	Modulator	Frontal cortex, dorsal hippocampus	Neurodegeneration, cardiovascular ischemia, cognitive disorder	91, 92, 93, 94
Kainate ¹⁺	LY23558	Antagonist (also for AMPA)	Hippocampus, lateral and medial habenulae, superior and inferior colliculi	Post-operative pain, anxiety	95, 96, 97
	Adogolide	Agonist	Ventral tegmental area, limbic forebrain, nucleus accumbens	Cocaine addiction	98, 99
5-HT _{2A} (G ₁₂)	Reserpine	Reuptake inhibitor (also for NE and 5-HT)	Striatum, frontal cortex	Antipsychotic	100, 101, 102
	Methylphenidate (Ritalin)	Reuptake inhibitor	Prefrontal cortex, hippocampus, striatum, hypothalamus	ADD, ADHD	103, 104, 105, 106
	Haloperidol (Haldol)	Antagonist (also for d ₂)	Mesocortex, limbic system, nigrostriatal pathway	Antipsychotic	107, 108, 109, 110
	Bupropion (Zyban, WELLBUTRIN)	Reuptake inhibitor	Frontal cortex, hippocampus, striatum, thalamus	Smoking cessation, depression	111, 112
5-HT _{2B} (G ₁₂)	Pramipexole (Mirapex)	Agonist	Hippocampus, prefrontal and posterior cingulate cortex, superior temporal gyrus	Restless legs syndrome	113, 114, 115, 116, 117, 118
	Antiprazole (Ablify)	Partial agonist	Putamen, caudate, thalamus, superior temporal cortex	Bipolar disorder	118, 119
	Ropinirole (Requip, Moxepa)	Antagonist	Mesencephalon	Restless legs syndrome	120, 121, 122
GABA _A (G ₁₂)	Baclofen (Lioresal)	Agonist	Hypothalamus, frontal cortex	Antispasmodic agent for multiple sclerosis	123, 124, 125
	Diazepam (Valium, Diastat)	Agonist	Cortex, telencephalon, hypothalamus	Anxiety, epilepsy	30, 126, 127
GABA _B (G ₁₂)	Methohexital (Brevital Sod)	Agonist	Thalamus, hippocampus	Anesthetic	128, 129
	Topiramate (Topamax)	Agonist (Na ⁺ blocker)	Prefrontal and occipital cortex	Epilepsy, SMEI (severe myoclonic epilepsy of infancy)	130, 131, 132, 133
Muscarinic (G ₁₂)	Sodium valproate (Depakote)	Breakdown inhibitor (also NE, DA and 5-HT modulator)	Occipital, parietal and frontal cortex, accumbens, substantia nigra	Mania, migraine, epilepsy, GEFS+ (generalized epilepsy with febrile seizures plus)	134, 135, 136, 137
	Donepezil (Arcept, Dyanzac)	Breakdown inhibitor	Cortex, hippocampus	Alzheimer	138, 139, 140
ACh	Phenantholine	Non-competitive antagonist	Muscles cells, cortex	Neurodegenerative disease, cognitive disorders	141, 142
	Nicotine (Nicotrol)	Agonist	Thalamus, striatum, anterior cingulate cortex	Smoking cessation	143, 144
NE	HP-184	Release stimulator (also for 5-HT)	Hippocampus	Spinal cord injury	145, 146
	DOV 21947	Reuptake inhibitor (also for DA and 5-HT)	Striatum, mesocorticolimbic, cerebellar, thalamus	Depression	147, 148
5-HT _{2A,2C} (G ₁₂)	Dextroamphetamine (Dexedrine)	Reuptake inhibitor	Insular cortex	ADHD	149, 150
	Atomoxetine (Strattera)	Release inhibitor	Caudate putamen, cortex (Prefrontal Ventral and Orbital)-basal thalamus, long	ADHD	151, 152

* All receptors are G-coupled unless noted with (ionotropic) [†] references check: www.gmu.edu/departments/krasnow/sgm/michele/

² Chloride ³ Drugs without brand name are not prescribable

⁴ Monovalent cations ⁵ Monovalent cations

⁶ Chloride ⁷ Monovalent cations

⁸ Chloride ⁹ Monovalent cations

¹⁰ Chloride ¹¹ Monovalent cations

¹² Chloride ¹³ Monovalent cations

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