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Research Article

Do Anesthestics Modulate Neural Traffic with in the Carotid Body

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Abstract

Highly unlikely is it that senior anesthesiologists have not heard of the carotid body (CB). In all probability they know something of its physiology since this receptor is of critical importance during general anesthesia. The following overview is addressed to younger anesthesia practioners. In it we point out the location, functional anatomy, sources of stimulation, reflex responses to stimulation, antagonists of the receptors, and the behavior of some of the CB's components in response to various anesthetics. Complicating an interpretation of the effect of anesthetics is the fact that the CB has cholinergic, purinergic, dopaminergic, and GABAergic receptors on parts of the CB, possibly involving a situation in which the action of one receptor negates the action of another.

Keywords: Carotid body (CB); Nicotinic ACh Receptor (nAChR); Muscarinic ACh Receptor (mAChR); Dopaminergic D2 (ReceptorD2R) ATP; Purinergic receptors (P2XR, P2YR); GABAA receptor (GABAAR)

Introduction

Organisms on this planet are characterized by an almost limitless number of interconnections. They must continually integrate the activity of their cells, tissues, systems. Exogenous substances, introduced via inhalation, infusion, transdermal application, have the potential of disrupting normal integrative operations. This study presents the impact of anesthetic agents on what is arguably the most significant interconnecting/integrating receptor in the organism, the carotid body (CB).

Location and Functional Anatomy of CB: This structure is located bilaterally near the bifurcation of the common carotid artery into the internal and external carotid arteries. At the base of the internal carotid artery is an expansion of the vessel, the carotid sinus, the high pressure baroreceptor. This structure is the primary detector and regulator of arterial blood pressure. The afferent nerve fibers from the sinus travel to the petrosal ganglion which contains their cell bodies; and from there the axons proceed to the nucleus of the solitary tract (NTS). And from there significant targets are the paramedian reticular nucleus of the sympathetic nervous system and the vagal nuclei in the medulla.

A few millimeters upstream from the sinus, a small artery branches out from the external carotid artery to perfuse the CB. Blood flow through the CB is the highest that has ever been measured through any organ in the body. In the feline model it was reported [1] to flow at better than two liters/min/100 gm of tissue. The structure is a chemoreceptor which «tastes» the composition of the arterial blood. In addition to the plentiful vasculature two cell types are found in the CB. The type I or Glomus cell (GC) is the principal chemodetecting unit.The type II cell is a supportive unit, but recent studies suggest it, too, participates in chemodetection as a paracrine modulator of the action [2]. Involved in its important impact on GC activity is 5HT [3]. Found in the CB on the GCs and abutting neurons are the receptors for ACh (nicotinic and muscarinic), for ATP (P2X, P2Y), for dopamine (D_2), and for GABA ($GABA_A$).

Stimulation of CB by Hypoxia: The CB increases its neural output to the CNS in response to a decrease in arterial PO_2 (P_aO_2) or [glucose], and to an increase in arterial PCO_2 (P_aCO_2) or $[H^+]_a$. In the instance of hypoxemia the lowered partial pressure of O_2 reduces traffic in some of the K+ ion channels of the GC. This inhibition of the outflow of K^+ depolarizes the cell. When the membrane potential becomes sufficiently less negative, voltage-gated calcium channels are activated; they open; extracellular calcium enters the cell, and attaches to neurotransmitter (NT)-containing vesicles which proceed to the inner surface of the GC'S membrane where they dock with the help of various proteins, such as synaptin 1. They exocytose their contents of excitatory NTs (e.g., acetylcholine [ACh], ATP). These agents cross a synaptic cleft between the GC and abutting sensory afferent neuron where they attach to an appropriate receptor to create an action potential

which proceeds to the petrosal ganglion and then on to the nucleus of the solitary tract in the medulla (NTS). Dopamine is also released from vesicles in the GCs, and acts to attenuate the excitatory action of ACh and ATP by adhering to the D_2 dopamine receptor on the abutting afferent neuron (Figure 1).

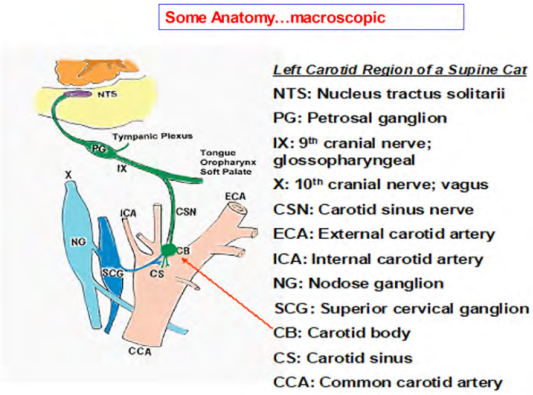

Figure 1: Macroscopic view of left carotid area of supine cat. Structures are labeled.

Reflex Responses: Why is the CB arguably the organism's most important interoreceptor? Stimulation of the CBs provokes reflex responses in the respiratory, cardiovascular, endocrine, and renal systems. Further, whereas increases in carotid sinus neural output to the CNS will significantly diminish outflow from the sympathetic nervous system (SNS), increased neural output from the CB stimulates SNS outflow (Figure 2).

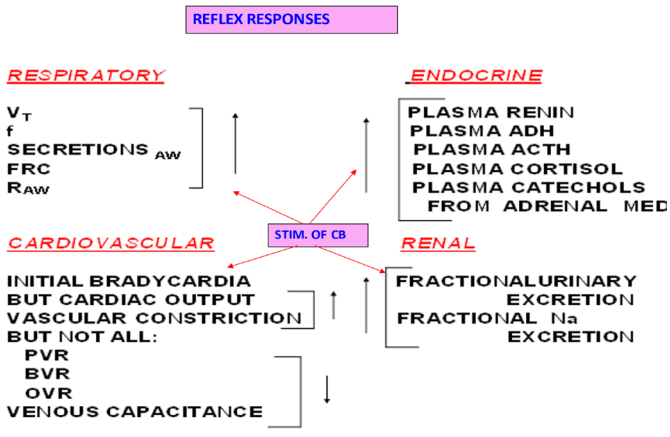

Figure 2: Reflex responses to stimulation of the carotid body.

Respiratory: Stimulation of the CB produces an increase in tidal volume, frequency, functional residual capacity [4], airways resistance [5], and secretions [6].

Cardiovascular: Stimulation of the CB produces an increase in cardiac output and contractility, and in total peripheral resistance [7,8]; this latter is due to vasoconstriction in many, if not most vascular beds. The combination of , increases in cardiac output and total peripheral resistance elevates arterial blood pressure. Somewhat paradoxically, stimulation of the CBs attenuates the classic hypoxia-generated pulmonary vasoconstriction [9-11].

Endocrine: Stimulation of the CBs would be expected to release renin by virtue of the increase in SNS input into the macula densa of the juxtaglomerular apparatus in the kidney [12]. Further, CB stimulation produces an increase in plasma levels of ADH (vasopressin) in both dogs and rats [13,14]. If ventilation is controlled, plasma levels of ACTH will increase upon CB stimulation in anesthetized dogs [15] and in conscious rats. The adrenal cortex will yield an increase in cortisol secretion even without the CBs; but this yield is only 47% of what is produced when the CBs are intact [16,17]. The adrenal medulla increases its release of both norepinephrine and epinephrine upon CB stimulation in both dogs and cats [18].

Renal: CB stimulation increases renal sodium and water excretion in normoxic mammals, while bilateral CB denervation abolishes the natriuretic response to CB stimulation in normoxic, anesthetized vagotomized animals [19].

Having seen what the CB does qualifyimg it as, arguably, the most important integrating receptor in the organism, and having seen above how it works with the use of neurotransmitters and appropriate receptors, we change focus to agents which could change the effect of endogenously released neurotransmitters. Anesthetics operate on neurotransmitter receptors and membrane channels in the CBs; this affects the characteristics of the neural traffic from the CBs. Some of the early work in this area began with studies treating the effect of muscle relaxants frequently used during general anesthesia. For example, vecuronium, a muscle relaxant, attenuates the ventilatory response to hypoxia, a well-known CB-based response [20,21]; pancuronium, also a relaxant, is a typical non-depolarizing curare-mimetic which competitively inhibits the nicotinic acetylcholine receptor (nAChR) at the neuromuscular junction by blocking the binding of acetylcholine. However, this nAChR differs from others due to its subunit composition. It is a homomeric pentamere the five subunits of which are all a7.

CB Receptors/Their Antagonists

(ACh; nicotinic, nAChR) The nAChRs in the CB are mostly heteromeric pentameres, and like those in the CNS made up of a2, a3, a4, b2, b3,and b4 subunits; some a7 subunits do exist in the CB. But in the CBs the subunits a2-4 and b2-4occur in different combinations and are blocked by different antagonists. For example, a-Conotoxin MII is quite specific for the a3b2 combination of subunits in the nAChR of the CB. And dihydro-

beta- erythroidine (DHbE) is a relatively specific blocker for the a4b2 combination of subunits of the nAChR. Hexamethonium is powerful, but non-specific. Mecamylamine also blocks.

(ACh; muscarinic, mAChR) The M1 and M2 receptors have a major representation in the CB on the GC and also the afferent nerves. They are G- protein coupled receptors which are often linked to the activation of K^+ channels in the CB. Blocking with atropine, gallamine, AFDX116 (vs M2), pirenzepine (vs M1) gives a picture of a very confusing situation since the density of these cholinergic receptors varies in different species. And other factors determine the activity of the CBs' cholinergic activity. No doubt exists as to their presence; but their activity depends on other factors which influence the union of endogenously released ACh and these cholinergic receptors.

(ATP; P2XR, P2YR) The P2XRs are ATP-gated nonselective cation channels composed of seven possible subunits (P2X1-7). The functional P2XRs are organized as both homomeric and heteromeric trimers having three ATP binding sites. The second active unit, P2YR, a G-protein coupled receptor, is also a ligand-gated receptor channel. Native agonist for the P2XR is ATP whereas both ATP and its metabolite ADP act as agonists for the P2YR. Two common antagonists are: Suramin and pyridoxal-5'-phosphate-6-azo-phenyl-2,4- disulfonate (PPADS). To date these receptors have been detected only on the afferent neuron abutting the GC of the CB.

(Dopamine; dopamine D_2 R) Dopamine attenuates CB neural output to the CNS by acting on the dopamine D2 receptor found in the afferent nerve abutting on the GC. Droperidol is an antagonist. Haloperidol has a high affinity for the D2receptor which it antagonizes.

(GABA; $GABA_A$R) GABA is found in the GCs of the CB. And the $GABA_A$ receptor has been found on some afferent fibers and some cells in the petrosal ganglion. Studies in the cat CB showed that the increased neural output inresponse to a perfusion of hypoxic Krebs solution was significantly reduced by mM doses of two benzodiazepines, midozolam and diazepam.

CB Components and Anesthestics: Many reports of the effects of anesthetics on breathing can be found [22-24]. And these phenomena involve the CB. However, studies of anesthetic effects on the CB structures are rare. An early study [25] reported that in cats 30 min of inhaling halothane (0.5-1.0 percent) reduced the slope of the chemoreceptor response curve to CO2 to about 48 percent of the control slope. The response to hypoxia was reduced to about 58 percent of the control response. The increase in firing after an intravenous injection of nicotine (100 mg) was reduced to 25 percent of the control response. The response to NaCN (25 mg) was reduced to 17 percent of the pre-nicotine value. The effect of halothane was half complete in 1-2 min and reversible. A later study of the effect of vecuronium, a muscle relaxant frequently used in general anesthesia cases, showed that the agent inhibited hypoxic neurotransmission in the rat CB [26].

Perhaps the most informative study of the effect of anesthetics on the components of the CB appeared recently [27]. The authors were using propofol, an anesthetic normally injected into a vein to induce short term general anesthesia, or to maintain the general anesthetic state. The authors, using propofol on isolated neonatal rat CB GCs, concluded that propofol does have a direct effect on hypoxic signaling in the isolated GC and this may be at least partially due to its ability to inhibit voltage-gated Ca^{++} channels. They also found that propofol suppressed nAChRs' action to excite GCs.

In hopes of gaining a broader understanding of anesthetics' effect we shall explore the behavior of cholinergic (nicotinic, muscarinic), GABAergic, dopaminergic, and purinergic receptors and their associated channels in some other preparations of animals and constructs. But caution must be the key word in extrapolating conclusions regarding general anesthesia in the CNS, or anesthetic effects elsewhere to what takes place in the CB. Receptors and channels in one tissue need not behave in the same way as they do in another tissue. And their presence/functioning in one organ need not be the same as in another tissue/organ. But the largest problem in describing the effects of anesthetics in the CB is that all of the receptors are present as are ACh, DA, ATP, and GABA. And one could reasonably assume all would be simultaneously released under conditions of hypoxemia, acidosis, and hypercapnic arterial blood. So does the operation of one type of receptor negate the operation of another? And what is the relative density of each type?

However, it might be helpful to recognize some generally held points of view derived from the significant corpus of previous studies in the CNS's neurons. This type of a brief overview could suggest directions for future investigation. Surgical concentrations of general anesthetics exert their principal effects on ligand-gated ion channels, not voltage-gated channels. They do so by influencing postsynaptic activity, working on synaptic transmission rather than axonal conduction.

(nicotinic, nAChR). In one study a heteromeric pentamere with the a4b2 combination of subunits was exposed to the volatile anesthetic halothane; the nAChR had been inserted into a Xenopus oocyte. Halothane reduced the current from 900 to 540 nAmp. In another study using cloned cells short chained alcohols and some volatile anesthetics produced both a stimulation and an inhibition of nAChR channels. Stimulation resulted from an apparent increase in the affiinity of ACh for the nAChR [28]. Part of the inhibitory effect was due to a reduction in duration of the single channel burst. Several have concluded that the drug binding sites responsible for the excitation differ from those responsible for inhibition. Further, two of the 16 member superfamily of genetically and structurally related receptor channels which are directly gated by neurotransmitters at central synapses and are sensitive to modulation by many anesthetics are the neuronal

nicotinic AChRs and the $GABA_A$Rs. The former in rat, of a4b2 subunit composition expressed in Xenopus oocytes, reduced its response to ACh to about 50 % of control when in the presence of 17.5 mM halothane [29]. Finally, studies of the nAChRs have pointed out how the volatile anesthetics like isoflurane and enflurane were particularly effective at inhibiting the receptor with the primary effect at the single channel level being to reduce the mean open time [30].

(muscarinic, mAChR). A recent study of the O_2 - sensitive TASK-like background K+ channel [31] identified one unit that controls CB behavior which dramatically responded to anesthetics: 1.5% halothane increased the oxygen-sensitive K^+current by 176%. They concluded from this study that the O_2-sensitive background K^+ channel of CB GCs is likely to be an endogenous TASK-1-like channel.

(GABAAR) Most anesthetics are very effective at potentiating responses to GABA. For example, 20 mM pentobarbital increases peak GABA responses by about three-fold in one preparation [30]. This is apparently due to an increase in the GABAAR's affinity for GABA. Further, halothane potentiates responses to low levels of GABA [30].

(dopamine, D2R). The inhaled anesthetic isoflurane inhibits dopaminergic synaptic vesicle exocytosis in some tissues (cultured neurons from rat ventral tegmental area). Central to this response is the activity of calcium channels [32].

(P2X_7R, P2YR). In experiments with a rat microglial cell line Inhaled anesthetics (sevoflurane, isoflurane, and halothane) at doses three times as high as minimum alveolar concentrations had no effect on the P2X_7Rs-mediated currents. IV anesthetics (ketamine, propofol, and thiopental) enhanced the P2X_7R-mediated currents reversibly. The P2YR-mediated mobilization of intracellular Ca^{2+} was not affected by any of these tested anesthetics [33].

Conclusion

From this brief overview it seems clear that it would be virtually impossible to describe precisely how the CB itself would behave since the array of neural receptors in the CB shows so many. And normal stimuli such as hypoxia and hypercapnia, and possibly even low glucose will provoke a release of ACh, ATP, dopamine and GABA. Does the behavior of one receptor in the organ influence the performance of another receptor in the same organ? The systemic reflex responses are indices of CB arousal. But a clear, precise causality behind the phenomena has yet to be parceled out (Figure 3).

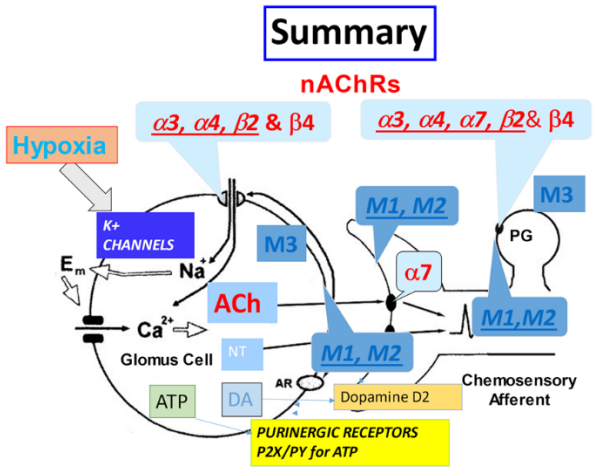

Figure 3: Array of nicotinic and muscarinic receptor subunits in the carotid body.

However, some few connections have been made. For example, during the cat's exposure to hypoxia ACh is released from the GCs to excite the afferent neuron abutting on it. But dopamine is also released. Dopamine attenuates both the ventilatory response and the CB neural responses to this stimulus. Thus, it appears that the dopaminergic apparatus trumps the cholinergic in CB behavior confronted with hypoxemia generated by a lowered P_aO_2.

In another system (cat CBs in an in vitro preparation with baroreceptor traffic eliminated) the increase in CB neural output due to hypoxia was reduced by two diazepines, indicating GABAA receptor action. In the presence of bicuculline, a GABAA receptor blocker, the reduction in CB hypoxia-generated neural output due to the presence of diazepam and midazolam was not observed. Here we see the GABAergic system being the dominant system. The most recent report from Buckler and his colleagues [27] comes closest to at least a partial solution to the problem of identifying what receptors are controlling CB behavior in the face of a stimulus. But, of course, if the stimulus is different, a different response among the receptors might well occur. Hence, though it is uncomfortable to leave this problem with no neat, complete answer, it simply is the reality of the situation, and a situation of which a practicing anesthesiologist might well be aware.

Loss of taste, loss of odor detection in CoVd19 patients presents an interesting and very important question. The above considerations show how a blocking of the CB's response to hypoxia can be generated. It would be important to see if CoVd19 patients have also lost their response to hypoxia. One clinical

observation was made that reported that COVd19 patients did respond to hypoxia, but the increase in their breathing frequency was less than what was expected for the degree of hypoxia. This suggests that these patients are now living their lives at subnormal oxygen saturation levels, a condition which could be damaging some tissues, most likely neural tissue.

References

1. Daly M deB, Lambertsen CJ, Schweitzer A. (1954). Observations on the volume of blood flow and oxygen utilization of the carotid body in the cat. J Physiol 125: 67-89.
2. Nurse CA, Leonard EM, Salman S. (2018). Role of glial-like type II cells as paracrine modulators of carotid body chemoreception. Physiol Genom 50: 255-262.
3. Leonard EM, Zhang M, Nurse CA. (2019). Evidence for protein kinase involvement in the 5-HT-[Ca2+]I - pannexin-1 signalling pathway in type II glial cells of the rat carotid body. Experimen Physiol 104: 244-253.
4. Garfinkel F, Fitzgerald RS. (1978). The effect of hyperoxia, hypoxia and hyper¬capnia on FRC and occlusion pressure in human subjects. Resp Physiol 33: 241-250.
5. Nadel JA, Widdicombe JG. (1962). Effect of changes in blood gas tensions and carotid sinus pressure on tracheal volume and total lung resistance to airlflow. J Physiol 163: 13-33.
6. Davis B, Chinn R, Gold J, Popovac D, Widdicombe JG, et al. (1982). Hypoxemia reflexly increases secretion from tracheal submucosal glands in dogs. J Appl Physiol 52: 1416-1419.
7. Fitzgerald RS, Dehghani GA, Kiihl S. (2015). Organismal responses to hypoxemic challenges. Adv Exp Med Biol 860: 101-113.
8. Marshall JM (1994). Peripheral chemoreceptors and cardiovascular regulation. Physiol Rev 74: 543-594.
9. Fitzgerald RS, Dehghani GA, Sham JSK, Shirahata M, Mitzner WA. (1992). Peripheral chemoreceptor modulation of the pulmonary vasculature in the cat. J Appl Phjysiol 73: 20-29.
10. Wilson LB, Levitzky MG. (1989). Chemoreflex blunting of hypoxic pulmonary vasoconstriction is vagally mediated. J Appl Physiol 66: 782-791.
11. Daly I deB, Daly M deB. (1957). The effects of stimulation of the carotid body chemoreceptors on pulmonary vascular resistance in the dog. J Physiol 137: 436-446.
12. Dorward PK, Burke SL, Janig W, Cassell J. (1987). Reflex responses to baroreceptor, chemoreceptor and nociceptor inputs in single renal sympathetic neurones in the rabbit and the effects of anesthesia on them. J Auton Nerv Syst 18: 39-54.
13. Share L, Levy MN. (1966). Effect of carotid chemoreceptor stimulation on plasma antidiuretic hormone titer. Am J Physiol 210: 157-161.
14. Harris MC. (1979). Effect of chemoreceptor and baroreceptor stimulation on the discharge of hypothalamic supraoptic neurones in rats. J Endocrinol 82: 115-125.
15. Raff H, Tzankoff SP, Fitzgerald RS. (1981). ACTH and cortisol responses to hypoxia in dogs J Appl Physiol 51: 1257-1260.
16. Lau C (1971). Role of respiratory chemoreceptors in adrenocortical activation. Am J Physiol 221: 602-606.
17. Raff H, Tzankoff SP, Fitzgerald RS. (1982). Chemoreceptor involvement in cortisol responses to hypoxia in ventilated dogs. J Appl Physiol 52: 1092-1096.
18. Critchley JAJH, Ellis P, Ungar A. (1980). The reflex release of adrenaline and noradrenaline from the adrenal glands of cats and dogs. J Physiol 298: 71-78.
19. Honig A. (1989). Peripheral arterial chemoreceptors and reflex control of sodium and water homeostasis. Am J Physiol 257: R1282-R1302.
20. Ericksson LI, Sato M, Severinghaus JW. (1993). Effect of a vecuronium-induced partial neuromuscular block on hypoxic ventilatory response. Anesthesiol 78: 693-699.
21. Ericksson LI . (1996). Reduced hypoxic chemosensitivity in partially paralysed man: a new property of muscle relaxants? Acta Anaesthesiol Scand 4: 520-523.
22. Hirshman CA, McCullough RE, Cohen PJ, Weil JV. (1977). Depression of hypoxic ventilatory response by halothane, enflurane, and isoflurane in dogs. Br J Anesth 49: 957-963.
23. Knill RL, GelB AW. (1978). Ventilatory responses to hypoxia and hypercapnia during halothane sedation and anesthesia in man. Anesthesiol 49: 244-251.
24. Ide T, Sakurai Y, Aono M, Nishino T. (1999). Contribution of peripheral chemoreception to the depression of the hypoxic ventilatory response during halothane anesthesia in cats. Anesthesiol 90: 1084-1091.
25. Davies RO, Edwards MW, Lahiri S. (1982). Halothane depresses the response of carotid body chemoreceptors to hypoxia and hypercapnia in the cat. Anesthesiol 57: 153-159.
26. Igarashi A, Amagasa S, Horikawa H, Shirahata M. (2002). Vecuronium directly inhibits hypoxic neurotransmission of the rat carotid body. Anesth Analg 94: 117-122.
27. O'Donohoe PB, Turner PH, Huskens N, Buckler KJ, Pandit JJ. (2019). Influence of propofol on isolated neonatal rat carotid body glomus cell response to hypoxia and hypercapnia. Respir Physiol Neurobiol 260: 17-27.
28. Liu Y, Dilger JP, Vidal AM. (1994). Effects of alcohols and volatile anesthetics on the activation of nicotinic acetylcholine receptor channels. Molec. Pharmacol 45: 1235-1241.
29. Franks NP, Lieb WR. (1998). Which molecular targets are most relevant to general anaesthesia? Toxicol Lett 100-101: 1-8.
30. Dilger JP, Brett RS, Lesko LA. (1992). Effects of isoflurane and acetylcholine receptor channels. 1. Single-channel currents. Molc. Pharmacol 41: 127-133.
31. Buckler KJ, Williams BA, Honore E. (2000). An oxygen-, acid- and anaesthetic-sensitive TASK-like background potassium channel in rat arterial chemoreceptor cells. J Physiol 525: 135-142.
32. Torturo CL, Zhou ZY, Ryan TA, Hemmings HC. (2019). Isoflurane Inhibits dopaminergic synaptic vesicle exocytosis coupled to CaV2.1 and CaV2.2 in rat midbrain neurons, eNeuro 6: ENEURO.0278-18.2018.
33. Nakanishi M, Mori T, Nishikawa K, Sawada M, Kuno M, et al. (2007). The effects of general anesthetics on P2X7 and P2Y receptors in a rat microglial cell line. Anesth Analg 104: 1136-1144.