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Review Article

Comparison of Catecholamine Physiological Effects in Vertebrates: Systematic Review

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Abstract: The goal of this review is to summarise and compare the physiological role of catecholamines in vertebrates from fishes to mammals. The catecholamines dopamine, norepinephrine and epinephrine are key regulators of various cell functions. They control numerous aspects of behaviour and response during acute or chronic stress. Considering the diverse habitats and the degree of improvement of the nervous and endocrine regulation in vertebrates, certain distinctions are to be expected in the spectrum of the released catecholamines and in the corresponding features of the observed physiological effects. They are released as both hormones and neurotransmitters in the nervous system. Dopamine is continuously secreted by neurons in order to decrease prolactin secretion. Norepinephrine is the major mediator of the sympathetic division of the autonomic nervous system in most vertebrates but not in amphibians. In lower vertebrates, the adrenergic signalling varies depending on the conditions of the environment, mainly temperature. Diversity in the metabolism and cardiac activity regulation are also observed as a result of the histologic features of the target cells. Both norepinephrine and epinephrine are secreted by the adrenal medulla in all vertebrates. Understanding the patterns of adrenergic signalling is essential for both scientific and practical purposes.

Key words: adrenoreceptors, cell metabolism, epinephrine, stress, vertebrates

Introduction

In all vertebrates, variation in the ratio between norepinephrine (NE) and epinephrine (Epi) released from the sympathetic nervous system and the adrenal medulla has been observed (Rome & Bell 1983, Reid et al. 1996, Azuma et al. 2017). There are also structural differences in the anatomy of the sympathetic nervous system (Nilsson 2011). In cyclostomes, it is presented as scattered ganglia near the main vessels (Brodal et al. 1963). In elasmobranchs, paravertebral ganglia are segmentally arranged but not connected in chains (lack of grey rami) (Young 1933). In teleost, sympathetic ganglia are in contact with several cranial nerves (Nilsson 1976) and form mixed trunks with cranial nerves IX and X in amphibians. Furthermore, chromaffin cells in sympathetic chain ganglia are found in urodeles but not in frogs and toads (Nicol 1952). The arrangement of the sympathetic nervous system in reptiles and birds does not deviate much from that in mammals (Kobayashi & Wada 1973, Berger & Burnstock 1979). Analysis of numerous literature data revealed that cyclostomes

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and elasmobranchs show the highest baseline levels of circulating catecholamines (CAs) while in birds, mammals and teleost fishes the baseline levels of circulating CAs is the lowest, which is directly related to the anatomical development of the adrenal medulla and the autonomic nervous system (Hart et al. 1989). In mice, the euthanasia method alters the NE/Epi in blood plasma. The NE release (sympathetic response) increases after decapitation without prior anaesthesia. Conversely, decapitation after anaesthesia increases Epi release (medullary response) even more. In both cases, CAs levels rise to values close to those after immobilisation as a stress factor. This is important when choosing a euthanasia method in sympathetic activity research (Lucot et al. 2005).

Biogenic CAs are synthesised from the amino acid tyrosine and contain amino groups ($R\text{-}NH_2$) and a catechol ring. Tyrosine can be formed from phenylalanine by the enzyme phenylalanine hydroxylase, but most often it is provided with food. It enters into the catecholaminergic neurons and adrenal medulla through a concentration gradient (Barrett et al. 2010). The biosynthetic pathway includes several enzymes located in both cytosol and large core-dense vesicles in varicosities of sympathetic nerves as well as vesicular monoamine transporters. The most common CAs are dopamine (DA), NE and Epi which are converted in each other depending on the set of enzymes expressed by the different cell types (Gardner & Shoback 2011, Widmaier et al. 2011). DA is a neurotransmitter in the dopaminergic neurons in the central nervous system and serves as a precursor of NE in all central and peripheral noradrenergic neurons. NE is the major mediator released from the endings of noradrenergic neurons in the brain, most of the postganglionic sympathetic neurons and the adrenal medulla chromaffin cells. It is stored in dense-core vesicles in the presynaptic terminals of neurons. The adrenal medulla secretes Epi as well as small amounts of DA and NE. Epi is not a neurotransmitter in postganglionic sympathetic endings. In humans, Epi is exclusively synthesised in the chromaffin cells in the adrenal medulla (Boron & Boulpaep 2012).

The following abbreviations are used in the text: ARs – adrenoreceptors; CAs – catecholamines; DA – dopamine; Epi – epinephrine; NE – norepinephrine.

Physiological Effects of Catecholamines

Individual AR subtypes have a tissue-specific distribution. In mammals, α_1-ARs are predominant in blood vessels and their activation leads to vasoconstriction of coronary vessels and arteries in the abdomen (Rang et al. 2003), kidney (Schmitz et al. 1981), skeletal muscles and systemic veins (Elliott 1997). Their activation in the sphincters of the digestive system and the bladder leads to their contraction. Moreover, activating them in the spermatic duct leads to a contraction of smooth muscles and ejaculation (Rang et al. 2003). In terms of cellular metabolism, increased glycogenolysis is observed (Kulcsar-Gergely & Kulcsar 1989). In fishes, gill blood flow is regulated by NE, which interacts with both AR types (α and β) (Djabali & Pic 1982, Randall & Ferry 1992, Chopin & Bennett 1995), while relaxation of slow skeletal muscles is mediated solely by α_1-ARs (Johnson & Johnson 1991. In the hepatocytes of amphibians and reptiles, only β-ARs are found, in birds α_1- and β-ARs are co-expressed, whereas in the liver of mammals α_1-ARs are more prevalent probably because of the considerable sympathetic innervation (Sulakhe et al. 1988).

α_2-ARs are mainly expressed in the presynaptic endings where feedback can reduce release of NE (Saunders & Limbird 1999). They are also found in the smooth muscles of some vessels such as skin arterioles and veins, where they are expressed alongside significantly more numerous α_1-ARs (Elliott 1997).

In the heart of mammals, β_1-ARs are prevalent and cause an increase in both the rate and strength of cardiac contractions and the velocity in the conduction system. In addition, they reduce the intestinal tone and motility and cause relaxation of the bladder wall. The stimulation of lipolysis in adipose tissue and the release of more renin from the juxtaglomerular apparatus are also mediated by β_1-ARs (Perez 2006). Compared to mammals, in birds CAs have a weaker effect on free fatty acid levels (Sturkie 1965).

ARs of the β_2 type are characteristic of the smooth muscles in bronchi and vessels – small coronary arteries, the liver artery and skeletal muscle arteries, where they cause phosphorylation-induced relaxation (and, hence, inactivation) of myosin light chain kinase. The tone of the gastrointestinal tract, the uterus and the wall of the bladder decreases by the same mechanism (Tanaka et al. 2005). Furthermore, they increase glycogenolysis by phosphorylation (activation) of glycogen phosphorylase (Rang et al. 2003).

The effects of Epi on adipose tissue are achieved through β_3-ARs that increase lipolysis, especially in brown adipose tissue (Ferrer-Lorente et al. 2005). They also enhance skeletal muscle thermogenesis (Rang et al. 2003). These ARs are

found in the walls of the gallbladder and bladder, but their physiological role is unclear (Sawa & Harada 2006).

In fishes, most CAs effects are mediated through β-ARs: the control of the cardiovascular system and respiratory functions is performed by β_2-ARs; β_1-AR-induced glycogen phosphorylase activation and pyruvate kinase inhibition (Wright et al. 1989, Reid et al. 1992) are responsible for carbohydrate and lipid metabolism regulation (Perry et al. 1988). β_1-ARs are presented in hepatocytes of all vertebrates. During embryogenesis, they are the only ARs and it is only after birth that α_1-ARs become dominant in liver metabolism regulation. Furthermore, with a decrease in temperature, the density of β_2-ARs in the heart increases, making cardiac muscle cells ten times more sensitive to Epi (Keen et al. 1993), while the number of β_1-ARs decreases, causing metabolism slowdown (Fabbri et al. 1998). Another peculiarity of fishes and frogs is the temperature-dependent shift in adrenergic signalling: in the winter, an α-adrenergic pathway is dominant, while β-adrenergic effects predominate in the summer (Hemmings & Storey 2011).

The β-ARs are found in the large arteries of teleost fishes (Forster 1981) and birds (Bolton & Bowman 1969), while they are absent in reptiles, which seems to be a physiological adaptation to the long body shape (Kirby & Burnstock 2003). On the other hand, Epi and NE have prolonged effects in snakes because the neuronal uptake is the only mechanism of deactivation. It is considered that extraneuronal uptake is not characteristic of these animal classes (Yamanouye et al. 1992).

The relatively small number of dopaminergic neurons in human CNS is located in several nuclei but they project toward many brain areas. They are found in the *substantia nigra*, ventral tegmental area, hypothalamus, arcuate nucleus, *zona incerta* and periventricular nucleus (Girault & Greengard 2004). The neurons of the *pars compacta* of *substantia nigra* have a projection to the *striatum* and this nigrostriatal pathway plays a key role in controlling movements and learning new motor models. They are responsible for movement planning and programming by transforming abstract thought into voluntary movement. These neurons are particularly vulnerable to disturbances and the destruction of a large number of them is characterised as Parkinsonism (Lang & Obeso 2004). Under normal physiological conditions, with age, the number of dopaminergic neurons and DA receptors decreases. Dopaminergic neurons from the ventral tegmental area are projected onto the prefrontal cortex and *nucleus accumbens* through the mesocortical and mesolimbic pathway, respectively. Together, they affect the amygdala, cingulate gyrus, hippocampus and olfactory bulbs, which are a part of the reward system and other aspects of motivation. The abuse of some substances affects this dopaminergic mediation. Morphine, cocaine, ethyl alcohol, amphetamines, cannabinoids and other drugs lead to DA release that interacts with D_3 receptors in *nucleus accumbens* and creates a sense of reward (Adinoff 2004). There is evidence that schizophrenia involves the altered activity of a dopaminergic group of neurons (Brisch et al. 2014).

Dopaminergic neurons from the posterior hypothalamus have projections to the spinal cord and disturbances in this pathway lead to the restless legs syndrome (continuous movement of the limbs leading to sleep disturbances). Other nuclei in the hypothalamus contain dopaminergic neurons (the arcuate nucleus and the periventricular nucleus), suppressing prolactin secretion from the anterior pituitary (Sapsford et al. 2012). In daylight, amacrine cells in the retina of the eye also secrete DA, which increases cone activity and suppresses rod activity (Li et al. 2013). This increases colour sensitivity and produces contrast under bright lighting at the expense of reduced sensitivity in low light. DA also has additional peripheral effects. It induces vasodilatation in kidneys through DA receptors activation, as well as Na^+ excretion with urine by phosphorylating and, thereby, suppressing the Na/K-pump (Hussain & Lokhandwala 2003). DA also causes vasodilatation of the mesenteric arteries but acts as a vasoconstrictor in all other vessels. On the other hand, DA induces a positive inotropic effect by activating β_1-ARs. Its cumulative effect on the cardiovascular system manifests through an increase in systolic pressure without affecting the diastolic one, making it convenient for use in traumatic and cardiogenic shock (Cavallotti et al. 2010). DA can also bind to α_2-ARs. Other molecules like octopamine, tyramine and L-Dopa also bind to these ARs. Such interaction of DA with ARs is a common feature among vertebrates. The affinity of DA to α_2-ARs is similar to that of NE, suggesting that this interaction is functionally equivalent (Cornil & Ball 2008, Nyrönen et al. 2018). DA-induced AR activation may cause an intracellular cascade involving changes in calcium and/or cAMP concentration or an effect on neuronal excitability (Malenka & Nicoll 1986, Zhang et al. 1999, 2004). Moreover, DA may activate a different intracellular NE cascade (Zhang et al. 2004). DA/α_2-ARs interaction is functionally significant

for the control of male sexual behaviour in mammals and birds (Absil et al. 1994, Balthazart et al. 1997, Dominguez & Hull 2005) as well as to sleep regulation (Crochet & Sakai 2003), participation in stress responses, memory consolidation, drug addiction, etc. (Cornil & Ball 2008).

Involvement of Catecholamines in Stress Response in Vertebrates

Depending on the affected organisational level and their rate, stress responses are summarised in three groups (Pickering & Pottinger 1995, Bonga 1997): primary responses – activation of brain centres, resulting in CAs and corticosteroids release; secondary responses – multiple brief effects of released hormones on tissue level; tertiary responses – effects at the organism and population level (increased vulnerability of additional stressors, growth and reproduction inhibition). The body adaptation to stressors, depending on their duration, is called a general adaptation syndrome. It is a three-stage process: (1) alarm reaction – "fight-or-flight" response; (2) resistance stage – normalisation of physiological parameters and hormonal levels or adaptation to higher stress levels and persistence of increased stress hormones; (3) exhaustion stage – anxiety, fatigue, depression, immune deficiency (Selye 1956). A modern approach to assess the degree of stress in all vertebrate taxa is based on changes in their haematological parameters (Davis et al. 2008), especially neutrophils (heterophils in birds and reptiles) to lymphocytes ratio which directly depends on glucocorticoid levels (Davis & Golladay 2019).

In teleost fishes, stress response is approximately identical to the one in terrestrial vertebrates: stimulation of oxygen uptake, mobilisation of energy substrates and their redirection from growth and reproduction to the stress response, suppression of immune functions, etc. However, fishes and other aquatic (especially marine) animals are more sensitive to environmental stress factors, since, in addition to their whole body being exposed to them, they do actually breathe, ingest and drink dissolved chemicals in the water. Stressors increase water and salts permeability of the epithelia, resulting in water-electrolyte imbalance. The key water-salt balance recovery regulator is cortisol/corticosterone, producing the combined effects of mammalian glucocorticoids and mineralocorticoids. In freshwater and seawater species, its co-regulators are prolactin and the growth hormone, respectively (Bonga 1997). At least in amphibians, the common stress axis corticotropin-releasing factor (hypothalamus) – adrenocorticotropic hormone (pituitary gland) – cortisol/corticosterone (adrenal cortex) is triggered by cocaine- and amphetamine-regulated transcript (CART) according to environmental conditions. Endogenous CART participate in the physiological adaptation of the circulatory system to limitations of energy consumption after prolonged food deprivation (Ivanova et al. 2007). Furthermore, Zhelev et al. (2013) have observed changes in the morphological content of the blood in amphibians such as increased erythrocyte counts and haemoglobin amount and alteration of differential blood formula as adaptive mechanisms to anthropogenic pollutants as fertilizers and pesticides. However, long-acting stressors cause a decrease in the blood oxygen capacity and a weakening of the immune system, making them more susceptible to infection (Zhelev et al. 2018).

In fishes, stress factors trigger Epi release from the chromaffin cells in the head kidney. It significantly increases the respiratory rate and blood flow in the gills (through the β-ARs pathway) but vascular resistance in the systemic circulation is mediated by α-AR signalling (Randall & Ferry 1992). In teleosts, there is a specific mechanism to increase blood oxygen capacity: β-ARs activate the Na^+/H^+ exchanger and inhibit the Cl^-/HCO_3^- exchanger. As a result, plasma pH decreases and cytosol pH becomes more alkaline, increasing haemoglobin affinity for oxygen (Nikinmaa 1992a, 1992b). Decreased pH reduces p_{CO2} and p_{O2}, shifts the CO_2/HCO_3^- equilibrium, increases haemoglobin affinity for oxygen, thus improving the oxygen transport capacity of blood (Thomas & Perry 1994). However, this unique mechanism shows significant species specificity related to the different β-AR density on red blood cell membranes (Perry & Reid 1992). In amphibians, there is a similar mechanism of β-AR mediated swelling of red blood cells by modulating the activity of Na^+/H^+- and Cl^-/HCO_3^-exchangers (Palfrey & Greengard 1981). Moreover, in fishes, blood CAs increase haematocrit by swelling erythrocytes (Soldatov 1996) and by the addition of more erythrocytes from the spleen by sympathetic Epi/α-AR- mediated vasoconstriction (Randall & Ferry 1992).

During stress response, glucose and free fatty acids are used as an energy source. Compared to NE, Epi is the more potent stimulant of hepatic glycogenolysis. Together, they activate glycogen phosphorylase through the β_2-AR pathway with the assistance of α-ARs (Mommsen et al. 1988, Wright et al. 1989, Danulat & Mommsen 1990). This activation is only mediated by β-ARs in amphibians (Janssens et al. 1983) and by α_1-ARs in mammals (Scheurink & Steffens 1990). In fishes,

gluconeogenesis is of minimal importance, at least until glycogen stores are exhausted (Janssens & Waterman 1988, Mommsen et al. 1988). The available data, while inconclusive on how CAs affect free fatty acid plasma levels, suggest that marine fish prefer free fatty acids to glucose and lactate as an energy source, which is a physiological adaptation to their saltwater habitat (Waring et al. 1996). In most domestic bird species, epinephrine strongly activates glycogen degradation to glucose in the liver. In various avian species and rodents, but not in humans, the main glucocorticoid hormone is corticosterone which causes an additional increase in blood glucose levels by enhanced liver gluconeogenesis (Snedecor et al. 1963, Joëls et al. 2018). The new glucose feeds protein synthesis, favours fat accumulation and increases the ratio of saturated to unsaturated fatty acids (Nagra & Meyer 1963). Although many of their neuroendocrine pathways are the same as those in mammals, studies on birds suggest greater independence of some elements of the hypothalamic-pituitary-adrenal axis. Thus, in domestic birds, such as quail, pigeon and duck, the pituitary is less likely to be controlled by the hypothalamus (Baylé et al. 1967). Besides, in birds, there are circadian and seasonal rhythms of corticosterone secretion, which cause different stress responses (Breuner et al. 1999). In amphibians, intensive or chronic activation of the axis hypothalamic-pituitary-interrenal gland cause increased corticosterone levels and neutrophils – lymphocyte ratio and immunosuppression (de Assis et al. 2015). However, these changes are species specific and depend on the habitat and life-cycle stage, so species with narrow habitat are less adaptable and stronger stress response is observed as compared to those with a wider range (de Assis et al. 2018).

Oxygen uptake, basal metabolic rate and used energy sources are highly dependent on environmental conditions. Tropical species have lower oxygen consumption and lower haemoglobin, while glucose is their energy fuel of choice. On the contrary, arctic species prefer free fatty acids as a substrate and have a higher basal metabolic rate. Therefore, stress response features are determined partly by species specificity and partly by habitat characteristics like temperature, humidity and other environmental variables.

Conclusion

Although CAs display similar effects in all vertebrates, there are certain differences that are associated with the amount and activity of enzymes in the biosynthesis pathways as well as with the type, density and sensitivity of ARs. Another possible reason for the observed variety of physiological effects of CAs are the various regulatory mechanisms, animal habitats and environmental factors leading to the most advantageous adaptation of the species. Knowledge of CAs synthesis and intracellular signalling pathways would promote the development of pharmacological agents for treating numerous socially significant diseases, improving animal living and transport conditions in economically significant sectors such as poultry and fish farming.

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