Article ID: WMC005307 ISSN 2046-1690

Naming the nomenclatures: Dotting the Antidotes, Antagonizing the Antagonists

Peer review status:
No

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Article ID: WMC005307

Article Type: My opinion

Submitted on:29-May-2017, 02:55:41 PM GMT **Published on:** 05-Jun-2017, 09:35:12 AM GMT

Article URL: http://www.webmedcentral.com/article_view/5307

Subject Categories:ANAESTHESIA

Keywords: Agonists; Antagonists; Inverse Agonists; Antidotes; Reversal Agents; Naloxone; Flumazenil; Neostigmine; Sugammadex

How to cite the article: Gupta D, Chakrabortty S. Naming the nomenclatures: Dotting the Antidotes, Antagonizing the Antagonists. WebmedCentral ANAESTHESIA 2017;8(6):WMC005307

Source(s) of Funding:

None

Competing Interests:

None

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My opinion

In our pursuit to explore and explain for ourselves about what happens if the "antagonists" are administered prior to the "agonists", we realized that we may have been naming our medications incorrectly although it can be considered honest mistake or outright ignorance on our behalves. The medications that initiated and ultimately prompted this revelation were our anesthesia medications, namely naloxone, flumazenil, neostigmine (and sugammadex) [1-4]. We may have been misconceiving that the medications, which "reverse" the effects of other medications, must be "antagonists" [5-10] when the "antagonism" in itself may be a misnomer even when it is being used in relation to medications' cellular actions.

When a molecule attaches to a receptor in an organism and induces the intended natural course of a cellular action due to that receptor's activation, then it must be and is called receptor agonist (with process being receptor agonism). Essentially, that endogenous receptor in the body has developed to respond to endogenous molecules although we named that receptor based on exogenous analogue of the endogenous molecule as utilized during the animal-human biomedical research that eventually discovered them. Some may even say that exogenous substances' exposure over the generations induced the evolution of particular receptors in a constantly evolving organism as a measure to induct a "new" ability in that organism to enjoy the fruits of the effects as potentially inducible by the naturally occurring substances in spite of those substances' exogenous existence as pertaining to that organism's universe till that point in the time.

Once the receptors evolved to induce a (+)X cellular action in response to a substance (primarily an endogenous one), then those similar receptors provided the opportunity to getting locked in with another structurally similar substance (endogenous if part of a natural physiological feedback within the organism or exogenous if a rarity within the organism's inner universe) but the cellular action generated turned out to be (-)X cellular action and this process is already termed as inverse agonism (with substance being called an inverse agonist [11]). The (+) and (-) as attached to the X cellular action are just matters of perspective as how the curious onlooker looks at it although it may be worth wondering if the most common (popular) cellular activity is being termed (+) with corresponding substance attached to the receptor being termed as agonist while the rare cellular activity is being termed (-) with corresponding substance attached to the receptor being termed as inverse agonist.

Where do the antagonists fit in this broader picture? The supposedly called "antagonists" are the substances who get attached to the receptors and allow neither agonism ((+)X cellular activity) nor inverse agonism ((-)X cellular activity). Hence essentially, these substances with ZERO cellular activity act as blockers of the receptors and preventers of the cellular activity, but they are certainly NOT antagonists unless we presume that (anti)-agonism = (preventing)-agonism. Still if we need to rename the misnamed as we can not work with the unnamed, then what is the harm in using the word antidote? Herein, as rechristened antidotes, the blockers of receptors or the preventers of cellular activity can take over the receptors by either flooding the receptors (differential concentration effect) or displacing from the receptor (differential affinity effect) the culprit substance that has ceased to be the medication for an organism when it has become a morbid-mortal "poison" due to either its overdose (concentration effect due to administrator's methodology) or its idiosyncrasy (immunology effect due to receiver's physiology).

If it is unacceptable for the medical fraternity to name a substance as an antidote as per the individual clinical scenarios wherein say substance-A, needed to counteract the overdose/idiosyncratic effects of say substance-B, will need substance-B to counteract its own overdose/idiosyncratic effects, then the medical fraternity can choose to name either substance's (A's or B's) use as a reversal agent's use depending on the clinical scenario where and when the substance is used. Interestingly, besides for "antagonists", nomenclature of reversal agent (or for that matter antidote) can be used for "agonists" or "inverse agonists" depending on what substance has turned into "poison" and what substance is being intended as "medication" for that "poison" in a particular clinical scenario.

Coming back to our anesthesia medications that started this conundrum for our intrusive minds, it seems like that each among the medications-naloxone, flumazenil, neostigmine (and sugammadex)-can come under different nomenclatures. The big questions that can be asked and answered in future medical research investigations are:

- Does naloxone given in the absence of opioids compete with the endorphins for binding the receptors and prevent endorphins' agonism? SO CALLED ANTAGONISM
- Does flumazenil given in the absence of benzodiazepines compete with endogenous gamma-aminobutyric acid (GABA) for binding the receptors and prevent GABA's agonism? SO CALLED ANTAGONISM
- Does naloxone given in the absence of opioids compete and then counteract the endorphins? INVERSE AGONISM
- Does flumazenil given in the absence of benzodiazepines compete and then counteract endogenous gamma-aminobutyric acid (GABA)? INVERSE AGONISM
- Does naloxone given in the absence of opioids compete and yet behave just like (but inferior to) the endorphins? PARTIAL AGONISM
- Does flumazenil given in the absence of benzodiazepines compete and yet behave just like (but inferior to) the endogenous gamma-aminobutyric acid (GABA)? PARTIAL AGONISM
- Does it mean that naloxone effects on exciting the respiratory efforts may actually be inverse agonism that may present as tachypnea when naloxone is given in the absence of opioids?
- Does it mean that flumazenil effects on exciting the central nervous system pathways may actually be inverse agonism that may present as seizures [12-14] when flumazenil is given in the absence of benzodiazepines?
- Does it mean that potential naloxone role in preventing withdrawal symptoms in opioid dependent patients may actually be partial agonism that may present as analgesia when naloxone is given in the absence of opioids?
- Does it mean that potential flumazenil role in preventing withdrawal symptoms in benzodiazepine dependent patients [15-16] may actually be partial agonism that may present as sedation when flumazenil is given in the absence of benzodiazepines?

Again, the abovementioned are the big questions that can be asked and answered in future medical research investigations.

As far as neostigmine is concerned, it is a clear cut reversal agent (or an antidote as per our understanding) acting by increasing endogenous acetylcholine concentration as neostigmine inhibits the enzyme that degrades endogenous acetylcholine; and it is this endogenous acetylcholine that displaces the neuromuscular blockers [17] occupying the receptor sites meant for the endogenous acetylcholine. Similarly, sugammadex is again a reversal agent (or an antidote as per our understanding) acting by capturing the rocuronium-vecuronium molecules [18] wherein their decreased concentrations in the body fluids forcing their molecules occupying the receptors to leave the receptors and equilibrate with their falling concentrations in the body fluids; and it is again the endogenous acetylcholine molecules which begin occupying the receptor sites meant for them.

In summary, we have realized that we will (at least for our understandings) rename the nomenclatures wherein we will be doting our newly-crowned antidotes while antagonizing the misnomer antagonists.

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