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IS THERE A HORMONAL REGULATION OF PHAGOCYTOSIS AT UNICELLULAR AND MULTICELLULAR LEVELS? A CRITICAL REVIEW

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Phagocytosis is an ancient cell function, which is similar at unicellular and multicellular levels. Unicells synthesize, store, and secrete multicellular (mammalian) hormones, which influence their phagocytosis. Amino acid hormones, such as histamine, serotonin, epinephrine, and melatonin stimulate phagocytosis, whereas peptide hormones, such as adrenocorticotropic hormone (ACTH), insulin, opioids, arginine vasopressin, and atrial natriuretic peptide decreased it, independently on their chemical structure or function in multicellulars. Macrophage phagocytosis of multicellulars is also stimulated by amino acid hormones, such as histamine, epinephrine, melatonin, and thyroid hormones, however, the effect of peptide hormones is not uniform: prolactin, insulin, glucagon, somatostatin, and leptin have positive effects, whereas ACTH, human chorionic gonadotropin, opioids, and ghrelin have negative ones. Steroid hormones, such as estrogen, hydrocortisone, and dexamethasone are stimulating macrophage phagocytosis, whereas progesterone, aldosterone, and testosterone are depressing it. Considering the data and observations there is not a specific phagocytosis hormone, or a hormonal regulation of phagocytosis neither unicellular, nor multicellular level, however, hormones having specific functions in multicellulars also influence phagocytosis at both levels universally (in unicellulars) or individually (in macrophages). Nevertheless, the hormonal influence cannot be neglected, as phagocytosis (as a function) is rather sensitive to minute dose of hormones and endocrine disruptors. The hormonal influence of phagocytosis by macrophages can be deduced to the events at unicellular level.

Keywords: phagocytosis, *Tetrahymena*, macrophage, evolution, hormonal effects

Phagocytosis is a basic life function for unicellulars. Corpuscular elements as nourishments or hostile other unicellulars are engulfed by it. Phagocytosis does not a universal function of all cells in the multicellular world, however, it is

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absolutely needed as a step of innate immunity, which initiates the adaptive immune response. Macrophages, neutrophil granulocytes, and dendritic cells recognize the large particles (at least 0.5 μm) and engulf them by using pseudopods [1, 2], which included the phagocytized cell or material. Actin filaments have a role in transporting the phagocytic vesicles, which finished their way after fusing with lysosomes. This is a complex process, which is spontaneously executed, however, it could take or tolerate hormonal regulation.

In multicellular organisms, hormones are at the service of chemical regulation and phagocytic cells are hormonally influenced [3]. Unicellulars synthesize, store, and secrete amino acid- and polypeptide-type hormones characteristic to multicellular animals (mammals) [4–14]. In addition, the cells have mammalian receptor-like structures in the plasma membrane, which bind these hormones and the cells react to them [15–19], as they have signal transducer pathways [20–23]. Many cell functions of the unicellular ciliate *Tetrahymena* are influenced by the hormones and their effect sometimes seems to be specific [19]. The first encounter with an artificially given hormone causes hormonal imprinting, which provokes a quantitatively altered reaction and this inherited to the progenies up to the thousandth generations [24, 25].

As hormones influence phagocytosis at both phylogenetic levels, it seems worth to study the character of the effect as well as the similarities and differences.

Facts at Unicellular Level

Amino acid hormones

Single histamine treatment increased the phagocytic activity of *Tetrahymena pyriformis* [26]. Chronic histamine treatment was more intense and the intensified activity remained high after some time in histamine-free medium [27]. The action of histamine was dose-dependent. Serotonin also stimulated phagocytosis in *Tetrahymena* [28] as well, as epinephrine [29]. In Tetrahymena *thermophila* histamine was ineffective, whereas the antihistamine, diphenhydramine increased it [30]. In other experiments, H1 and H2 antagonists were studied and these substances did not influence phagocytosis in *T. pyriformis*. However, H1 antagonist phenindamine counteracted the phagocytosis stimulating effect of histamine, whereas H2 antagonist metiamide was ineffective [31]. Serotonin and catecholamine stimulated phagocytosis in *T. thermophila* [32]. Serotonergic antagonists spiperone and metergoline also stimulated the process, whereas propranolol, alprenolol, and ergocryptine, which are beta and alpha adrenergic antagonists were ineffective or inhibitors [32]. In *Paramecium aurelia*, beta adrenergic

agonists (isoproterenol and norepinephrine) enhanced phagocytosis stereospecifically and dose-dependently. The effect was inhibited by propranolol and alprenolol [33]. Histidine, the basic amino acid for histamine formation also stimulated phagocytosis in *T. pyriformis* even stronger than histamine itself [34].

The pineal hormone, melatonin, between 10^{-6} and 10^{-10} M concentrations significantly stimulated the *E. coli* phagocytosis of *T. pyriformis* [35, 36].

The effect of amino acid-type hormones is manifested through the adenylate cyclase–adenosine monophosphate (cAMP) system. Treatment with cAMP or cPDE inhibitors (as theophylline) increases phagocytic activity of *T. pyriformis* [37, 38].

Peptide hormones

Adrenocorticotropic hormone (ACTH) and insulin inhibited the phagocytic activity of *Tetrahymena*. [39]. In addition, insulin antagonized the phagocytosis increasing action of histamine in *T. pyriformis* [40]. Arginine vasopressin decreased the phagocytic activity of *T. pyriformis* [41]. Atrial natriuretic peptide is also a potent inhibitor of phagocytosis in *T. pyriformis* [42].

Tetrahymena synthesizes beta-endorphin-like proteins [43] and have receptors for opioid peptides [43], which are suitable for testing opioid peptides of metazoa. These latter inhibit the phagocytotic activity of *T. thermophila* [44]. *Tetrahymena* opioids inhibit phagocytosis of *Tetrahymena* by a naloxone-reversible mechanism [45]. The opioid receptors of *Tetrahymena* are more sensitive to beta-endorphin and most sensitive to morphine [46], which points to the mu-likeness in some pharmacological characters. Chronic treatment with an opioid causes tolerance [47].

Steroid hormones

Dexamethasone and prednisolone stimulated the phagocytosis by *T. pyriformis*, but prednisolone-sodium-succinate and deoxycorticosterone-glucoside inhibited it [48].

Facts at Multicellular Level

Amino acid hormones

Histamine is believed to be the physiological activator of phagocytosis, since the basic works of Jancsó [49]. These data were supported by the

experiments with tubercle bacilli [50] and staphylococci [51]. However, there were studies, which demonstrated neutral or negative effects [52]. Epinephrine stimulated macrophage phagocytosis [53], whereas norepinephrine suppressed phagocytosis of wound neutrophils [54].

Induction of phagocytosis in murine macrophages is positively influenced by thyroid hormones through a glutamine mechanism [55]. Exercise (swimming) increases phagocytosis and thyroid hormones are responsible for it [56]. Triiodothyronine (T3) stimulated granulocytes' phagocytic activity [57, 58]. Melatonin increased engulfment of latex beads [59]. Physiological phagocytosis by neutrophil granulocytes seems to be dependent on the presence of nocturnal melatonin surge [60]. Alcohol treatment provokes a drastic decrease in neutrophil phagocytosis, which is restored by melatonin. Stress caused by swimming to exhaustion provoked lower melatonin peak and consequently higher phagocytic activity of macrophages [61]. Melatonin also suppressed phagocytic activity of cultured retinal pigment cells [62].

Peptide hormones

Prolactin increases the *in vitro* phagocytic capacity of macrophages [63] and helps to stimulate the exercise (swimming) induced phagocytosis [56]. Follicle-stimulating hormone (FSH) negatively influences phagocytic activity of Sertoli cells in tissue cultures [64]. ACTH suppresses phagocytosis of murine peritoneal macrophages [65], however, contradictory results are also known [66]. Chorionic gonadotropin suppresses the phagocytic activity of blood leukocytes and peritoneal macrophages [67, 68]. Opioids, such as endorphin and dynorphin, stimulate phagocytosis of mouse macrophages [66]. Insulin supports the onset of phagocytosis in inflammatory macrophages by a glutamine-transmitted mechanism [55] and restores neutrophil phagocytosis in diabetic patients [69]. Chronic treatment with insulin strongly depressed the macrophage phagocytosis in rats [70]. The phagocytic activity is low in type 2 diabetes and improves after metabolic improvement [71]. Insulin inhibits phagocytosis of normal human neutrophils [72]. It also enhances immunological phagocytosis by macrophages [72]. Glucagon and somatostatin stimulated macrophage phagocytosis [70]. Met-enkephalin, leu-enkephalin, and beta-endorphin reduced phagocytosis of *Candida albicans* by human monocytes [73]. Beta-endorphin also suppressed the phagocytic activity of splenic phagocytes and this was antagonized by opioid receptor antagonist, naltrexone [74]. Ghrelin decreased the phagocytic activity of cold-restraint stress exposed rats [75]. Leptin, the adipocyte hormone activates mononuclear phagocytes by a JAK/STAT signaling pathway [76].

Steroid hormones

Estrogen (E2) or progesterone significantly enhanced the phagocytosis of rat peritoneal macrophages [77]. Phagocytosis by human mononuclear cells was stimulated by dexamethasone or hydrocortisone [78]. In tissue culture, murine Sertoli cell phagocytosis was stimulated by hydrocortisone [79]. Prednisolone inhibited the latex phagocytic capacity of human granulocytes, by a receptor-mediated manner [80]. When prednisolone depressed phagocytic function, vitamin D3 or vitamin E partially restored it [81]. Progesterone reduced *E. coli* phagocytosis of cultured human decidual cells [82]. Gonadectomy in both sexes (in mice) significantly reduced phagocytic activity of peritoneal macrophages. In females, estradiol supplementation restored the normal condition, however, dihydrotestosterone treatment in males was insufficient [83]. In freshwater snake, *Natrix piscator* testosterone depressed phagocytic activity of splenic macrophages [84]. In common carp, *Cyprinus carpio*, beta-estradiol, 11 ketotestosterone, and progesterone suppressed phagocytosis of kidney macrophages in a dose-dependent manner [85, 86]. In tilapia, cortisol and dexamethasone decreased phagocytosis, and aldosterone had a weaker effect [87]. A chronic treatment with estradiol, testosterone, or dihydrotestosterone in chicks significantly depressed the phagocytic activity of macrophages [88].

Conclusions

Tetrahymena produce amino acid-type hormones as well as peptide ones. However, at unicellular level, there was not systematic investigation of these hormones in case of phagocytosis, but typical hormones were studied which allows the drawing of some conclusions. At multicellular level, more experiments and observation were performed and practically all important mammalian hormones were studied, sometimes with contradictory results, mainly depending on the used methods and subject species. This is understandable, as multicellular phagocytosis is part of the immune process, which have decisive role in the manifestation or healing of human diseases. Nevertheless, although phagocytosis is a rather complex process, mostly the engulfment of neutral particles or bacteria was studied under the effect of hormones and hardly are data on the behavior of actin network, on the encounter and fusion of endocytotic vesicles, etc. However, this has not importance from the aspect of our evaluation as phagocytosis, as a function is studied irrespective of details.

It is indisputable on basis of the data that at both levels of phylogeny hormones can influence phagocytosis. However, it is not known whether it is a

physiological interaction (regulation), which is needed for the normal execution of the function or coincidental because of the chemical structure of molecules. From evolutionary aspect, the problem seems to be more simple at unicellular level, as all of the amino acid hormones studied positively influenced phagocytosis (Table I), whereas peptide hormones affected it negatively (Table II). As the chemical structures inside the group given are very different and the modified amino acid molecule is easily distinguishable from a peptide chain this could mean that amino acid hormones – or may be amino acids, which were not fully studied from this point of view – are stimulating phagocytosis and polypeptide hormones – or may be peptides, which also have not studied from this point of view – are influencing negatively the process. This is supported by a study, in which histamine and serotonin enhanced the adsorption of fluorescein isothiocyanate (FITC)-labeled bovine serum albumin (BSA) to the plasma membrane of *Tetrahymena*, while a similar action by insulin was not significant. The degree of BSA binding was similar to the degree of phagocytosis [89]. However, the effect of epinephrine on BSA binding was also not significant which weakens the conclusion.

Steroid hormones positively influenced phagocytosis in *T. pyriformis* (Table III), however, it is questionable whether steroids are used for

Table I. Hormone-influenced phagocytosis in unicellulars: amino acid hormones

Hormone	Species	Effect +/−
Histamine	TP	+
Histamine/chronic	TP	+
Serotonin	TP	+
Serotonin	TT	0
Serotonin	TT	+
Epinephrine	TT	+
Epinephrine	P	+
Melatonin	TP	+
Histidine (amino acid)	TP	+

Note: TP: *Tetrahymena pyriformis*, TT: *Tetrahymena thermophila*, P: paramecium.

Table II. Hormone-influenced phagocytosis in unicellulars: peptide hormones

Hormone	Species	Effect +/−
ACTH	TP	−
ANP	TP	−
Opioids	TP	−
Insulin	TP	−
Vasopressin	TP	−

Note: TP: *Tetrahymena pyriformis*.

Table III. Hormone-influenced phagocytosis in unicellulars: steroid hormones

Hormone	Species	Effect +/−
Dexamethasone	TP	+
Prednisolone	TP	+
Prednisolone-sodium-succinate	TP	−
Deoxycorticosterone-glucoside	TP	−

Note: TP: *Tetrahymena pyriformis.*

communication at all, as the unicells are living in a watery milieu in which steroids are not dissolved, in addition they have not steroid receptors and their induced steroid receptors are not individual hormone-specific [90].

The ideal phagocyte models in multicellulars are the macrophages as they are the "professional" phagocytes. The effect of amino acid hormones on macrophages is identical with the unicellular ones (Tables IV and VII). However, the effect of peptide hormones is not so clear from this point of view (Table V). At a rough estimate the same amount of them is observed with positive, as negative

Table IV. Hormone-influenced phagocytosis in multicellulars: amino acid hormones

Hormone	Cell type	Effect +/−
Histamine	Macrophage/granulocye	+
Epinephrine	Macrophage	+
Nor-epinephrine	Macrophage	−
Thyroid	Macrophage	+
Melatonin	Macrophage	+
Melatonin	Retinal pigment	−

Table V. Hormone-influenced phagocytosis in multicellulars: peptide hormones

Hormone	Cell type	Effect +/−
Prolactin	Macrophage	+
ACTH	Macrophage	−
HCG	Macrophage/granulocyte	−
FSH	Sertoli cell	−
Opioids	Macrophage	+
Endorphin	Macrophage	−
Insulin	Macrophage	+
Insulin/chronic	Macrophage	−
Insulin	Granulocyte	−
Glucagon	Macrophage	+
Somatostatin	Macrophage	+
Ghrelin	Macrophage	−
Leptin	Macrophage	+

Table VI. Hormone-influenced phagocytosis in multicellulars: steroid hormones

Hormone	Cell type	Effect +/–
Estrogen	Macrophage	+
Estrogen/chronic	Macrophage	–
Progesterone	Macrophage	–
Progesterone	Macrophage (carp)	–
Testosterone	Macrophage	–
Ketotestosterone	Macrophage (carp)	–
Aldosterone	Macrophage (carp)	–
Hydrocortisone	Macrophage	+
Hydrocortisone	Sertoli cell	+
Dexamethasone	Macrophage	+
Prednisolone	Granulocyte	–
Testosterone	Splenic macrophage (snake)	–

effects. This could mean that in the case of amino acid hormones the amino acid character is dominant, whereas in the case of polypeptide hormones the specificity of the peptide chain. Considering immunity, phagocytosis belongs to the innate immunity, which is absolutely needed for the expression of adaptive immunity, however, this type of phagocytosis is not identical with the unicellulars' phagocytosis, from hormonal aspect. In addition, in multicellulars, the same hormone can participate in the control of innate and adaptive immunity alike [91, 92]. In the case of steroid hormones – and in multicellulars these are working – again their individual character has the decisive role (Table VI). "Glucocorticoids are the main effectors" which are bound by glucocorticoid receptors of immune cells (in macrophages included) [93].

As it was mentioned above, the unicellular *Tetrahymena* synthesize, store, and secrete hormones characteristic to multicellular animals (mammals). These

Table VII. Comparison of hormone-influenced phagocytosis in unicellulars and multicellulars

	Effect in unicellulars	Effect in multicellulars
Histamine	+	+
Epinephrine	+	+
Melatonin	+	+
ACTH	–	–
Insulin	–	+
Opiates	–	Uncertain
Dexamethasone	+	+
Prednisolone	+	Uncertain

unicellular hormones act to cells of metazoa similar to hormones of their own [94]. The unicell also has receptors for mammalian hormones and the receptors' structure is similar to mammalian ones [15, 16, 95], and can transmit hormonal information into the cells, which provokes response. However, the hormones which are classified to a group (e.g. amino acid type or peptide) are provoking similar (identical) reactions (positive by amino acid and negative by peptide). This means that there is not an individual hormone-specificity, but a hormone-type specificity which is not suitable for a hormonal regulation, but enough for being the base of a phylogenetic development of later hormonal control. This makes likely that the regulation by polypeptide hormones and steroids can be deduced to this type of group regulation. It is interesting that in the professional phagocytes (macrophages) of multicellular organisms, the amino acid hormones affect phagocytosis similar to the unicellulars (grouplike), but peptide hormones have individual effect. This could mean that the influence of phagocytosis in the frame of the evolution of immune mechanisms [96] runs parallel with the differentiation of hormones [93] and many components of unicellular phagocytosis have been conserved in higher ranked animals [97].

Phagocytosis is a form of endocytosis, when corpuscular elements are engulfed by the cell and it is a very ancient process [98]. The other form is pinocytosis when dissolved materials are taken up. These materials could be amino acids and these are utilized by the phagocyte for building up proteins. This means that the presence of amino acids in the environment is a positive signal for endocytosis which is also studied by the engulfment of particles (phagocytosis). This could also mean that amino acid hormones stimulate phagocytosis by their amino acid character, and this could explain the uniform effect of them.

The unicellular animal is composed of one cell, however, it is also a complete organism, which has all of the organs (organelles) which are needed for life. It synthesizes all of the water-soluble hormones which have been studied and also can react to them if these materials are present around it in the watery milieu. The macrophages of the multicellular organisms are able to synthesize hormones, however, these are produced by professional hormone producing organs or cells, as there is a division of labor in the organism. Steroid hormones are also produced and transported to the site of the effect. This means that in both cases there is a possibility of hormonal regulation of the phagocytic function [19].

Answering the question in the title of this paper: in our present knowledge, there is not a hormonal regulation of phagocytosis, neither unicellular, nor multicellular level. However, hormones are synthesized, stored, and secreted by unicells which can influence phagocytosis [99, 100] and there is a similar situation in multicells, where hormones which has specific functions (e.g., regulation of sugar metabolism, blood calcium level, ovarian cycle, etc.) are also influencing the

phagocytosis of professional cells (macrophages and neutrophil granulocytes). There is a similar situation if other cell functions would be studied, as specific hormones always have side effects on cells which are not in the mainstream of the hormonal effect. I cannot be excluded the existence of a specific phagocytosis hormone, or hormone-like molecule with specific phagocyte regulating activity at any levels of phylogeny, however, it is not known. At the same time, the hormones presently have been studied permits some evolutionary conclusions: their effects on phagocytosis of macrophages can be deduced to the effects on unicells.

Although in our present knowledge, there is not exist a hormonal regulation of phagocytosis, or specific phagocytosis hormone, the influence of hormones to phagocytosis cannot be undervalued. This is especially very important in our modern world, where hormone-like endocrine disruptors are present in increasing number and increasing amount. There are many data that these materials can alter normal immune functions, phagocytosis included [101–105] and the functional alterations of phagocytosis could cause or promote diseases in the present and future human generations [106–108].

Conflict of Interest

The author declares no conflict of interest.

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