Do urocortins have a role in treating cardiovascular disease?

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Corticotropin-releasing factor (CRF) and the three homolog neuropeptides, urocortin (UCN) 1, 2 and 3, are the major neuroendocrine factors implicated in the response of the body to stress. Recent evidence suggests that UCNs have a significant role in the pathogenesis and management of cardiovascular disease, such as congestive heart failure, ischemic heart disease, and hypertension. These data led to the initiation of clinical trials testing a possible role of UCNs in the diagnosis and therapy of cardiovascular disease, with encouraging results. Here, we summarize the available literature concerning the role of UCNs in the cardiovascular system, focusing on the emerging data creating a potential for clinical applications.

Introduction

Cardiovascular disease is a major problem of the modern world. According to reports from the WHO, more people die annually from cardiovascular diseases than from any other cause, with ischemic heart disease being the first cause of death worldwide. Trying to unravel the underlying pathophysiological mechanisms could lead to the development of new therapy concepts.

The involvement of the neuroendocrine system in cardiovascular functions is prominent. Several neurohormones, such as angiotensin II, arginine, vasopressin, and natriuretic peptides, are involved in the homeostasis of the cardiovascular system. An increasing amount of evidence involves the CRF system of neuropeptides in the physiology and pathophysiology of the cardiovascular system, which is unsurprising given the well-recognized role of stress in this system. CRF and its homologs, UCNs, have a significant role in the homeostasis of the human organism. Recent clinical evidence suggests that targeting the CRF system could offer a promising alternative in the management of cardiovascular disease, such as congestive heart failure, ischemic heart disease, and hypertension. Data from preclinical studies showing CRF peptide and CRF receptor expression in heart tissue and evaluating their diverse actions are abundant and conclusive. Here, we focus on data emerging from studies that highlight clinical perspectives for these molecules, thus opening the way for clinical applications.

The CRF system

The CRF system in mammals comprises four peptide members (CRF, UCN1, UCN2 and UCN3) along with their receptors [1]. Apart from regulating adrenocorticotropic hormone (ACTH) secretion by the pituitary gland, CRF is implicated in neuroendocrine and behavioral stress responses, because its receptors are also distributed in the neocortex, amygdala, and brainstem nuclei [2]. UCN1 is expressed in the Edinger–Westphal locus, hypothalamus, and forebrain, as well as in the periphery, gastrointestinal system, cardiac muscle, coronary arteries, thymus, and other tissues [3–6]. UCN2 and UCN3 are expressed in different areas of the central nervous system (CNS). In the periphery, UCN2 has been detected in heart, blood cells, adrenals, muscles, gut, and other tissues [7–9]. All 3 UCNs have been detected in all four chambers of the heart

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https://doi.org/10.1016/j.drudis.2018.09.004

[10–12]. All these neuropeptides exert their multiple actions through activation of two distinct receptor types [CRF receptor 1 (CRFR1) and 2 (CRFR2)], which both belong to class B of the G-protein-coupled receptor (GPCR) superfamily [13,14].

CRFR1 is expressed primarily in the brain and pituitary, whereas the expression of three CRFR2 splice variants (CRF2a, CRFR2b, and CRFR2c) has been reported in the CNS, as well as in heart, skeletal muscles, and testis. CRF and UCN1 have equal affinity for the CRFR1 receptor, although UCN1 is 40 times more potent than CRF in binding CRFR2. By contrast, UCN2 and UCN3 bind selectively to CRFR2, possibly being the endogenous ligands for this receptor subtype [15].

Main actions of urocortins

The role of urocortins in both the CNS and periphery has been intensively studied. Some actions in the CNS include the contribution of UCN1 to the control of anxiety, depression, and drug abuse, and the development and maintenance of normal hearing [16]. UCN2 is involved in the inhibition of gastric emptying through sympathetic pathways [17], and it might also have a regulatory role in the hypothalamic–pituitary–adrenal axis (HPA) activity at the hypothalamus level via a paracrine or autocrine manner through a vasopressin-dependent mechanism [16]. Finally, UCN3 acts on the CNS to control food intake [16].

Regarding the peripheral actions of UCNs, UCN1 is found in liver, where it could represent an autocrine and/or paracrine modulator of the local immune response [5]. UCN1 might also be involved in the control of gastric acid secretion, inhibition of gastric motility, and increasing the motility of the colon, whereas UCN2 selectively delays gastric emptying without an effect on colon mobility [16,18]. Regarding the adrenal glands, UCN1 leads to the induction of catecholamine secretion, whereas UCN2 has the opposite effect [19]. In kidney, all UCNs induce vasodilation and, thus, are implicated in the regulation of arterial blood pressure (BP) [20]. UCN1 has also been shown to induce the secretion of proinflammatory cytokines [21]. In the reproductive system, UCNs might have an important role in the physiology of pregnancy and childbirth by modulating the resistance of placental vessels to blood flow and increasing the contractility of the uterus [16].

The role of the CRF system in the cardiovascular system

Expression of UCNs and their receptors in the human cardiovascular system

In humans, CRF expression is low or undetectable in the heart and blood vessels, and circulating plasma levels are also low, suggesting that CRF is unlikely to be an endogenous ligand for CRFR2 expressed in the heart [22]. Conversely, UCN1 mRNA is expressed in all four chambers of the heart and it has been suggested that this peptide is the endogenous physiological ligand of CRFR2 in the heart [10]. UCN3 was also found to be expressed in all four heart chambers [11].

Animal studies revealed an expression of CRF receptors in the cardiovascular system, in vessels as well as in the heart. As far as the vessels are concerned, expression of CRF receptors is higher in arteries than in veins and the receptors were found to be expressed on smooth muscle fibers and endothelium [23]. Their expression in the smooth muscle of vessels might explain the strong vasorelaxant actions of CRF [23]. CRF receptors are also strongly expressed in the coronary arteries of rats and mice [23]. Their expression in the heart muscle is stronger in mice than in rats [23]. Pharmacological studies in mice proposed the cardiovascular actions of CRF and UCNs to be mainly mediated by CRFR2 [23]. From the three CRFR2 isoforms, CRFR2b is the main one expressed in the periphery (i.e., heart and skeletal muscle in rats|) [24]. Administration of lipopolysaccharide, corticosterone, UCN1, interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-α have been shown to reduce the expression of CRFR2b in rat heart and in cell lines of nondifferentiated smooth muscle cells derived from the aorta of embryonic rats, implying that the levels of CRFR2b in the cardiovascular system are associated with inflammation and stress [24–26].

The expression of UCN1 was found to be increased in diseased heart compared with healthy heart tissue in rats and humans [12,27]. Furthermore, researchers observed that plasma levels of UCN1 are elevated in patients with chronic heart failure in proportion to the degree of cardiac dysfunction and can function as an independent predictor of heart failure [28]. Studies conducted in hearts of 40 archival human fetuses revealed the expression of the complete CRF system and, interestingly, an isolated expression of UCN3 only in hearts of fetuses with chromosomal abnormalities or congenital disorders [29].

Animal studies

Data from animal studies showing CRF peptide and receptor expression and regulation in heart tissue as well as preclinical evaluation of different actions are numerous and conclusive and have been recently reviewed elsewhere. The most important findings are summarized in this section.

CRF produces powerful actions on the cardiovascular system that depend on whether the peptide is administered peripherally or directly to the CNS [30]. Intravenous administration of CRF caused vasodilation in rats and dogs [30], whereas intracerebral administration of CRF in sheep increased BP, cardiac output, and heart rate [31]. As far as UCNs are concerned, there are numerous studies assessing their actions, combined, or not, with other cardiovascular medication. Available published data on the effect of UCNs in the function of vascular endothelium are equivocal. The protective effects of UCNs in the vascular endothelium are caused by a decrease in the production of active oxygen radicals by the action of proinflammatory cytokines, endothelin-1, serum angiotensin-converting enzyme (ACE), and angiotensin II, and a decrease in superoxide dismutase activity with a parallel increase in production of nitric oxide (NO) [32,33]. Moreover, UCNs have proinflammatory and procoagulant effects mediated by increased production of IL-6 and IL-1β [33].

In cultures of rat neonatal myocytes, UCNs stimulated the secretion of natriuretic peptides through the CRFR2 receptor [34]. Furthermore, they caused hypertrophic changes to cardiac myocytes as well as an increase in protein synthesis and collagen levels, with UCN3 being considered to be the factor responsible for these actions [35]. Furthermore, UCNs reduced reperfusion injury in isolated rat hearts subjected to ischemia and reperfusion; the protective effect was observed when the peptide was administered either at preischemia or at reperfusion [6,36–38]. Finally, UCNs have been shown

TABLE 1

Cardiovascular actions of UCNs in animal models of cardiovascular disease

Disease	Change in hemodynamic and other parameters	Refs
Arterial hypertension	BP ↓; LV hypertrophy ↓; Deterioration of LVEF ↓	[53]
Heart failure	BP ↓; Cardiac output ↑; SVR ↓; urine volume ↑, sodium excretion ↑, creatinine clearance ↑	[54]
Dilated cardiomyopathy	Cardiac output ↑; ↓SVR	[55]

Abbreviations: BP, blood pressure; LV, left ventricular; LVEF, left ventricular ejection fraction; SVR, systemic vascular resistance.

TABLE 2

Cardiovascular actions of the combination of UCNs with other medication in animal models with cardiovascular disease

Combination	Changes in hemodynamic and other parameters	Refs
UCN2 + furosemide	BP ↓; vasopressin ↓, renin ↓; natriuretic peptides ↓; diuresis ↑, sodium excretion ↑	[56]
UCN2 + metoprolol	Cardiac output ↑; SVR ↓	[57]
UCN2 + aldosterone receptor inhibitor	SVR ↓; right atrium pressure ↓; diuresis ↑, sodium excretion ↑, potassium levels ↓; vasopressin ↓, renin ↓, aldosterone ↓, Ang II ↓	[58]
UCN2+ captopril (ACE inhibitors)	BP ↓; vasopressin ↓, renin ↓, aldosterone ↓, endothelin 1 ↓	[59]

Abbreviations: ACE, angiotensin-converting enzyme; ARI, aldosterone receptor inhibitor; BP, blood pressure; RA, right atrium; SVR, systemic vascular resistance.

to cause beneficial cardiovascular effects, such as coronary vasodilation, positive inotropic action, and increase in cardiac output, all mediated by the CRFR2 receptor [31,39]. In a study in sheep, UCN1 administration gradually increased BP, which was attributed to elevated heart rate and cardiac output [31]. The most important action observed with intravenous administration was prompt and important enhancement of heart contractility [31]. According to experimental data, the hemodynamic actions of UCNs are not mediated by the autonomic nervous system, but rather through direct myocardial CRFR2 binding [30].

The cardiovascular actions of UCNs have also been studied in combination with cardiovascular medication. In particular, UCNs were studied in animal models of heart failure in combination with loop diuretics, aldosterone receptor antagonists, beta-blockers, and ACE inhibitors, demonstrating a promising and protective role. Tables 1 and 2 offer a synopsis of published data opening the way for clinical applications.

Ex vivo *and* in vitro *human studies*

Hasegawa and co-workers examined the role of UCN1 in atherosclerosis using human mononuclear cells isolated from healthy volunteers as well as commercially available smooth muscle cells [40]. They showed that UCN1 suppressed the inflammatory response and proliferation of endothelial cells, macrophage foam cell formation and migration, and proliferation of smooth muscle cells. The protective effects of UCN1 against atherosclerosis were confirmed in human umbilical vein endothelial cells (HUVECs) [32]. Endothelial urocortin was upregulated by inflammatory cytokines and pitavastatin and suppressed reactive oxygen species (ROS) production. Most interestingly, the same study showed that treatment with pitavastatin for 4 weeks increased the serum urocortin level in humans.

Vasodilatory effects of UCN1 were observed in samples of internal thoracic artery obtained during coronary artery bypass graft surgery [41]. In particular, UCN1 produced both endothelium-dependent and -independent vasodilation. The administration of potassium channel blockers, such as tetraethylammonium, charybdotoxin, and iberiotoxin, inhibited vasodilatation, suggesting the involvement of these channels in the mediation of urocortin results. Wiley and colleagues confirmed the above findings for CRF, UCN1, UCN2, and UCN3 in a study utilizing samples of human internal mammary artery after endothelium removal [42]. UCN2 and UCN3 caused strong, sustained, and direct vasodilatation, independent of the endothelium, whereas UCN1 produced endothelium-dependent vasodilatation in this model, probably mediated by NO.

Smani and co-workers conducted experiments on coronary artery samples from patients with heart failure undergoing orthotopic heart transplantation and whose heart failure was caused by dilated cardiomyopathy of ischemic etiology [43]. Cumulative concentration of UCN2 was measured and concentration-dependent vasodilatation was demonstrated. Furthermore, UCN2 induced endothelium-independent vasodilatation in this study. The cardioprotective effects of UCN1 have been studied in patients undergoing coronary artery bypass graft surgery using extracorporeal circulation with warm blood cardioplegia [44].

Finally, UCN2 appears to have a role in the pathophysiology of abdominal aortic aneurysm formation. In a study conducted in patients with such aneurysms, it was found that UCN2 and CRFR2 were significantly upregulated in biopsies from the aneurysm body and that median plasma concentrations were higher in patients with abdominal aortic aneurysms compared with patients with non-aneurysmal vascular disease.

Studies evaluating the clinical use of urocortins in healthy subjects and patients

UCNs as biomarkers in cardiovascular disease

Patients with heart failure have higher levels of UCN1 compared with patients without heart failure, the levels of UCN1 increasing with increasing age and NYHA classification [45]. Wright and co-workers showed that plasma UCN1 levels in patients with heart failure were related to symptoms, measures of cardiac function, and levels of other circulating neurohormones, such as N-terminal pro-brain natriuretic peptide (BNP) [28].

Topal and co-workers measured serum levels of UCN2 in patients with systolic and diastolic dysfunction and ischemic heart disease and found higher serum levels in patients with mild and moderate congestive heart failure [46]. In the group of patients with ischemic heart disease, without prior myocardial infarction, and those with diastolic dysfunction, serum levels of UCN2 were comparable with those of the control group.

The above results show that UCN1 and UCN2 could serve as biomarkers in the diagnosis and prognosis of heart failure.

TABLE 3

Phase 1 clinical trials using UCNs[a]

Authors	Factor/Administration	Number of patients	Type of study	Results	Refs
Davis *et al.*, 2004	50 μg of UCN1 i.v. over 1 h	*N* = 8 healthy males	Placebo controlled, crossover, randomized	↑ ACTH, cortisol, ANP; ↓ ghrelin	[47]
Davis *et al.*, 2007	25 μg and 100 μg of UCN2 and placebo i.v. over 1 h	*N* = 8 healthy males	Single-blind, placebo controlled, dose escalation	↑ CO, HR, LVEF; ↓ SVR, urine volume, natriuresis; 100 μg ↑ renin, Ang II, and norepinephrine activity	[48]
Davis *et al.*, 2007	25 μg and 100 μg of UCN2 and placebo i.v. over 1h	*N* = 8 male patients with HF	Single-blind, placebo-controlled, dose escalation	↑ CO, LVEF; ↓ MAP, SVR, CW, urine volume	[49]
Venkatasubramanian *et al.*, 2013	UCN2, UCN3, and substance P with/without aspirin, fluconazole, or L-NMMA	*N* = 18 healthy males	Double-blind, randomized, crossover	UCN2 and UCN3 evoked arterial vasodilatation, L-NMMA reduced vasodilatation to substance P and UCN2	[51]
Chan *et al.*, 2013	5 ng/kg/min of UCN2 or placebo i.v. over 4 h	*N* = 53 patients with acute decompensated HF	Double-blind, randomized, placebo controlled	SBP ↓, HR ↑, CO ↑, SVR ↓, PAP ↓, PCWP ↓, urine volume ↓, CrCl ↓, plasma renin activity ↑, BNP levels↓	[50]
Gheorghiade *et al.*, 2013	5, 15, and 30 ng/kg/min of UCN3 or placebo i.v. over 1 h	*N* = 62 patients with HF and LVEF ≤35%	Double-blind, randomized, placebo-controlled, dose escalation	↓ CI and SVR with 15 and 30 ng/kg/min; ∼BP, ∼HR, ∼SBP	[52]
Stirrat *et al.*, 2016	1st: intra-arterial infusion of UCN2 (3.6–36 pmol/min), UCN3 (360–3600 pmol/min) and substance P (2–8 pmol/min); 2nd: i.v. infusion of sodium nitroprusside (573–5730 pmol/kg), UCN2 (36–360 pmol/min), UCN3 (1.2–12 nmol/min), and placebo	1st: *N* = 8 patients with HF and *N* = 8 age- and gender-matched healthy controls, 2nd: *N* = 9 patients with HF and *N* = 7 healthy controls	1st: randomized, dose escalation, 2nd: randomized, double-blind, placebo controlled crossover study, dose escalation	1st: arterial vasodilation CN2, UCN3, and substance P in patients with HF and controls (no difference); 2nd: HR ↑, CI ↑, SVR ↓, MAP ↓ with UCN2, HR ↑, CI ↑ only significant in patients with HF and controls with UCN2	[60]

[a] Abbreviations: ANP, atrial natriuretic peptide; CO, cardiac output; CI, cardiac index; CrCl, creatinine clearance; CW, cardiac work; HR, heart rate; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure; SVR, systemic vascular resistance; ∼, no change.

Clinical trials using UCN1

In a Phase 1 study by Davis and co-workers, UCN1 was intravenously administered over 1 h in eight healthy male volunteers [47]. Elevated levels of ACTH, cortisol, and atrial natriuretic peptide and reduced levels of ghrelin were noted in the group receiving UCN1 compared with the control group receiving placebo. The above dose and method of administration did not produce significant hemodynamic and renal effects in healthy individuals, but the observed decrease in ghrelin levels might explain the anorexia known to be induced by UCN1. The results of published clinical trials are summarized in Table 3.

Clinical trials using UCN2

In a single-blind Phase 1 study by Davis and co-workers, two intravenous doses of UCN2 and placebo were administered to eight healthy male volunteers, and cardiovascular, hemodynamic, renal, and neurohormonal effects were evaluated [48]. Dose-related increases in cardiac output, heart rate, left ventricle ejection fraction (LVEF), and contraction velocity of mitral valve tissue were observed, as well as a dose-dependent reduction in end-systolic volume, a decreased peripheral vascular resistance, and a decreased diastolic and mean arterial pressure compared with the control group. Declines in diastolic BP and mean arterial pressure, with no statistically significant reduction in systolic BP were noted in the UCN2 group.

Furthermore, Davis and co-workers administered intravenous UCN2 to patients with heart failure to study its effect on the cardiovascular system in a Phase 2 single-blind study [49]. Eight male patients with congestive heart failure were enrolled. The subjects were administered placebo, low-dose, or high-dose UCN2 intravenously over 1 h and with an interval of 2–5 weeks between each dose. As a result, an increase in cardiac output (CO) and LVEF was observed and a decrease in systolic and diastolic BP, mean arterial pressure, systemic vascular resistance (SVR), and cardiac work. Additionally, a continuous decrease in SVR, cardiac work, and BP after the infusion was noted, whereas longer and clearer effects were demonstrated after the high dose compared with that of the low dose.

The therapeutic use of UCN2 in acute decompensated heart failure as an adjunct to conventional therapy was tested for the first time in the study UNICORN [50]. This was a randomized, double-blind study that enrolled 53 patients with acute decompensated heart failure treated with UCN2 or placebo for 4 h as an adjunct therapy. The changes in vital signs, plasma neurohormonal and renal biomarkers during treatment were compared using analysis of covariance with repeated measurements. Regarding hemodynamic effects, it was shown that UCN2 induced rapid and pronounced hypotensive activity, with maximal effect occurring between 1.5 and 2.5 h, as well as an increase in heart rate [50]. Additionally, UCN2 administration resulted in vasodilatation, increased cardiac output, a prolonged decline in BNP levels, and

a transient decline in renal function, most likely reflecting falls in renal perfusion pressure, associated with temporarily increased renin and decreased creatinine excretion [50].

Clinical trial using a combination of UCN2 and UCN3

Clinical effects of UCN2 and 3 were studied by Venkatasubramanian and colleagues in a double-blind, randomized crossover study in 18 healthy male young volunteers [51]. Eight healthy volunteers received discontinuous or continuous gradually increasing doses of intraarterial UCN2 or UCN3, whereas ten healthy volunteers received progressively increasing doses of intraarterial UCN2, UCN3, and substance P in the presence of: (i) a placebo; (ii) 600 mg aspirin orally; (iii) an inhibitor of NO synthesis; (iv) intraarterial fluconazole; and (v) the combination of aspirin, intra-arterial fluconazole, and inhibitor of NO synthesis. UCN2 and UCN3 caused significant vasodilation but were moderately inhibited by the NO synthesis inhibitor, slightly more intense for UCN2 compared with UCN3. Although vasodilation mediated by UCN2 and UCN3 was inhibited by the combination of three inhibitors, vasomotor activity remained to a significant degree.

Clinical trials using UCN3

Gheorghiade and co-workers examined the safety, pharmacokinetics, and effects on hemodynamics and biomarkers of the intravenous administration of human acetate stresscopin (UCN3) in patients with stable heart failure in a double-blind randomized study [52]. The main study involved the administration of gradually increasing doses of study drug or placebo at successive intervals of 1 h (3 h total). Results showed significant increases in cardiac index and a decrease in SVR with both medium and high doses. No significant changes were seen in heart rate or systolic BP, although there was a decrease in diastolic BP. No statistically significant decrease in pulmonary capillary wedge pressure was observed with any dose tested in the primary analysis, although a reduction trend was observed. The aforementioned findings could imply a possible advantage of the peptide over classical inotropic agents to improve cardiac function with fewer negative impacts on myocardial oxygen demand [52].

Concluding remarks

The therapeutic potential of UCNs in cardiovascular disorders has been highlighted not only in animal studies, but also in clinical trials. UCNs have differential effects on the cardiovascular system, some of which have been highlighted here.

It was previously proposed that UCNs could prove to be valuable drugs in the future, either as monotherapy or as an adjunct to conventional therapy, for the treatment of 'cardiorenal' or 'renal-cardiac' syndrome [20]. Besides cardiac parameters, all UCNs also improved renal function in experimental heart failure models and caused a significant improvement in most, if not all, dysregulated parameters in cardiorenal syndrome by diminishing multiple vasoconstrictive stimuli, improving the cardiac output through a positive inotropic action, and removing sodium and water excess through the improvement of renal function.

Based on the data presented here, UCN2 appears to be a promising choice in the treatment of cardiovascular diseases, such as hypertension, ischemic heart disease, and heart failure. The immediate and sustained reduction in BP resulting from UCN2 administration could be a new and attractive approach for new antihypertensive treatments. Another interesting property that makes UCN2 potentially suitable for use in patients with heart failure is that UCN2 acts both dependently and independently of the endothelium, considering that patients with heart failure have some degree of endothelial dysfunction. Absence of adverse effects from the CNS is an additional advantage.

By contrast, UCN1 failed to demonstrate hemodynamic effects in humans. Moreover, adverse effects because of the activation of CRFR1 and stimulation of the hypothalamic–pituitary axis were observed. However, it might have a role as a biomarker in the early diagnosis of heart failure.

UCNs cause vasodilatation without signs of tachyphylaxis and with good reproducibility. This is important, especially because of their potential application in the therapy of chronic diseases, where predictability and reproducibility of pharmacological actions are required. They also have positive inotropic, chronotropic, and lusitropic effects on the heart. This, in combination with their favorable effects on hemodynamic, renal, and neurohormonal parameters, makes these peptides a potentially attractive agent for the treatment of heart failure. Several studies showed interesting actions of UCNs in animal models of heart failure as well as in humans in the context of clinical trials. Although many human studies dealt with the combined systemic effects of UCNs, the relative contributions of UCN-induced hemodynamic changes in increasing cardiac output have not yet been adequately studied. Additionally, further studies are needed to examine the potential effects of long-term administration of these peptides. Finally, the administration of a peptide for diseases such as hypertension or heart failure poses important practical difficulties. In particular, the low oral bioavailability of a peptide makes a parenteral administration necessary, a fact that probably limits the use of UCNs in acute conditions and hospitalized patients, such as patients with acute decompensated heart failure and hypertensive crisis. Developing modified, long-acting peptides that can be given subcutaneously, gene delivery therapies that augment endogenous UCN synthesis and release, as well as small bioavailable molecules capable of activating UCN receptors could be some of the ways to overcome these difficulties.

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